Special Article

Update in Pathophysiology and Histopathology of Focal Segmental Glomerulosclerosis

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Focal segmental glomerulosclerosis (FSGS) is the leading cause of nephrotic syndrome in an adult worldwide. The prevalence of FSGS is estimated as being 20-30% in adults over the age of 15 years and slightly higher (30-35%) in the elderly (age > 60 years). The diagnosis solely relies on pathologic findings, which sclerosis involves some, but not all glomeruli (focal), and sclerosis affects a portion, but not the entire, glomerular tuft (segmental). The pathogenesis remains inconclusive but podocyte injury has been postulated. Even though steroid is the mainstay treatment, only 20-40% of patients are complete respond.

Keywords : *FSGS, Pathology, Glomerulosclerosis, Pathophysiology*

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1. Epidemiology and definition of FSGS

In recent years, focal segmental glomerulosclerosis (FSGS) has emerged as a leading cause of nephrotic syndrome (NS) in adults and children in many countries worldwide[1]. In the US, the incidence and prevalence of FSGS which resulted in end stage renal disease (ESRD) has increased exponentially during the past two decades[2] (Fig. 1 and 2). This might in part be both due to changes in disease classification as well as a genuine increase in the frequency of FSGS. The increase in ESRD attributed to FSGS in the US is observed in all races, but is most marked in the African-Americans. In the US, the adjusted annual incidence rates of ESRD due to FSGS (expressed per million) were 21 for Blacks, 5 for Whites, 5 for Asians, and 3 for Hispanics; although, these rates are likely underestimates of the true incidence since many patients do not receive a kidney biopsy. Among Asian countries, minimal change disease (MCD) or mesangial proliferation are often still the leading cause of NS, but FSGS is the commonest cause of nephrosis that is resistant to treatment associated with progressive decline in renal function[1]. In Thailand, the prevalence of FSGS has not been well established. The frequency of FSGS depends on the criteria used to select patients for renal biopsy and the proportion of those biopsies who had already received a trial of corticosteroids. From the authors, previous report[3], FSGS was the commonest primary glomerular diseases accounting for 28%. In another series, FSGS only accounted for 12% of primary glomerular diseases and only 15% of primary glomerulonepathy presenting with NS[11]. Obviously, FSGS was even less common in the series from Sririraj Hospital with an incidence of 2.8%. However, the incidence tended to increase from 1.7% during the years 1983-1987 to 9% in the last couple of years (year 2003-2005).

FSGS is a glomerular disease which is defined by a clinicopathologic syndrome manifestating as proteinuria and discrete segmental consolidation of the glomerular tuft by increased extracellular matrix, causing obliteration of the glomerular capillary lumen, named

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"sclerosis". If the disease is more advanced, most of the glomeruli will progress to global sclerosis. The pathologic change does not result from immune complex deposition, but podocyte depletion is postulated as the crucial mechanism in initiation of pathogenesis. Sometimes, definite diagnosis may be difficult to obtain from kidney biopsy because of juxtamedullary location of early glomerular lesions. The biopsy specimen may not include the glomeruli in this region.

2. Histopathology[4,5,13]

The diagnosis of FSGS exclusively relies on the demonstration by light microscopy (LM) of glomerular sclerosis that involves some, but not all glomeruli (focal), and the sclerosis affects a portion, but not the entire, glomerular tuft (segmental). Since this pattern of scarring may occur in many settings, immunofluorescense (IF) staining is necessary for differentiating the immune-complex mediated glomerular diseases such as post-inflammatory glomerulonephritis.

The PAS-positive acellular material in the sclerosis lesions of the glomerulus may have different composition depending upon the diverse pathophysiologic mechanisms discussed below. The sclerotic process is defined by glomerular capillary collapse with an increase in matrix. This segmental scarring contrasts with the global glomerulosclerosis which occurs nonspecifically with aging. Uninvolved glomeruli show no apparent lesions by LM. The glomerulosclerosis may be associated with hyalinosis, resulting from insudation of plasma proteins, producing a smooth, glassy (hyaline) appearance. This occurs particularly in the axial, vascular pole region. Of note, arteriolar hyalinosis may occur with hypertensive injury and should not be taken as evidence of a sclerosis lesion.

Differentiation of MCD from FSGS relies upon obtaining a large enough number of glomeruli in the biopsy specimen in order to detect the sclerotic glomeruli since the detection of even a single glomerulus with segmental sclerosis is sufficient to invoke a diagnosis of FSGS rather than MCD. Thus, it is apparent that the distinction of MCD and FSGS may be difficult, especially with the smaller biopsy samples obtained with current biopsy guns and smaller needles. A sample of only 10 glomeruli has a 35% probability of missing a focal lesion which affects 10% of the nephrons, decreasing to 12% if 20 glomeruli are sampled. The glomeruli in the juxtamedullary region should be included in the sample. This is where early segmental sclerosis

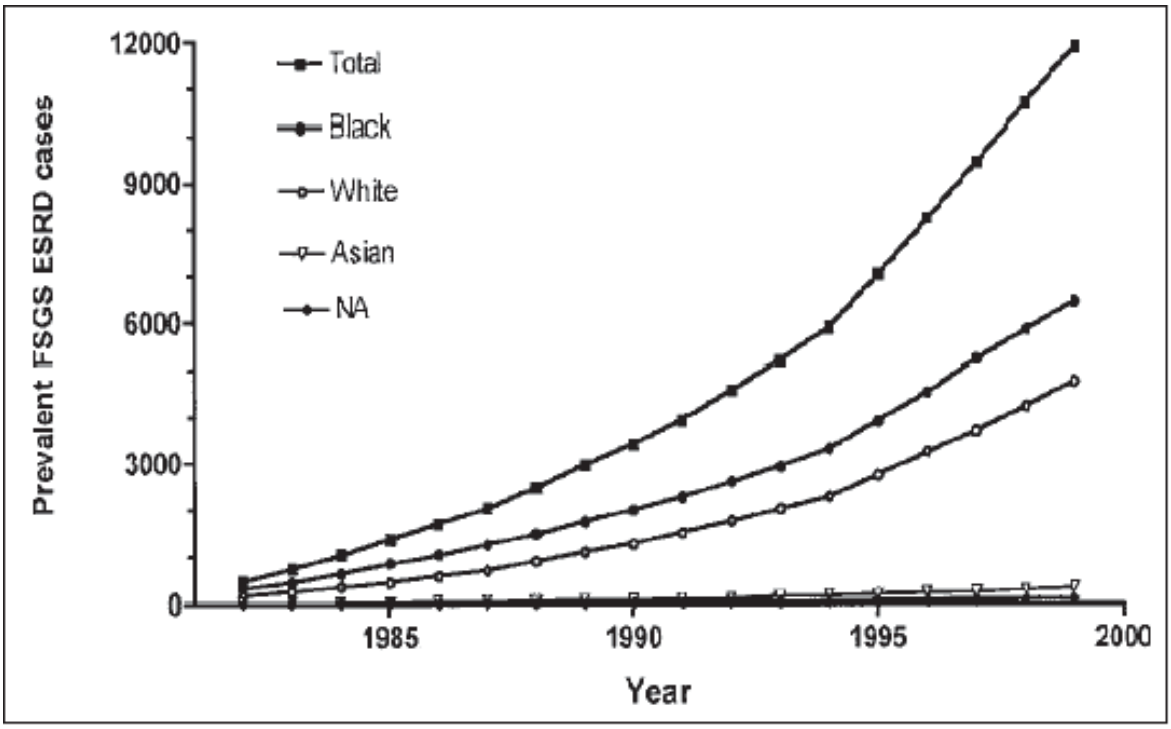

Fig. 1 he prevalence of FSGS which resulted in ESRD, data from USRDS in 1999. NA, Native American

occurs[45]. Conversely, sampling on one section by definition cannot identify all of the focally and segmentally distributed scars. The postulate has therefore been put forth that the sclerosis in FSGS, if studied extensively enough, would show diffuse distribution, i.e. affecting all glomeruli. However, recent three-dimensional studies examining serial sections of glomeruli in cases of idiopathic FSGS have demonstrated that the process indeed is focal, i.e. glomeruli without any sclerosis exists even when disease is well established.

