

Review

Clinical characteristics and renal survival of focal segmental glomerulosclerosis morphologic variants

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Abstract

Background. A number of morphologic variants of primary and secondary focal segmental glomerulosclerosis (FSGS) are now recognized. Histological variants may have specific clinical characteristics and prognosis. Our study utilized a large cohort of FSGS patients to determine if the pathologic variants defined by the Columbia proposal are distinct clinico-pathologic entities.

Methods. It was a single center study, 115 adult patients with biopsy proven FSGS were included. Renal biopsies were reviewed by two pathologists. Demographic and clinical data were obtained by charts. Statistics included One-way ANOVA, Kruskal-Wallis and Mann-Whitney tests.

Results. The frequency of FSGS variants was as follows: collapsing 15 (13%), tip lesion 24 (20,8%), perihilar 28 (24,4%), cellular 40 (34,8%) and not otherwise specified (NOS) 8 (6,9%) patients. Tip patients were younger (age $28,67 \pm 3,84$), compared to perihilar ($p=0,000$), cellular ($p=0,007$) and NOS ($p=0,012$). Diastolic blood pressure was the highest in perihilar variant, significantly higher comparing only to tip variant ($p=0,05$). There was not noted difference in serum creatinine levels at biopsy among the variants ($p=0,091$). Plasmaproteins level was significantly lower in collapsing variant ($55,13 \pm 2,68\text{g/l}$) and cellular ($57,6 \pm 1,92\text{g/l}$) compared to perihilar ($66,21 \pm 1,24\text{g/l}$) and NOS ($66,25 \pm 1,83\text{g/l}$), $p=0,02$. The mean value of proteinuria was as follows: collapsing $7,35 \pm 1,7\text{g/d}$, tip lesion $4,76 \pm 0,77\text{g/d}$, perihilar $2,6 \pm 0,4\text{g/d}$, cellular $5,16 \pm 0,75\text{g/d}$ and NOS $1,7 \pm 0,41\text{g/d}$, the difference among the groups was significant, $p=0,000$. We also noted differences in survival of patients. 5-year survival rate of collapsing variant was 25%, NOS variant 45%, perihilar 55%, tip lesion 63% and patients with cellular variant 67%.

Conclusion. We can conclude that FSGS variants are with different histopathological and clinical features and different outcome of the disease.

Keywords: collapsing nephropathy; focal segmental glomerulosclerosis; glomerulonephritis; nephrotic syndrome; proteinuria

Introduction

A pattern of focal segmental glomerulosclerosis (FSGS) may result from diverse pathogenetic mechanisms including heritable mutations of podocyte-specific proteins (nephrin, podocin, alpha actinine 4) [1-6], infections, especially viral (HIV, parvovirus B19) [8-11], drug toxicities and adaptive responses to reduced functioning renal mass [12-14]. For most patients with FSGS who present with nephrotic syndrome or heavy proteinuria, no secondary cause is identified and then we can use the term "idiopathic FSGS" [15-19]. But, data from the literature present different clinical and pathological features and different outcome of the disease. Idiopathic FSGS is clinically and pathologically heterogeneous, and these variants display variable renal outcomes [20-22]. Widely accepted Columbia FSGS Classification [22-26] recognizes five variants of FSGS, as follows:

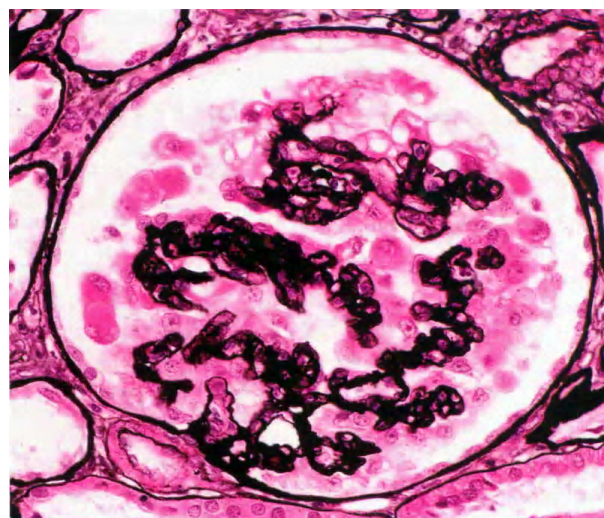


Fig. 1. Collapsing variant of FSGS: glomerular capillary tuft collapse, podocyte hypertrophy and hyperplasia

1. Collapsing variant (COLL)

At least one glomerulus with defining features (glomerular capillary tuft collapse, overlying podocyte hypertrophy and hyperplasia), other glomeruli may have segmental lesions of any subclass. Tubulointerstitial changes are severe. COLL FSGS has a more aggressive clinical course, with fewer remissions and more frequent end-stage renal disease.

