병리 (Mini-Lecture)

Histologic Classification of FSGS and its Clinical Meaning

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기 정 혜

Definition of FSGS

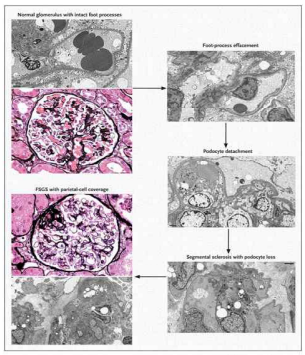
- Pattern of glomerular injury characterized by segmental obliteration of the glomerular tuft by matrix accumulation (sclerosis) and/or hyaline often with synechial attachment b/w the glomerular tuft and Bowman's capsule
- Major target is podocyte from diverse pathophysiologic mechanism.

Etiologic classification of FSGS

Primary (Idiopathic) FSGS
Mediated by circulating permeability factor

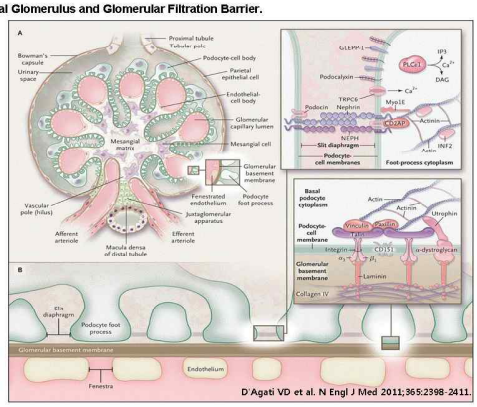
Secondary FSGS
Familial/genetic
Mutation in nephrin/ podocin/α-actinin-4 /transient receptor potential cation 6 channel (TRPC6)/ Wilm's tumor-1(WT1)phospholipase c epsilon 1(PCE1)/ mitochonral protein/ β4-integrin/ tetraspanin/laminin β2, etc.
Virus associated
HIV-1/parvovirus B19/CMV/SV40
Drug induced
Heroin/ Interferon-α/sirolimus/lithium/pamidronte
Mediated by adaptive structural/ functional responces
Reduced renal mass
Oligomeganephrosis
Unilateral renal agenesis
Renal dysplasia
Reflux nephropathy
Surgical renal ablation
Initially normal renal mass
Hypertension
Atheroemboli
Obecity
Cyanotic congenital heart failure
Sickle cell anemia

Morphogenesis of Focal Segmental Glomerulosclerosis (FSGS).



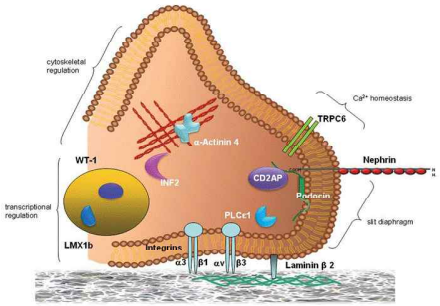
D'Agati VD et al. N Engl J Med 2011;365:2398-2411.

Normal Glomerulus and Glomerular Filtration Barrier.



D'Agati VD et al. N Engl J Med 2011;365:2398-2411.

Schematic overview depicting so far identified players in genetic forms of FSGS. Several different cellular podocyte compartments and functions can be affected by genetic mutations.



Schell C , and Huber T B Nephrol. Dial. Transplant. 2012;27:3406-3412

NDT Nephrology Dialysis Transplantation

Pathogenesis of primary FSGS

- FSGS : Disorder of podocytes → Circulating permeability factor
- "Permeability" :
  increased leakiness of the glomerular filtration barrier leading to proteinuria
- "Circulating" evidence :

① Primary FSGS can recur very rapidly after kidney transplantation (~30% of cases in adults, >50% in children). Conversely, FSGS can often be prevented or delayed in high-risk patients with pretransplantation plasmapheresis, which presumably removes the factor or factors from the circulation.

② Injection of plasma or plasma fractions from patients with FSGS into rats causes proteinuria.