Because of these limitations, other diagnostic features in glomeruli uninvolved by the sclerotic process have been sought to diagnose FSGS even without sclerosed glomeruli. Abnormal glomerular enlargement (Fig. 3) appears to be an early indicator of the sclerotic process even before overt sclerosis can be detected. The presence of marked glomerular enlargement in a biopsy of otherwise apparent MCD would, therefore, rather suggest an early, incipient stage of FSGS. Diffuse mesangial hypercellularity may be a morphological feature superimposed on changes of either MCD or FSGS, with or without IgM deposits, without defined prognostic significance.

Vascular thickening may be prominent late in the course of FSGS. Tubular atrophy is often accompanied by interstitial inflammation, proportional to the degree of scarring in the glomerulus. In HIV nephropathy and collapsing nephropathy, tubular lesions are disproportionately severe.

Global glomerulosclerosis, in contrast to the segmental lesion, is not of special diagnostic significance in considering the differential of MCD versus FSGS. Globally sclerotic glomeruli may be normally seen at any age, and are thought to result from normal "wear and tear," and not specific disease mechanism in most cases. Previous studies suggested that up to 10% of glomeruli may be normally sclerosed in people younger than 40 years. The extent of global sclerosis increases with aging, up to 30% by age 80. The percentage of global glomerulosclerosis in normal adults can be calculated by half the patient's age and then minus 10.

IF may show non-specific entrapment of IgM and C3 in sclerotic areas or areas where mesangial matrix is increased (Fig. 4) or may be completely negative. The presence of IgM staining in otherwise apparent MCD biopsies without segmental sclerosis has been a source of previous controversy, with some authors considering this a specific entity, so-called "IgM nephropathy".

Electron microscopy (EM) shows foot pro-

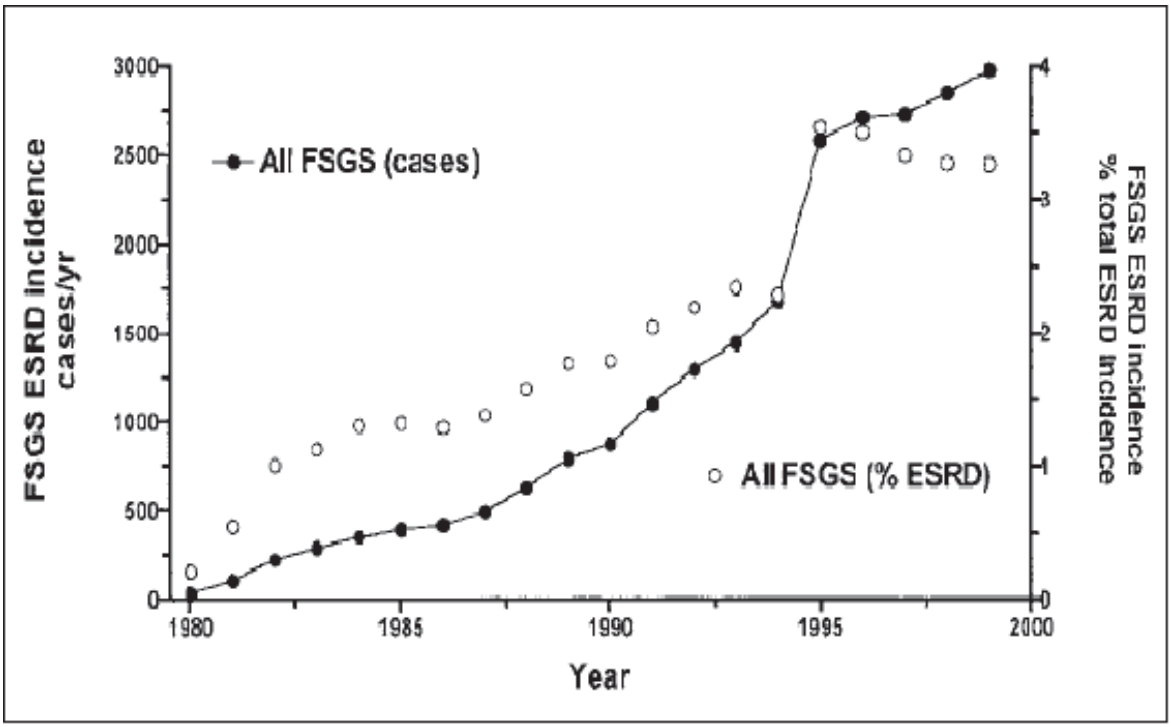

Fig. 2 The incidence of FSGS which resulted in ESRD, data from USRDS in 1999. NA, Native American

cess (FP) effacement, vacuolization and microvillus transformation of epithelial cells in both MCD and FSGS (Fig. 5A). FP effacement is typically extensive in MCD; on the contrary, it is often not complete in FSGS. However, steroid treatment may partially restore FP architecture in both entities, thus the extent of FP effacement does not allow precise distinction between the disease processes. FP effacement tends to be more

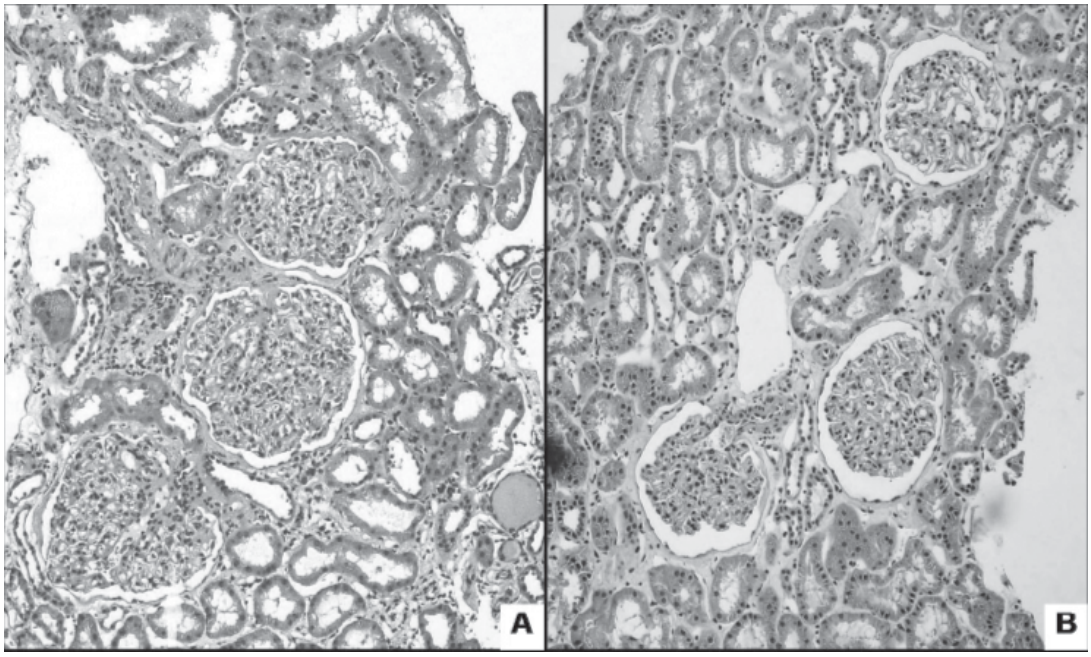

Fig. 3 The glomeruli in both pictures appear to be normal; however, the size of three glomeruli shown in A is approximately 2-time larger than the size shown in B. The presence of glomerulomegaly prompted the authors to search for FSGS rather than MCD[4] (H&E, original magnification x 100)