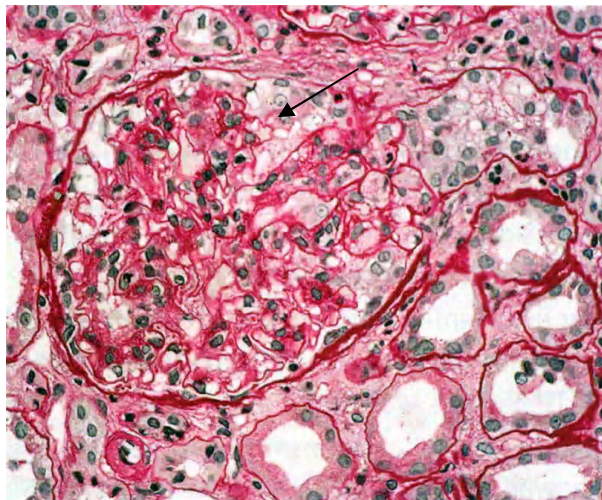


Fig. 2. Tip lesion FSGS: segmental lesion of glomerular capillary tuft, confluence with origin of proximal tubule

2. Glomerular “tip” lesion (TIP)

Collapsing and perihilar lesion has to be excluded. At least one glomerulus must have defining features (segmental lesion involving 25% of glomerular tuft, adhesion or confluence of glomerular lesion with origin of proximal tubule, segmental lesion may be foam cells or endocapillary hypercellularity). Less expressed tubulointerstitial changes. Severe nephrotic syndrome is present in most of the patients, but the response to steroid treatment is good, as well as the survival of the patients.



Fig. 3. Cellular variant of FSGS: segmental endocapillary proliferation, foam cells are visible

3. Cellular variant (CELL)

Collapsing and tip lesion must be excluded. At least one glomerulus must have defining features (segmental endo-

capillary proliferation, segmental endocapillary foam cells with occlusion of capillary lumina). Other glomeruli may have segmental sclerotic lesions. Severe nephrotic syndrome is the common, the response to treatment and renal survival is poor.

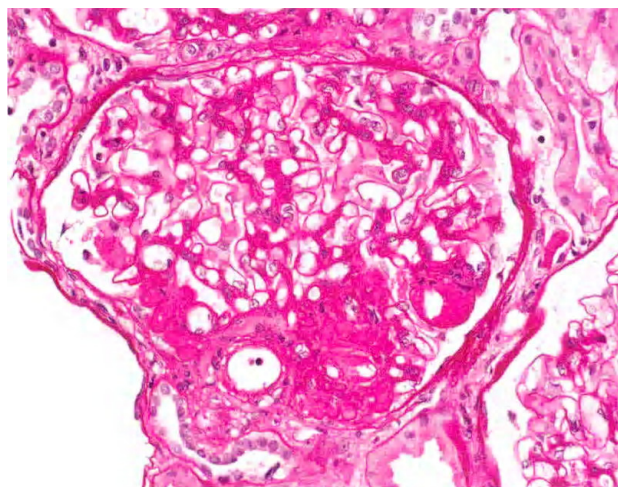


Fig. 4. Perihilar variant of FSGS: segmental occlusion of glomerular capillaries with matrix accumulation and hyalinosis

4. Perihilar variant (PH)

Collapsing, “tip” lesion and cellular variant must be excluded. More than 50% of glomeruli must present segmental occlusion of glomerular capillaries by matrix accumulation and hyalinosis. The lowest frequency of nephrotic syndrome and the highest frequency of hypertension are characteristics of this pattern. The response to steroid treatment is poor, but on the other hand the survival is the best.

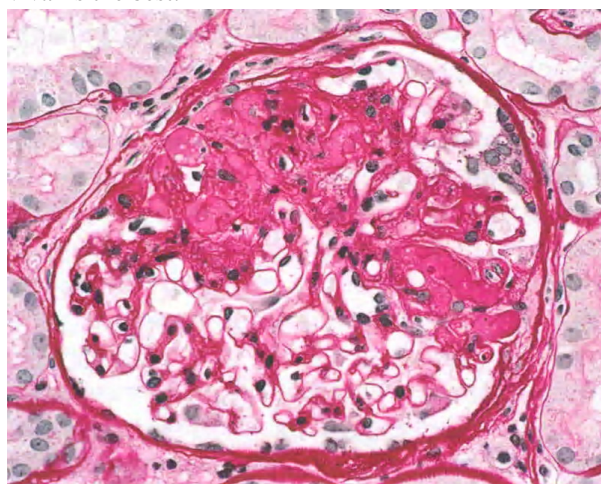


Fig. 5. NOS variant of FSGS: non-specific segmental capillary tuft lesion

5. Not otherwise specified (NOS variant)

Other variants have to be excluded. Any number of glomeruli may be involved, segmental glomerular tuft lesion is necessary, capillary tuft collapse may be found, but without podocyte hyperplasia. Patients tended to have clinical and pathologic parameters that were intermediate with respect to the spectrum of findings in the other distinctive variants. Hypertension is frequent, but nephrotic syndrome, too. Complete remission is rare.

In this study, we classified our patients with FSGS according to Columbia Classification of FSGS [22] and compared their clinical characteristics and renal survival. We also tried to compare our results found in each variant with previously reported data about that variant of FSGS.