③ Sera from patients with FSGS increase albumin permeability in an isolated glomerulus model ex vivo

④ A transient nephrotic syndrome has been transmitted to a newborn from a mother with FSGS

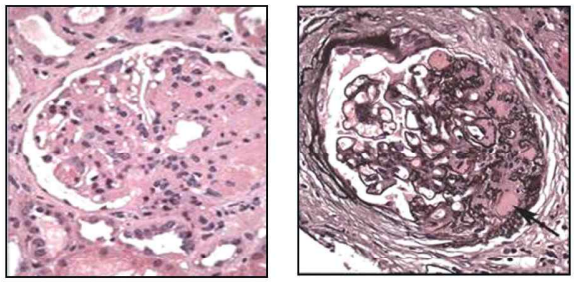
→ suPAR (Soluble urokinase plasminogen activator receptor)
: protelolytic claeavage of membrane bound urokinase plasminogen activator receptor in podocyte

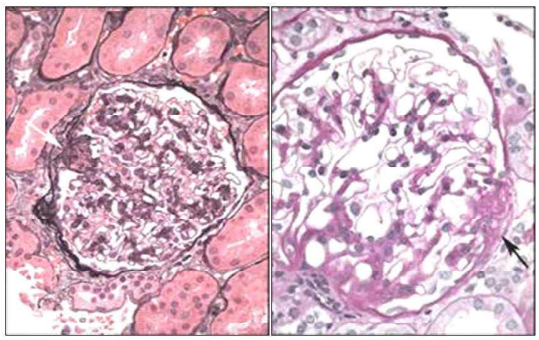
Morphologic variants of FSGS

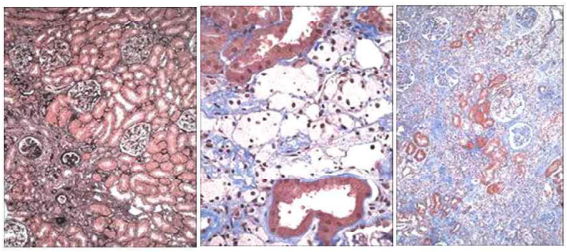
- FSGS is morphologically heterogenous with variable degree of sclerosis & cellularity.

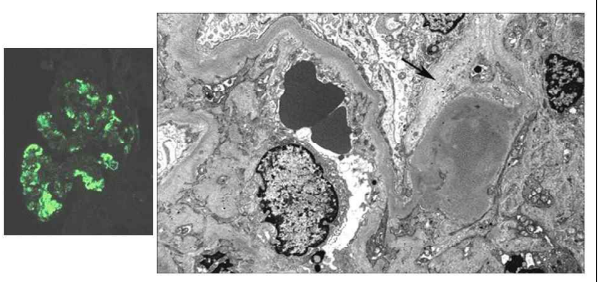
Typical ("classic") :

- Segmental sclerosis with obliteration of glomerular tuft by eosinophilic, PAS positive acellular matrix and/or hyaline material (hyalinosis), usually with adhesion of the glomerular tuft to the Bowman's capsule.
- Early: Solely of synechial attachment b/w the glomerular tuft and Bowman's capsule.
- Advanced: Near complete glomerular sclerosis → Global sclerosis



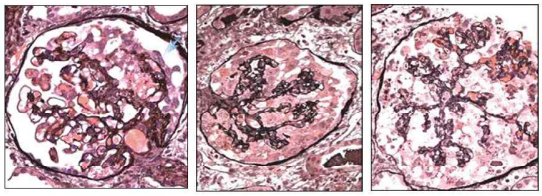






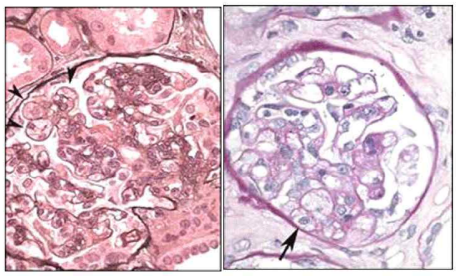
Collapsing Variant:

- segmental/global collapse of capillary tuft without matrix increase
- Usually with severe epithelial hyperplasia in Bowman's space (mimicking crescent)



Cellular variant:

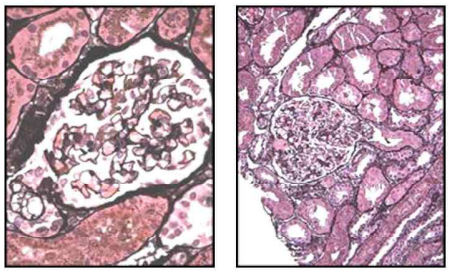
- Expansion of capillary tuft by endocapillary hypercellularity (edothelial proliferation, foam cells and/or inflammatory cells) without collapse



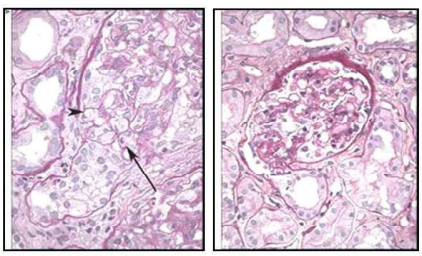
Tip variant:

- Prolapse of segmental lesion into the lumen of the proximal tubule with confluence of overlying epithelial cells, proximal tubular epithelial cells, or synechial attachment to Bowman's capsule at tubular pole.

** Chronic tulointerstitial injury is generally minimal despite of older age compared to the other FSGS subgroup.

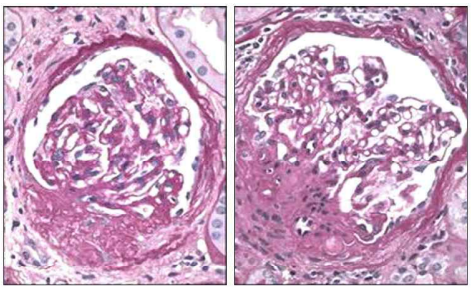


Tip variant:



Perihilar lesion:

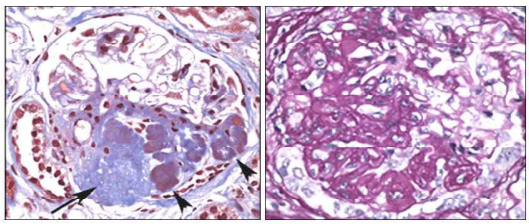
Segmental hyalinosis/sclerosis contiguous with glomerular hilus



NOS variant :

- "Classic" FSGS lesion
- segmental solidification by relatively acellular collagenous matrix (TRC-blue), hyalinosis, plasma insudation (TRC-red)

** Not severe chronic tubulointerstitial injury & global sclerosis
→ Not advanced phase of other variant!



Meaning of histologic finding….

- Spectrum of these lesions occur in 1' & 2ndary FSGS
- Different type of lesion may coexist in the same biopsy or in repeat bx.

- Morphologic variant of FSGS may represent the stage of glomerular lesion ---????
- **Standardization of the pathologic Dx of FSGS : "Columbia Classification"**

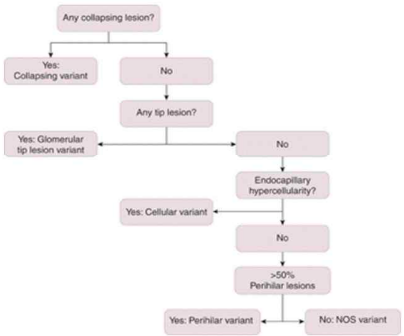
Semin Nephrol. 2003 Mar;23(2):117-34.
Pathologic classification of focal segmental glomerulosclerosis.
D'Agati V.