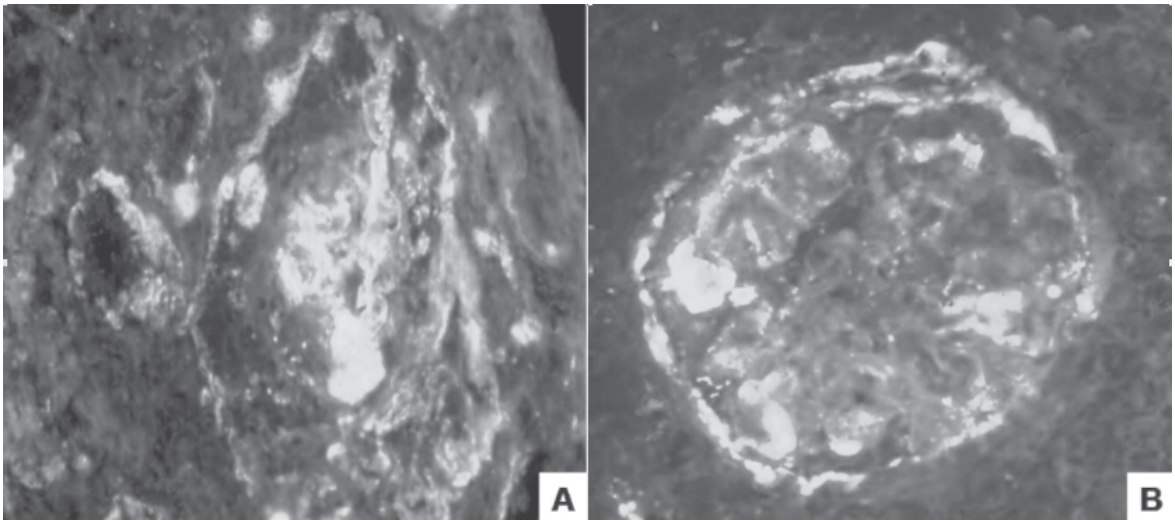

Fig. 4 By immunofluorescence, there is segmental staining for IgM (A) and C3 (B) involving the sclerotic portion of the tuft, with weaker mesangial positivity involving the adjacent non-sclerotic segments[4] (original magnification x400)

extensive in primary FSGS compared to secondary FSGS; however, the overlap between these two categories does not allow one to use this as diagnostic feature individual cases. The absence of any FP effacement should cast doubt on the diagnosis of FSGS. The presence of numerous reticular aggregates in endothelial cells in the setting of segmental glomerulosclerosis suggests possible HIV infection (Fig. 5B).

In summary, a specific diagnosis of FSGS sometimes cannot be definitively made, since rare sclerotic lesions may not be sampled in the biopsy. The possibility of unsampled segmental sclerosis in cases of NS with apparent MCD lesion, when the glomerular number is less than 25, should be considered in the patients with the following features: glomerular enlargement, mesangial proliferation, interstitial fibrosis, tubular atrophy, and increased matrix. Synechiae of the capillary tuft to Bowman's space is a very early lesion indicative of the process leading to FSGS. Likewise, prominent hypertrophic epithelial cells, sometimes even with proliferation, are seen in the early stage of FSGS.

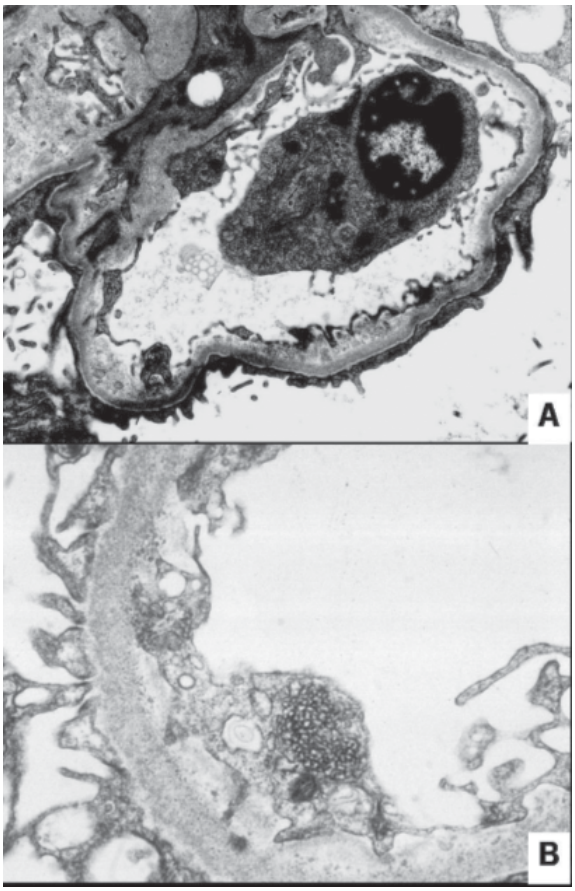

Fig. 5 By electron microscopy: A) non-sclerotic segment showing extensive foot process effacement and microvillus projections. B) The reticular aggregates are demonstrated in cytoplasm of the endothelial cell in patient with HIV-associated nephropathy[4]

3. Classifications

In general, there are two FSGS classifications.

Table 1. Etiologic classification of FSGS[7]

Primary (idiopathic) FSGS
C1q nephropathy
HIV-associated nephropathy
Heroin nephropathy
Familial FSGS
Mutation in α-actinin 4 (autosomal dominant)
Mutation 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
Thrombotic microangiopathies

1) According to etiology, FSGS can be divided into primary (or idiopathic) form and secondary form (as shown in Table 1).[7-9] Before a diagnosis of primary FSGS can be reached, secondary causes such as diabetes, chronic hypertension, and other co-morbid diseases must be carefully excluded. This classification may be advantageous in treatment planning but it cannot predict disease prognosis or treatment response. 2) According to histopathology (as shown in Table 2) [7,10], these morphologic variants were defined at a consensus conference of renal pathologists in New York City known as the Columbia Classification. The categorization 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 diabetic glomerulosclerosis, membranous nephropathy and hereditary nephritis) Five main light microscopic patterns of FSGS have been defined, including collapsing variant (collapsing FSGS), tip lesion variant, cellular variant, perihilar variant, and FSGS not otherwise specified (NOS).

Some, but not all studies have shown that the latter classification might correlate with disease prognosis and treatment response but, up to date, it is still unclear. The discrepancies could partly be explained by the different criteria using in their articles. The study by Lewis *et al* compared 3 FSGS variants, but only two of the variants were defined by using the Columbia Classification[41]. Instead of using the collapsing variants, they classified the lesion as a "cellular FSGS". Dijkman *et al*[46] reported an interesting patient with a coexistence of collapsing, tip, perihilar, and NOS variants in the single nephrectomized kidney. Of note, affected quadrants within a single glomerulus were sometimes assigned to different categories depending on the plane of sectioning. The patient presented with

Table 2. Morphologic variants of FSGS

Variant	Defining Features	Negative Criteria
FSGS (NOS)	May be segmental capillary wall collapse (without podocyte hyperplasia), segmental sclerosis (peripheral or perihilar). Any number of glomeruli are involved.	Exclude perihilar, cellular, tip, and collapsing variants
Perihilar	At least *one* glomerulus must have perihilar hyalinosis. More than 50% of glomeruli with segmental lesions must have perihilar sclerosis. More than 50% of glomeruli must have the defining features.	Exclude cellular, tip and collapsing variants
Cellular	Endocapillary hypercellularity, typically expansive and foam cells, in any segment of glomerular capillary tuft (at least 25%), with capillary lumen occlusion. Other glomeruli may have segmental sclerosing lesions.	Exclude tip and collapsing variants
Tip	Origin of proximal tubule must be identified. Segmental lesion involves the glomerular 'tip domain (outer 25% of glomerular tuft)'. Adhesion or confluence of glomerular tuft *lesion* in the 'tip domain' with the identified origin of the proximal tubule. *Lesion* in 'tip domain' may be foam cells or endocapillary hypercellularity (<50% of glomerular tuft), or sclerosis (< 25% of glomerular tuft). o Presence of 'perihilar lesion'*rules out* FSGS, tip variant.	Exclude collapsing variant Exclude any perihilar sclerosis
Collapsing	Glomerular capillary tuft collapse. Overlying podocyte hypertrophy and hyperplasia. At least *one* glomerulus with defining features. Other glomeruli may have segmental lesions of any subclass.	None

recurrent idiopathic FSGS after transplantation and was resistant to all standard immunosuppressive therapy including plasmapheresis. Recently, Jennette *et al*[53]conducted a cohort study of adult patients with biopsy-proven FSGS to determine whether subclass strictly defined by the Columbia Classification were associated with renal outcome. After a mean follow-up of 1.8 years, the author found that collapsing variant had a worse 1-year as well as 3-year renal survival when compared with other variants, whereas the tip variants had the best renal survival, less severe tubulointerstitial injury (a marker of chronicity), and more likely to achieve complete remission after steroid treatment. They concluded that different histologic variants of FSGS have substantial differences in clinical features at the time of biopsy diagnosis and substantial differences in renal outcomes. Thus, further studies are necessary to determine the prognostic value of this classification system.

3.1 Classical variant (not otherwise specified: NOS) (7,10)

The histopathologic findings show segmental sclerosis at the area in which is not nearby tubular and hilar poles, as such this variant is also known as a peripheral lesion (Fig. 6). Wrinkling of glomerular basement membrane (GBM) can be observed, but hypertrophic and/or hyperplastic podocytes should be absent, since their presence are parts of the definition of collapsing variant. In fact, characteristics of collapsing, tip, cellular, and perihilar variants must be excluded before making a diagnosis of classical variant. The presence of mesangial hypercellularity in FSGS (NOS) is most commonly noted in children and appears to represent an early stage of disease.

The authors recently found, yet not been reported, that peripheral lesions tended to be associated

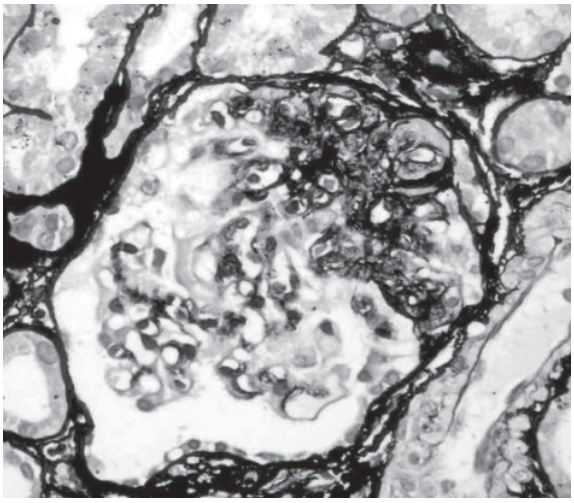

Fig. 7 FSGS, perihilar variant: The lesion of segmental sclerosis and hyalinosis is located at the glomerular vascular pole, or hilus (PAS, original magnification x400)

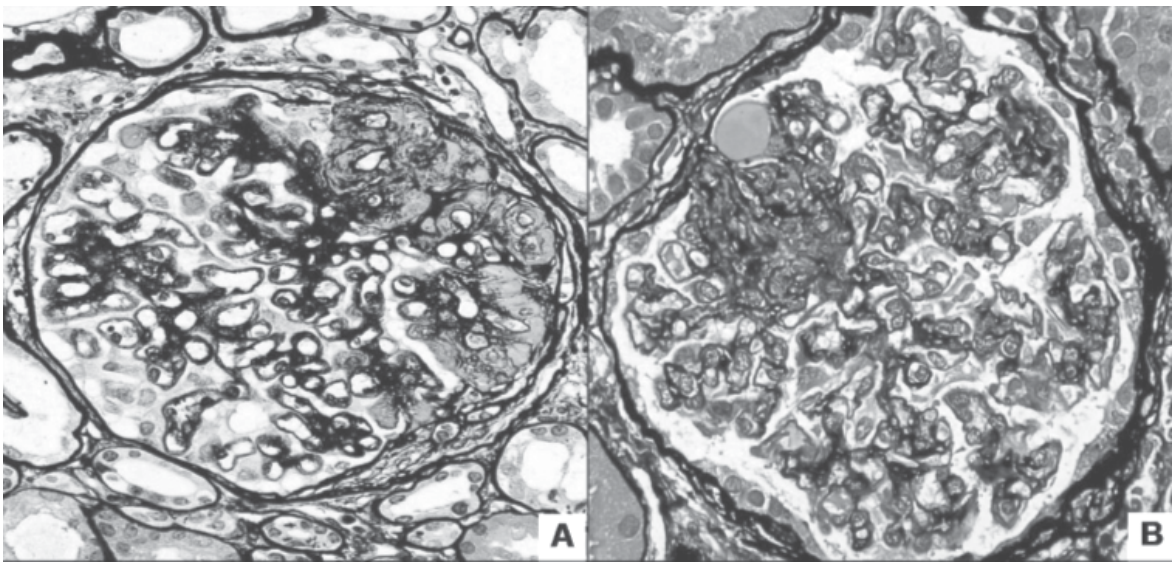

Fig. 6 Light microscopic finding in FSGS (NOS), tuft adhesion and occluded glomerular capillary lumen in segmental sclerotic parts are demonstrated by Jones methenamine silver staining[4] (original magnification x400)

with better prognosis than predominantly hilar or mixed lesion. In the present series, peripheral lesions were most common in children, contrasting with the mixed and hilar lesions which were more prominent in adults. However, both patterns of sclerosis can occur in both age groups.

3.2 Perihilar variant[7,10]

This category requires that the cellular variant, tip variant, and collapsing variant must be excluded. It is defined by the presence of perihilar sclerosis and hyalinosis involving greater than 50% of segmentally sclerotic glomeruli (Fig. 7). There often are glomerulomegaly and arteriolar hyalinosis, sometimes in continuity with hyalinosis in the perihilar segment. IF and ultrastructural findings are similar to those described in the section on FSGS (NOS). This variant 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 such as obesity, reflux nephropathy, or any advanced renal disease with a reduced number of functioning nephrons.

3.3 Cellular variant[7,10]

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, which consists of endothelial cells, foam cells, and infiltrating leukocytes. Some of these lesions are accompanied by foamy hyaline material, fibrin, and karyorrrhexis, resembling segmental necrotizing lesions of immune complex glomerulonephritis, but without

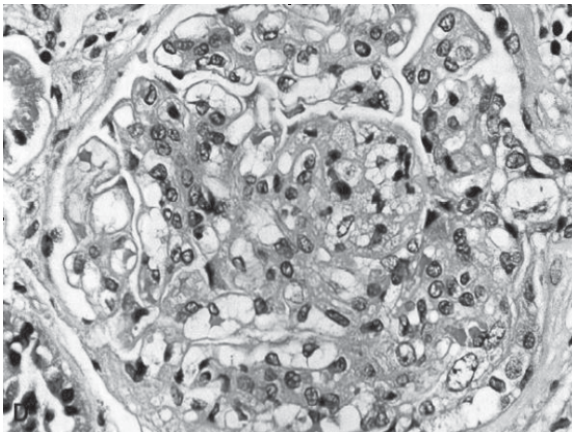

Fig. 8 Cellular variant: The glomerular capillary lumen are segmentally obliterated by endocapillary hypercellularity including numerous infiltrating leukocytes, resembling a proliferative glomerulonephritis. There is hypertrophy of the overlying podocytes[52] (H&E, original magnification x400)

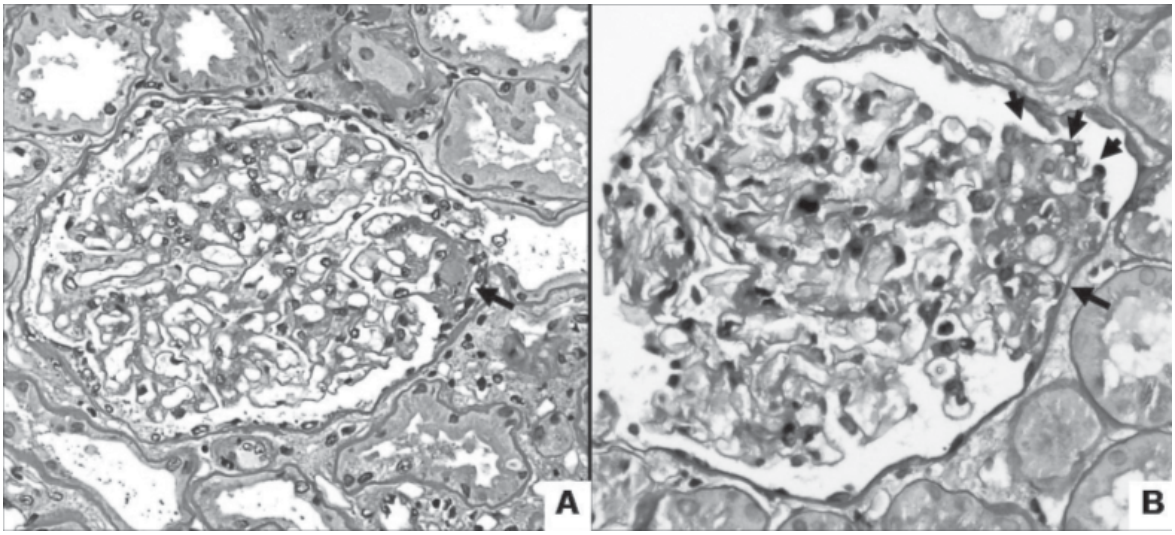

Fig. 9 Tip variant: There are segmental lesion with endocapillary foam cells that forms an adhesion to Bowman's capsule at the origin of the tubular pole (long arrow). The podocytes are capped over this segment (short arrow) and merge with the tubular epithelial cells[4] (PAS, original magnification x400

rupture of GBM and crescentic formation (Fig. 8). This lesion bears similarity to the collapsing lesion described below but appears to be a much more focal process, without the associated severe tubular changes seen in collapsing glomerulopathy. As such, a diagnosis of cellular FSGS requires the exclusion of tip and collapsing variant.