Am J Kidney Dis. 2004 Feb;43(2):368-82.
Pathologic classification of focal segmental glomerulosclerosis: a working proposal.
D'Agati VD, Fogo AB, Bruijn JA, Jennette JC.
"subclassifications of disease on morphological grounds are valid only if they carry meaningful clinical or pathogenetic implications"

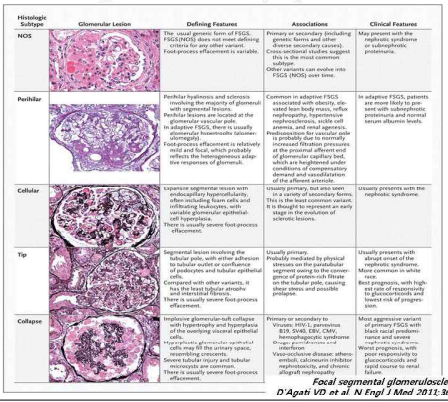
Defining characteristics in the Columbia Classification

Variant	Inclusion Criteria	Exclusion Criteria
FSGS (NOS)	At least 1 glomerulus with segmental increase of matrix obliterating the capillary lumina. There may be segmental glomerular capillary wall collapse without overlying podocyte hyperplasia	Exclude perihilar, cellular, tip, & collapsing variant.
Perihilar	At least 1 glomerulus with perihilar hyalinosis with or without sclerosis. Greater than 50% of glomeruli with segmental lesions must have perihilar sclerosis and/or hyalinosis.	Exclude cellular, tip, & collapsing variant.
Cellular	At least 1 glomerulus with segmental endocapillary hypercellularity occluding lumina, with or without foam cells and karyorrhexis.	Exclude tip, & collapsing variant.
Tip	At least 1 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 lumina or neck. The tip lesion may cellular or sclerosing.	Exclude collapsing variant.
Collapsing	At least 1 glomerulus with segmental or global collapse and overlying podocyte hypertrophy or hyperplasia.	None

Kidney biopsies algorithm of FSGS for Columbia classification



Histologic Variants of Focal Segmental Glomerulosclerosis (FSGS).



Focal segmental glomerulosclerosis.
D'Agati VD et al. N Engl J Med 2011;365:2398-2411

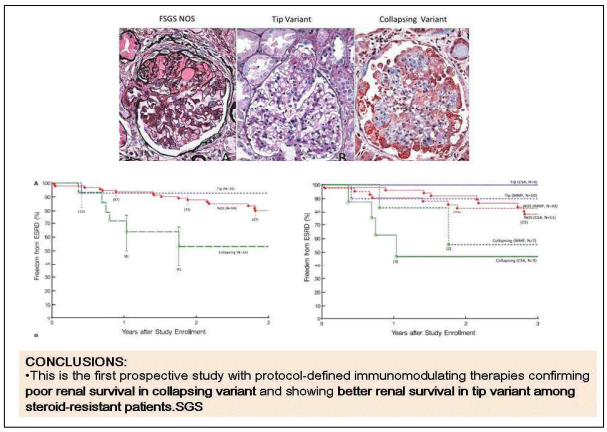
Association of histologic variants in FSGS clinical trial with presenting features and outcomes.

D'Agati VD, Alster JM, Jennette JC, Thomas DB, Pullman J, Savino DA, Cohen AH, Gipson DS, Gassman JJ, Radeva MK, Moxey-Mims MM, Friedman AL, Kaskel FJ, Trachtman H, Alpers CE, Fogo AB, Greene TH, Nast CC.

Clin J Am Soc Nephrol. 2013 Mar;8(3):399-406.

- Renal biopsies of 138 FSGS Clinical Trial (age: 2-38 years, from 2004 to 2008, steroid resistent primary FSGS) were analyzed using the Columbia classification.
- This study assessed the distribution of histologic variants and examined their clinical and biopsy characteristics and relationships to patient outcomes.
- Well defined prospective cohort

RESULTS:
- FSGS, NOS: 68% (n=94), Collapsing: 12% (n=16), Tip: 10% (n=14), Perihilar: 7% (n=10), Cellular: 3% (n=4)
- FSGS, NOS: more subnephrotic proteinuria
- 33% of teenagers and adults had tip or collapsing variants compared with 10% of children
- Tip & Collapsing variants had greater proteinuria and hypoalbuminemia than NOS
- Tip variant: white race (86%) & the lowest pathologic injury scores, baseline creatinine, and rate of progression.
- Collapsing variant: black race (63%) & the highest pathologic injury scores, baseline serum creatinine, and rate of progression
- At 3 years, collapsing(47%), NOS(20%), & tip (7%) variant patients reached ESRD (P=0.005).