By IF, the findings are similar to NOS. At the ultrastructural level, cellular lesions consist of segmental occlusion of glomerular capillaries by endocapillary hypercellularity including foam cells and monocytes but the GBM is intact.

Clinically, these patients with the cellular lesion had an abrupt onset of NS[14], These patients typically show transition to progressively less cellular, more sclerotic lesions, becoming indistinguishable clinically and morphologically from classical FSGS. Moreover, the cellular variant is uncommon comprising less than 5% of the total[53] thus raising the question whether the cellular variant is a distinctive category of FSGS. The hallmark of the cellular lesion can be observed in the other variants of FSGS and are particularly conspicuous in many examples of the tip variant. Thus, the morphologic appearance does not clearly represent a distinct clinicopathologic entity, but rather is postulated to represent an early, active lesion.

3.4 Tip variant[7,10]

The tip variant of FSGS is defined by the presence of at least one glomerulus with a segmental lesion involving the tip domain (i.e., 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 (Fig. 9). The designation of tip lesion requires that the collapsing variant and segmental sclerosis in a perihilar location should be excluded.

Tip lesions were proposed to represent an early lesion with good prognosis; although, later follow-up studies have revealed a less than favorable prognosis. Furthermore, tip lesions are not specific, but may occur in the setting of a variety of glomerular diseases including MCD, membranous nephropathy, and others. Therefore, other glomerulopathies must be excluded before FSGS, tip variant is defined. Some evidences concluded that tip lesions might arise as a non-specific response of the peritubular segment of the glomerular tuft to flux of protein-rich filtrate in the setting of NS. Some groups have reported a greater likelihood of steroid responsiveness and excellent long-term prognosis resembling that of MCD. On the other hand, there is evidence that although patients with glomerular tip lesion had higher response to steroid treatment than patients with classical form, both groups showed similar long term renal survivals[15,16]. .

3.5 Collapsing variant[7,10]

The definition of collapsing variant is applied

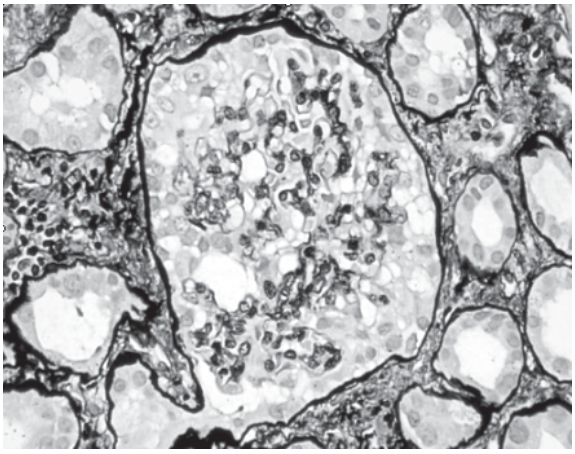

Fig. 10 Collapsing variant: In the collapsed tuft, the GBMs are imploded, without appreciable increase in matrix material. The podocytes overlying the collapsed tuft are marked hyperplastic with enlarged vesicular nuclei and crowding of the urinary space[4] (JMS, original magnification 400)

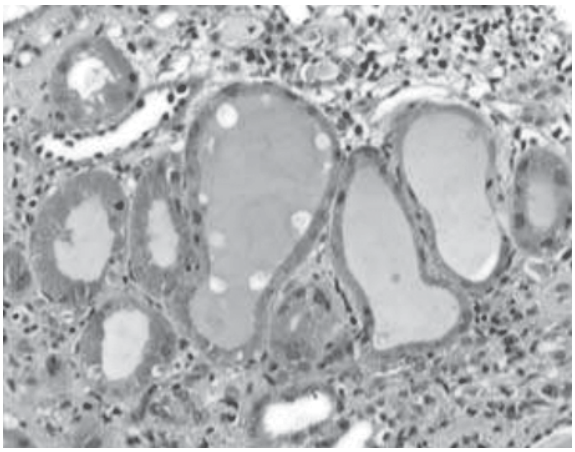

Fig. 11 Collapsing FSGS. The tubules are markedly dilated forming microcysts with voluminous proteinaceous casts[4] (H&E, original magnification x400)

to FSGS in which at least one glomerulus displays segmental or global obliteration of the glomerular capillary lumen by wrinkling and collapsing of GBMs associated with podocyte hypertrophy and hyperplasia. Podocytes may be crowded and fill the urinary space, forming pseudocrescents, and often contain prominent intracytoplasmic protein resorption droplets (Figure 10). Collapsing variant is distinguished from the cellular form by the absence of endocapillary hypercellularity. There is often an apparent reduction in the number of glomerular endothelial cells in collapsed lobules and lacking of hyalinosis and adhesions to Bowman's capsule.

Tubulointerstitial disease, consisting of tubular atrophy, interstitial fibrosis, edema, and inflammation, is an important component of this condition and often appears out of proportion to the degree of glomerular sclerosis. About 40% of cases may have tubular microcysts that contain loose proteinaceous casts; therefore, HIV-associated nephropathy must be ruled out [17] (Fig. 11). The other putative causes of collapsing FSGS have also been recently reported in patients treated with intravenous pamidronate (osteoclast inhibitor) [19], or infections with parvovirus B19 [20] and SV40 [21].

At the ultrastructural level, the collapsed lobules display wrinkling GBMs and the overlying podocytes are markedly hypertrophied with severe foot process effacement, but no electron dense deposits are observed. In contrast to HIV-associated nephropathy, no endothelial reticular aggregates are identified in idiopathic collapsing FSGS.

Upon comparing with classical FSGS, patients with idiopathic collapsing FSGS have higher proteinuria and presenting serum creatinine with poor prognosis, rapid loss of renal function, and virtually no response to corticosteroids alone. The median renal survival is 13.0 months, regardless of etiologies, compared to 62.5 months in the classical variant [18]. This variant has been seen most frequently in selected geographical regions, including New York. In Dr. D'Agati's recently reported series, the incidence of this lesion has increased from 11% of all cases of idiopathic FSGS from 1979 to 1985, to 20% of this group from 1986 to 1989, and to 24% of idiopathic FSGS from 1990 to 1993. In a large renal biopsy practice centered in Chicago, the collapsing variant accounted for only 4.7% of FSGS biopsies. Series of patients with collapsing FSGS from the USA show a strong preponderance of African Americans, and most patients were adults. Collapsing FSGS has, however, also been reported in Caucasians in Europe, with similar dire prognosis as in the US patients. The etiology has not yet been defined. A possible viral agent has been proposed. To the authors' knowledge, only 2 Thai females have been identified with primary collapsing FSGS; although, these cases have not been formally reported. As expected, both patients had severe NS with 24-hour protein excretion of more than 10 grams and were resistant to standard dosage of corticosteroid. One of them died because of massive edema and secondary infection.

3.6 Secondary forms of FSGS[7,10,22,49,56]

Many insults to the kidney may result in secondary FSGS, either as the sole manifestation of injury, or superimposed on other disease manifestations. The lesion of FSGS may be seen in association with e.g. substantial loss of nephron mass, diabetes, obesity, HIV infection, or heroin abuse. Secondary sclerosis occurs in the chronic stage of many immune complex or proliferative diseases. In some of these settings, the morphologic appearance of sclerosis can indicate the nature of the initial insult. In FSGS secondary to reflux nephropathy, there is frequently prominent periglomerular fibrosis and thickening of Bowman's capsule and patchy interstitial scarring, in addition to the heterogeneous glomerulosclerosis. FSGS associated with heroin usage does not show pathognomic features, although global glomerulosclerosis, epithelial cell changes, interstitial fibrosis, and tubular injury tend to be more prominent than in idiopathic cases of FSGS. In HIV nephropathy, the tubules show severe injury, including cystic dilatation, out of proportion to the focal segmental glomerular scarring. Glomeruli show tuft collapse, and reticular aggregates are numerous in endothelial cells. HIV has been found by some investigators in glomeruli and in tubular epithelium, and is postulated to directly cause the renal injury. Alternatively, cytokines produced in response to HIV infection may be responsible for the renal injury. The development of HIV nephropathy, like primary collapsing FSGS, is highly dependent on the patient's racial background with black subjects being at much higher risk. In Thailand, a survey of renal biopsy from 26 cases of HIV-infected Thai patients with proteinuria greater than 1.5 g/d of protein did not reveal any patients with features of HIV nephropathy[10]. From the present series, HIV nephropathy was found in only one patient from the pool renal registry, which was composed of 35 HIV-positive patients. As expected, HIV status of the patient was classifeid as symptomatic HIV stage with a CD4-count level of lower than 400 cll/mm3 and a viral

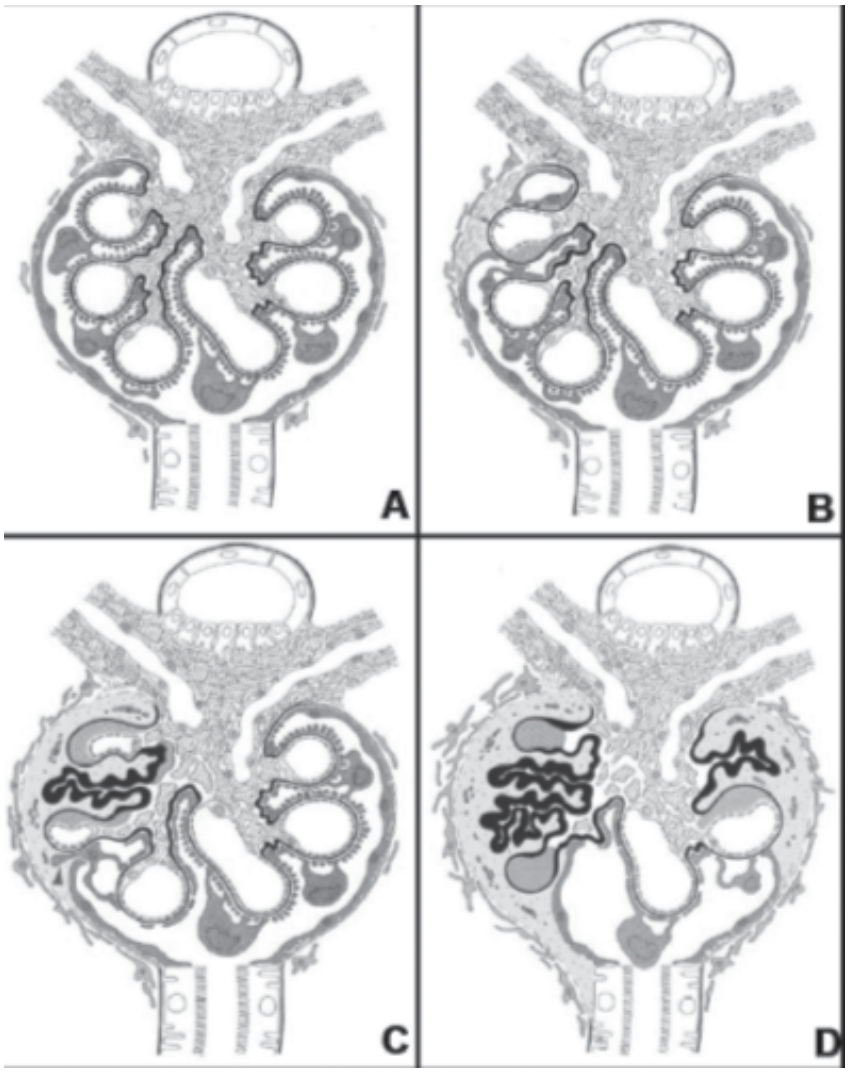

Fig. 12 The sequence of events in the development of glomerulosclerosis. A) Podocyte loss, and the inability to replace those lost because of a lack of proliferation, results in a localized "bare"or denuded GBM at that site. B) The lack of tensile support normally provided by podocytes is lost in the area of denudation and leads to the outward bulging of the capillary loop (due to hydrostatic capillary pressures). C) the 'expanding" capillary loop causes the denuded basement membrane to abut on Bowman's capsule, leading to synechia formation D) Inspissated proteins and hyalinosis develop in the capillary loops, forming a proteinaceous crescent, and finally ensues progressive scarring[34]

load of more than 100,000 copies/ml. The clinical prognosis was grave with unresponse to standard dosage of corticosteroid and cyclosporin as well as HARRT therapy. She finally ended up with massive generalized edema and secondary septicemia.

FSGS also can develop in association with decreased renal mass. The best example is oligomeganephronia, where nephron number is greatly reduced, resulting in markedly enlarged of the remaining glomeruli, and occurrence of FSGS. Patients with unilateral renal agenesis show an apparent higher risk of FSGS than the general population. Loss of one kidney later in life does not elicit the same degree of growth response in the remaining kidney as in the young, and has a lesser association with scarring in the remaining kidney. However, when one kidney and a portion of the

other are lost in the adult, patients appear to have increased risk of developing FSGS.

Much evidence has pointed to the participant of abnormal glomerular adaptation and growth factors in the pathogenesis of glomerulosclerosis. A recent study showed that patients with apparent remission of FSGS as judged by remission of NS, actually had reversal of abnormal glomerular hypertrophy. Patients with abnormal glomerular growth even on initial biopsies that did not show overt sclerotic lesion, subsequently developed overt glomerulosclerosis, documented in later biopsies. A cut-off of > 50% larger glomerular area than normal for age was a sensitive indicator of increased risk for progression in one series of children with NS. Of note, glomeruli grow in size until approximately age 18 years, although no new glomeruli are formed after birth, so age-matched controls must be used in the pediatric population.

4. Pathogenesis of FSGS

4.1 Central role of podocytes in the pathomechanism of FSGS[23, 34-36]

FSGS has been established as the final common pathway of nephron loss for a decade regardless of the nature of initial insult. The precise mechanism remained obscure and it is only recently that podocyte injury has been identified as having a central role in the development of FSGS and progressive renal failure. In 1998, Kestila *et al*[48] isolated the gene mutated in congenital NS of Finnish type, a rare autosomal recessive disease characterized by massive non-selective proteinuria at birth and widespread effacement of podocyte FP. The disease gene was shown to encode nephrin, which in the kidney is solely located in glomerular podocyte[45]. A year earlier, there has been an important advance in research into podocyte biology with the development of a conditionally immortalized podocyte cell line by Mondel *et al* from a transgenic mouse. Prior to this, studies were performed in primary cultures of the podocytes, which showed little proliferative activity or in SV40 transformed cell lines, which do not possess mature podocyte properties[36,37]. Since these recent developments, there has been marked interest in podocyte research worldwide, and podocyte injury is now recognized to play a pivotal role in the initiation and progression of the FSGS in various circumstances[35]. In fact, loss of podocyte number, regardless of the type of renal injury except the collapsing variant, contributes to the development of glomerulosclerosis.