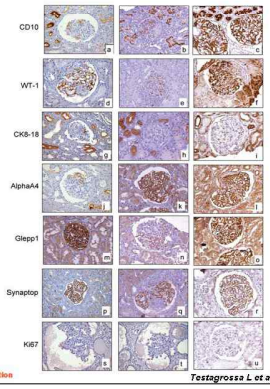
CONCLUSIONS:
•This is the first prospective study with protocol-defined immunomodulating therapies confirming **poor renal survival in collapsing variant** and showing **better renal survival in tip variant among steroid-resistant patients.SGS**

Immunohistochemical expression of podocyte markers in the variants of focal segmental glomerulosclerosis.
Testagross L, Azevedo Neto R, Resende A, Woronik V, Malheiros D
Nephrol Dial Transplant. 2013 Jan;28(1):91-8

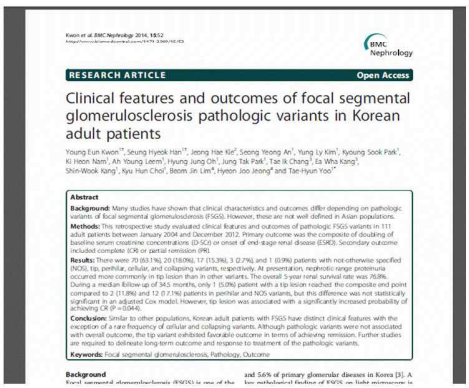
- The Columbia FSGS classification: total 131cases
- NOS(38.2%), collapsing(36.6%), tip (14.5%), perihilar (6.9%), & cellular (3.8%)
- Immunohistochemical stain:
  differentiation related podocyte marker (CD10, WT-1, Vimentin),
  dedifferentiation related podocyte marker (CK8/18, CK19, Ki-67),
  cytoskeletal& membrane related podocyte marker
  (α-actini-4, GLEPP-1, synaptopodin)
- Collapsing variant: loss of expression of CD10, WT1 and α-actinin-4 (P < 0.05)
  & gain of expression of CK8/18 and CK19 (P < 0.05)

- Conclusions: COL variant presented immunohistochemical characteristics that distinguished it from others pointing to additional studies in this area. The distinct immunohistochemical properties of COL might be of help in the comprehension of this aggressive form of FSGS

Expression of immunohistochemical markers in podocytes among FSGS variants.



NDT Nephrology Dialysis Transplantation
Testagrossa L et al. Nephrol. Dial. Transplant. 2013;28:91-98



RESEARCH ARTICLE Open Access

Clinical features and outcomes of focal segmental glomerulosclerosis pathologic variants in Korean adult patients

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Abstract

Background: Many studies have shown that clinical characteristics and outcomes differ depending on pathologic variants of focal segmental glomerulosclerosis (FSGS). However, these are not well defined in Asian populations.

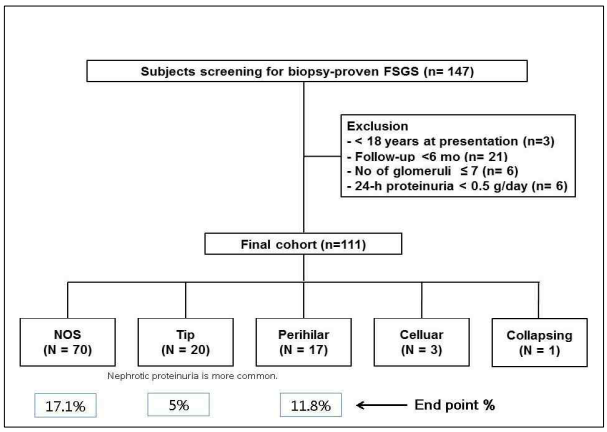
Methods: This retrospective study evaluated clinical features and outcomes of pathologic FSGS variants in 111 adult patients between January 2004 and December 2012. Primary outcome was the composite of doubling of baseline serum creatinine concentrations (D-SC) or onset of end-stage renal disease (ESRD). Secondary outcome included complete (CR) or partial remission (PR).