Podocytes are highly differentiated cells and line the outer aspect of the GBM. In this regard, they function to support and maintain the filtration surface via primary, secondary, and FP. The FP of neighboring podocytes regularly interdigitate, leaving between them meandering filtration slits that are bridged by an extracellular structure, known as the slit diaphragm[37]. The slit diaphragm is generally considered to be a major hindrance to the passage of large plasma molecules, particularly plasma albumin, into the urine. Thus, the podocyte slit diaphragm is the size-selective molecular sieve. Although the ultrastructural morphology of the slit diaphragm has been demonstrated three decades ago by Karnovsky; the composition and functional elements of the slit diaphragm remains not completely known[45]. Up to now, at least 3 transmembrane (nephrin, Neph1, and a large cadherin-like protein FAT), 3 intramembrane proteins (podocin, zona occludens: ZO-1, CD2-adapter protein: CD2-AP), and 2 awiting for publication have been identified[45]. *In vitro* studies have indicated that nephrin and colocalized Neph1 can form homo- and heterodimers through their extracellular domains[24,25] and the intracellular domains[26] of both proteins react with podocin. The fact that mutations in the following genes: nephrin, Neph1, FAT, podocin, and CD2-AP, has been associated with a FSGS and NS-like phenotype in humans[42] or mice, emphasizes a crucial role of these genes and their protein products as a major plasma protein hindrance, and determinant of slit diaphragm permselectivity. Not all proteins located in the slit diaphragm have the above function. For example, P-cadherin, a transmembrane protein, does not appear to be crucial for glomerular development or function[45].

In adults, the podocytes are incapable of regenerative cell replication. Lost podocytes cannot be replaced by new cells[45]. An inability to repopulate a damaged glomerulus with functional podocyte was in good accordance with the progression of filtration barrier failure and progressive proteinuria since the podocytes normally oppose the hydrostatic capillary pressure to provide a tensile support to the underlying glomerular capillary loop[45]. The correlation was nicely established by two excellent reports in type II diabetic nephropathy[27,32]. The average values from these two studies for percentage of podocyte loss (relative to normal glomeruli) in individuals with type II diabetes and relatively normal renal function were as follows: normoalbuminuria was associated with 16% podocyte loss, microalbuminuria was associated with 24% podocyte loss, and macroalbuminuria was associated with 36% podocyte loss.

Type I diabetic nephropathy and IgA nephropathy are also reported to show similar degrees of podocyte depletion from glomeruli in proportion to injury[33,37,38]. As glomerular disease progresses in FSGS, podocytes can be detected increasingly in the urine. This suggests that podocytes loss in these conditions is correlated with progression of glomerular disease and therefore support the concept of direct relationship between the progression of glomerular disease and podocyte loss.

In contrast to the decrease in podocyte number, mesangial and glomerular endothelial cell number remained normal. Recently, Lemley *et al*[38] showed that despite injury to the mesangial cell in IgA nephropathy, a decrease in podocyte number correlated significantly with reduced renal function and global glomerulosclerosis. Morioka *et al*[42] provided further support for accepting that FSGS is a podocytopathic disease by using the anti-Thy 1.1 mesangial proliferative glomerulonephritis model. They found that in mice with prior podocyte injury developed irreversible glomerular damage and FSGS after anti-Thy1.1 monoclonal antibody injection. On the contrary, the glomeruli of the control group with normal podocytes healed completely without scar formation after the anti-Thy 1.1 antibody injection.

As mentioned above, the podocyte has a limitation to divide and therefore to be replaced if lost. The hypertrophy of the remaining podocytes is the only way to maintain the integrity of the filtration barrier. The additional workload on these cells increases their vulnerability. A vicious circle is initiated. The podocytes eventually are too few to maintain a complete cover of the tuft. Naked areas of GBM occur, to which parietal epithelial cells can adhere. Such a parietal cell bridge goes necessarily along with the formation of a local gap within the parietal epithelium, including the formation of naked areas of parietal basement membrane (PBM). By establishing further cell bridges between the PBM and the GBM adjacent to the first and deposition of some matrix between the bridging cells, an adhesion of the tuft to Bowman's capsule is finally established[34,28].

The adherent tuft portion generally contains at least one capillary loop that bulges with its naked (podocyte-deprived) GBM surface toward the core of the adhesion. As a consequence, such capillaries deliver their protein-rich filtrate into the interstitium instead of Bowman's space[29,30]. In response, interstitial fibroblasts create a multilayered cellular patch around the focus of misdirected filtration, limiting the entry of fluid into the interstitium. This results in the formation of a crescent-shaped space filled with a proteinaceous fluid overarching the adhesion (proteinaceous crescent); hyaline material also frequently accumulates within the adherent portion of the tuft[23]. Actually, the hyalinosis[31] inside the GBM and the proteinaceous crescent outside are the two sides of the same coin (i.e., of misdirected filtration through a podocyte-deprived filtration barrier: Plasma proteins accumulate on both sides (Fig. 12).

If the plasma leakage is extended to vascular pole, vascular supplies will be disturbed and the change of global sclerosis will appear. On the other hand, if the leakage is extended to the tubular pole, there is the disconnection between subepithelial peritubular space and interstitium by fibroblast cell layer and tubules of individual glomeruli will be destroyed later[23].
This postulate was additionally demonstrated by labeled ferritin infusion in an animal model[30]. Accumulation of such ferritin was found around tuft adhesion and periglomerular space including glomerulo-tubular junction and outside of proximal tubule, which is connected to segmentally sclerotic glomeruli. Moreover, no ferritin staining was found in other parts of interstitium except tubular areas of the involved glomeruli[34]. Some glomeruli with tuft adhesions had no staining indicating that misdirected filtration did not continuously occur. It was postulated that there was hyalinization at the adhesion sites for leakage inhibition, thus, segmental sclerosis did not progress to global sclerosis. But if the leakage continued, the pathologic findings might be two characteristics:

1. If the periglomerular leakage was equal to peritubular leakage, the degree of tubular destruction was similar to the degree of glomerular damage.

2. If the peritubular leakage was the main pathologic change, there was higher tubular damage and cyst-like appearance of the involved glomeruli called atubular glomerular cyst.

When nephrons are progressively destroyed, the intraglomerular pressure of the remaining nephrons is increased, and then further glomerulosclerosis is initiated. Moreover, proteinuria is the other cause of tubulointerstitial fibrosis, which contributes to ESRD finally.

4.2 Pathophysiology of podocyte injury in primary FSGS[13,41]

As mentioned, podocyte injury and death play a central role in the pathogenesis of FSGS; however, the initiating causes of podocyte injury remain incon-

clusive in primary FSGS. Injuries which compromise the structural rather than a functional integrity of podocytes appear to result in a worse outcome and much progressive loss of the cells[52]. In some cases, primary FSGS is thought to result from an undefined circulating factor, which mediate abnormal glomerular permeability and ultimately sclerosis. The strongest supporting evidence for circulating factors as causative agents for podocyte injury is mostly derived from patients with recurrent FSGS after transplantation. Since most of the recurrences occur within the first few months after transplantation or even occur perioperatively, it is likely that the pathogenic factors are already present in the recipient circulation and are ready to cause injury to the transplanted graft. FP effacement is present at the time of recurrence of proteinuria and precedes the development of sclerosis, typically by weeks to months. Glomerular enlargement at this stage of recurrent FSGS is prominent in children, who otherwise do not undergo glomerular enlargement when receiving an adult kidney. In contrast, an adult recipient of a single kidney will normally have marked renal and glomerular growth to provide adequate GFR. Overt sclerosis is not noted until weeks to even months after recurrence of NS. A circulating factor found in some patients with recurrent FSGS induces increased *ex vivo* glomerular permeability, and also mildly increased in proteinuria when injected in rats. Plasmapheresis has been proposed as a treatment to remove this factor in recurrent or even in native kidney FSGS. However, improvement in proteinuria was not achieved in all patients with primary FSGS despite successful removal of the measurable circulating factor activity, and some patients went into remission although the circulating factor activity remained high. These observations imply that other factors probably play a significant role in the proteinuria. Whether the circulating factor contributes to the development of sclerosis is also not yet known.

Although primary FSGS is usually regarded as a sporadic disease, genetic factors may play a role, as primary FSGS seems more severe in African-Americans, but the recurrence rate after transplantation is lower in such a population. Moreover, inherited cases of both steroid-resistant and steroid-sensitive FSGS, although rare, have been increasingly reported and have currently been intensely studied to identify genetic components contributing to its development. The pattern appears to be autosomal dominant or possibly recessive. The gene of steroid-sensitive FSGS has now been localized to ACTN4, at chromosome 19q13 in family FSGS in 3 kindred with autosomal dominant inheritance. In other kindred there is linkage to chromosome 11q22 or 1q. ACTN4 encodes alpha-actinin-4, implicating possible altered actin cytoskeleton in podocytes in the pathogenesis of this disease. The prognosis of family FSGS has been poor, with progression to renal disease in 50% of patients by age 30. Recurrence in the transplant has been very rare. Recently, genetic studies have suggested that mutations in NPHS2 allele, which encodes podocin, are putative causes for a familial form of steroid-resistant FSGS. Affected patients were characterized by early-onset disease (age 6 years or less), rapid progression to ESRD, and, in most cases, FSGS on the renal biopsy. NPHS2 mutations have now also been reported in children with sporadic (non-familial) as well as adult or adolescent (average age at disease onset 24 years)[6]. Recently, Ruf, *et al*[54] searched the NPHS2 mutation in sporadic cases of steroid-resistant. Homozygous or compound heterozygous mutations in such genes were detected in 43 of 190 cases from165 different families. Of note, no mutations were observed for 120 steroid-sensitive FSGS.

Genetic defects also underlie the development of FSGS in association with some clinical syndromes. Denys-Drash syndrome, a rare childhood disease with diffuse mesangial sclerosis, XY hermaphroditism, and high risk of Wilm's tumor, and also Frasier syndrome, a disease with FSGS, XY hermaphroditism, and high risk of gonadoblastoma are both linked to the defect of WT-1 (Wilm's tumor) suppressor gene[41]. Abnormal splice variants of WT1 have also been associated with non-syndrome cases of FSGS.

Even though both of MCD and FSGS are believed to be linked with the unknown circulating factors, substantial information indicated that such factors were not the same kind. Since many experts believe that MCD and FSGS are different diseases from the onset. Wiggins et al found that the glomerular epithelial protein 1(GLEPP 1), a podocyte receptor membrane tyrosine phosphatase normally expressed on the apical cell membrane of the podocyte, was shifted away from the apical membrane in MCD, and absent in FSGS even in nonsclerosis glomeruli. Other differential markers of podocytes, including the podocalyxin and synaptopodin were investigated by Dr. D'Agati's group. They found that these podocyte markers are retained in proteinuria caused by MCD or membranous GN, but disappear (or decrease for synaptopodin) in collapsing glomerulopathy or HIV-associated nephropathy, with lesser change in typical FSGS. These observations point to a dysregulated phenotype of the

podocyte in the pathogenesis of the collapsing and HIV-associated forms of FSGS. Dystroglycan, a protein involved in podocyte to GBM binding, is decreased in MCD, but not in FSGS, further supporting the hypothesis that podocyte injury in FSGS occur by different mechanisms to that of other proteinuric diseases[39].

It is not known whether mechanisms underlying proteinuria and sclerosis are parallel or identical. Some investigators propose that sclerosis is the initial event, whereas other have different views.

5. Clinicopathologic correlations[13,55]

The typical clinical course associated with FSGS is progressive decline in GFR. However, as many as one-third of adult patients with FSGS may respond to intensive; prolonged steroid therapy with remission of their NS. Several other variants of FSGS have also been investigated for their prognostic significance. The location of the lesion may relate to the pathogenetic mechanism.

Genetic factors are also likely to influence prognosis. Outcome of FSGS is worse in African American children than in Caucasians. Genotype analysis has indicated that homozygosity for the insertion (I) polymorphisms of the angiotensin I converting enzyme (ACE) is associated with better prognosis of FSGS in children, whereas patients with homozygous for the deletion (D) polymorphisms had worse prognosis. This may relate to the postulated functional consequences of these polymorphisms. The I variant codes a silencer element, and thus the deleting genotype is associated with increased ACE. This results in increased angiotensin, which has many adverse effects on renal disease. In one study, children with FSGS also had a higher prevalence of the ACE D versus I polymorphisms, when compared to MCD patients.

In summary, FSGS is now recognized as secondary to abnormalies of podocytes from many insults. It might not be a single unique disease but rather be a common pathologic finding which represents the chronicity of glomerular alteration. Extensive exploration of the seconday cause is the key to success of the treatment. The question of whether the circulating factor is the real pathogenic insult resposible for primary FSGS still awaits resolution. Since unknown pathogen has not yet been explored, a kidney biopsy remains the gold standard of diagnosis.

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ความก้าวหน้าในพยาธิกำเนิดและพยาธิวิทยาของภาวะไตอักเสบชนิด *focal segmental glomerulosclerosis*

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Focal segmental glomerulosclerosis (FSGS) เป็นกลุ่มโรคที่มีลักษณะร่วมทางพยาธิสภาพ คือมีพังผืดเกิดขึ้นในบางส่วน (segmental) ของ glomerulus และเกิดลุกลามเพียงบาง glomeruli ส่วนใหญ่พังผืดมักเริ่มต้นเกิดที่ glomeruli ในส่วนลึกของ renal cortex (juxtamedullary glomeruli) ทำให้ยากในการให้การวินิจฉัยโดยเฉพาะในระยะแรก แต่ถ้ารอยโรคดำเนินต่อเนื่องเรื้อรัง อาจพบพังผืดลุกลามขยายอาณาบริเวณกว้างขึ้นจนในที่สุดอาจพบพังผืดเกิดขึ้นทั้ง glomerulus และกระจายเกือบทุก glomeruli ภาวะ FSGS เป็นสาเหตุลำดับต้นๆของภาวะ nephrotic syndrome ทั้งในผู้ป่วยเด็กและผู้ใหญ่ มีการพยากรณ์โรคไม่ดี ผู้ป่วยร้อยละ 60 ถึง 70 จะเกิดไตวายเรื้อรังระยะสุดท้ายภายในระยะเวลา 10 ถึง 15 ปี โดยเฉพาะผู้ป่วยที่มี nephrotic proteinuria และไม่ตอบสนองต่อการรักษาด้วยยาสเตียรอยด์ พบว่ามีโรคต่างๆ เป็นจำนวนมากที่ก่อให้เกิดพยาธิสภาพดังกล่าว โรคเหล่านี้มีจุดร่วมอย่างเดียวกันคือเป็นโรคที่มีการบาดเจ็บอย่างรุนแรงต่อเซลล์ podocyte จนทำให้เซลล์ podocyte เหล่านี้หลุดลอกออกจาก glomerular basement membrane โดยทั่วไปนิยมแบ่ง FSGS โดยอาศัยสาเหตุออกเป็นสองกลุ่มคือ 1) primary (idiopathic) FSGS เป็นภาวะ FSGS ที่ไม่พบความผิดปกติของอวัยวะอื่นใดนอกจากไต ส่วนใหญ่จะไม่ทราบสาเหตุก่อโรค 2) secondary FSGS เป็นภาวะ FSGS ที่พบความผิดปกติของอวัยวะอื่นร่วมกับความผิดปกติของไต ส่วนใหญ่จะทราบสาเหตุก่อโรค ได้แก่ ภาวะความดันโลหิตสูง เบาหวาน ภาวะอ้วน ภาวะหัวใจผิดปกติแต่กำเนิด การติดเชื้อไวรัส การได้รับยาบางชนิด ภาวะพิการแต่กำเนิด เป็นต้น แม้ว่าการแบ่งภาวะ FSGS ออกโดยอาศัยสาเหตุจะเป็นที่นิยมก็ตาม แต่การแบ่งโดยวิธีนี้ไม่สามารถใช้ทำนายอาการทางคลินิก การดำเนินโรค และการตอบสนองต่อการรักษา ด้วยเหตุนี้องค์กรพยาธิแพทย์โรคไตแห่งสหรัฐอเมริกาจึงได้ร่วมมือกันเสนอวิธีใหม่จำแนกภาวะ FSGS โดยใช้ลักษณะทางพยาธิสภาพที่ตรวจพบโดย light microscope เป็นหลัก เรียกข้อตกลงนี้ว่า “Consensus conference on the pathologic classification of FSGS”