Results: There were 70 (63.1%), 20 (18.0%), 17 (15.3%), 3 (2.7%), and 1 (0.9%) patients with not-otherwise specified (NOS), tip, perihilar, cellular, and collapsing variants, respectively. At presentation, nephrotic range proteinuria occurred more commonly in tip lesion than in other variants. The overall 5-year renal survival rate was 76.8%. During a median follow-up of 34.5 months, only 1 (5.0%) patient with a tip lesion reached the composite end point compared to 2 (11.8%) and 12 (17.1%) patients in perihilar and NOS variants, but this difference was not statistically significant in an adjusted Cox model. However, tip lesion was associated with a significantly increased probability of achieving CR (P = 0.044).

Conclusion: Similar to other populations, Korean adult patients with FSGS have distinct clinical features with the exception of a rare frequency of cellular and collapsing variants. Although pathologic variants were not associated with overall outcome, the tip variant exhibited favorable outcome in terms of achieving remission. Further studies are required to delineate long-term outcome and response to treatment of the pathologic variants.

Keywords: Focal segmental glomerulosclerosis, Pathology, Outcome

Background and 56% of primary glomerular diseases in Korea [3]. A



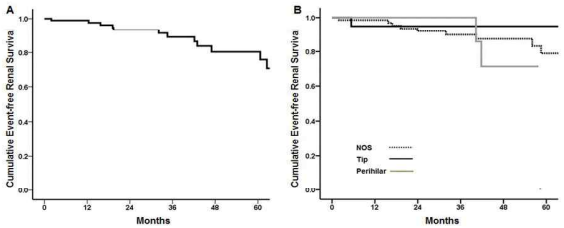


Figure 2. Kaplan-Meier plots for (A) overall event free renal survival and (B) event free renal survival by FSGS pathologic variants. Overall 5-renal survival rate was 76.8%. There were no significant difference in renal survival rates between patients with NOS, perihilar, and tip variants.

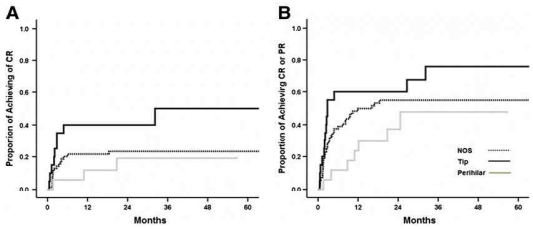


Figure 3. Kaplan-Meier plots for (A) complete remission (CR) and (B) complete or partial remission (PR). Patients with tip lesion had higher probability of achieving CR and CR or PR.

Clinical features and outcomes of focal segmental glomerulosclerosis pathologic variants in Korean adult patients.

Kwon YE, Han SH, Kie JH, An SY, Kim YL, Park KS, Nam KH, Leem AY, Oh HJ, Park JT, Chang TI, Kang EW, Kang SW, Choi KH, Lim BJ, Jeong HJ, Yoo TH.
BMC Nephrol. 2014 Mar 25;15:

Conclusion

Similar to other populations, Korean adult patients with FSGS have distinct clinical features with the exception of a rare frequency of cellular and collapsing variants. Although pathologic variants were not associated with overall outcome, the tip variant exhibited favorable outcome in terms of achieving remission. Further studies are required to delineate long-term outcome and response to treatment of the pathologic variants.

Histologic classification of FSGS: does form delineate function?

Choi MJ.
J Am Soc Nephrol. 2013 Mar;8(3):344-8

- The ideal histologic classification of FSGS???
- Barisoni and colleagues proposed an alternative classification system based on the type of podocyte injury.
- Nevertheless collapsing FSGS is distinguishes as having a dismal prognosis.
- Collapsing variant is characterized by loss of podocyte maturity markers and e-expression of immaturity markers. Therapies for collapsing FSGS may focus on promoting podocyte differentiation
- It remains to be determined how the differences in morphologic subtypes of FSGS may reflect differences in etiology, pathogenesis, prognosis, or optimal therapy. It does appear that identifying the histologic form of FSGS helps delineate clinical course and prognosis.
- FSGS is not a single disease but a manifestation and the morphologic variants likely underpin differing mechanisms.