Patients and Methods

We conducted a retrospective, clinicopathological analysis of adult patients (>15yr age at presentation) who had primary FSGS, diagnosed at our Department. The diagnosis of primary FSGS was established when there was no immunopathologic evidence for another primary glomerular disease or pathologic and clinical evidence for a systemic disease associated with secondary segmental glomerular sclerosis (morbid obesity, reflux, HIV infection, nephrectomy, solitary kidney, intravenous drug abuse, family history of renal disease). On the basis of these criteria, we identified a total of 115 patients with primary FSGS during a period of time of 10 years and they were basis of this study.

Renal biopsy tissue was divided and processed for light, fluorescence and electron microscopy. Semi-thin sections were done in all cases, and ultra-thin unfortunately only in 18. Inclusion in this study required a minimum of 8 glomeruli in the light microscopic section. Light microscopic examination of slides stained with hematoxylin/eosin, PAS and methenamine silver-PAS (Jones stain) provided the diagnosis of FSGS and categorization into one of 5 groups, according to previously described criteria of Columbia Classification of FSGS [22]. Tubular, interstitial and vascular changes were not taken into consideration. Renal biopsy specimens were analyzed by two pathologists.

Demographic, clinical and laboratory information at the time of renal biopsy and at follow-up was obtained on each patient. Clinical records were reviewed to determine the patients' gender, age, blood pressure, level of protein excretion, serum creatinine and serum plasmaprotein at the time of biopsy.

Renal insufficiency was defined as serum creatinine >120 $\mu\text{mol/l}$. The date of the start of dialysis treatment was the date of the end of renal survival. Nephrotic-range proteinuria proteinuria was defined as >3g/d protein loss and massive proteinuria defined as >10g/d protein. Hypertension was defined as a systolic BP>140mmHg and a diastolic BP>90 mmHg. Complete remission was defined as a urine protein of <0,4g/d and partial remission was defined as a urine protein between 0,41 and 2,9g/d.

Patients with normal renal function and nephrotic syndrome were treated with steroids, sometimes combined with cyclophosphamide and past 5 years with mycophenolate mofetil. This treatment was also performed in patients with serum creatinine < 220 $\mu\text{mol/l}$. Patients with non-nephrotic proteinuria and renal failure (creatinine > 220 $\mu\text{mol/l}$) were treated with ACE-inhibitors. Renal "death" was defined as need of dialysis treatment.

Statistics included One-way ANOVA, Kruskal-Wallis, Mann-Whitney tests and Kaplan-Mayer survival curves.

Results

This pattern was found in 13 patients, aged $35,47 \pm 3,89$ (M \pm SE, mean \pm standard error). Diastolic blood pressure (DBP) at renal biopsy was $96,67 \pm 2,66$ mmHg, serum creatinine $101,93 \pm 6,6$ $\mu\text{mol/l}$, daily protein loss of $7,35 \pm 1,7$ g/d and plasmaproteins level of $55,13 \pm 2,68$ g/l. Complete remission was not achieved in any patient, partial in 2/13. All 13 patients developed chronic renal failure during follow-up, and 5-year survival rate was 25%.

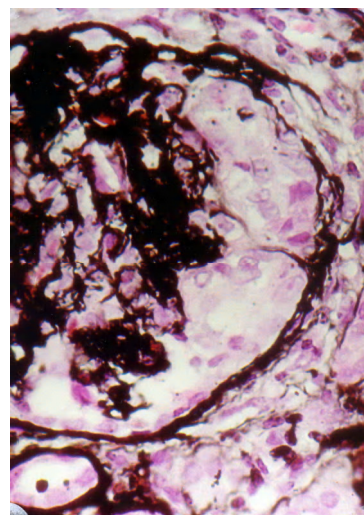


Fig. 6. Hyperplasia and hypertrophy of visceral epithelial cells with hyaline droplets in collapsing variant of FSGS

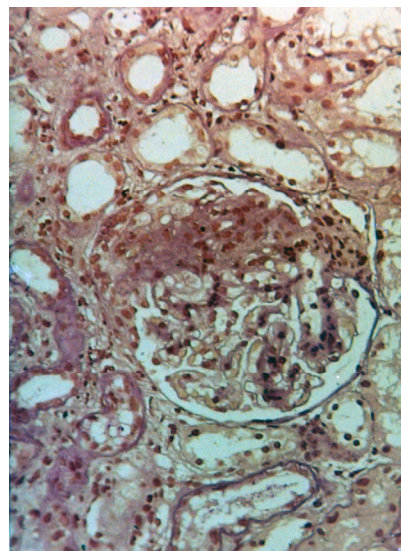


Fig. 7. Affection of urinary pole of glomerulus in "tip" lesion of FSGS

This histopathological form was diagnosed in 24 patients, aged $28,67 \pm 2,38$. DBP at start of the study was $90 \pm 2,6$ mmHg, serum creatinine $106 \pm 12,37$ $\mu\text{mol/l}$, plasmaproteins $60,5 \pm 2,4$ g/l and daily protein loss of $4,7 \pm 0,76$ g. Complete remission was noted in 2/24 patients, without relapse during follow-up, partial in 8/24. 14/24 patients developed chronic renal failure during follow-up and 5-years survival rate was 63%.

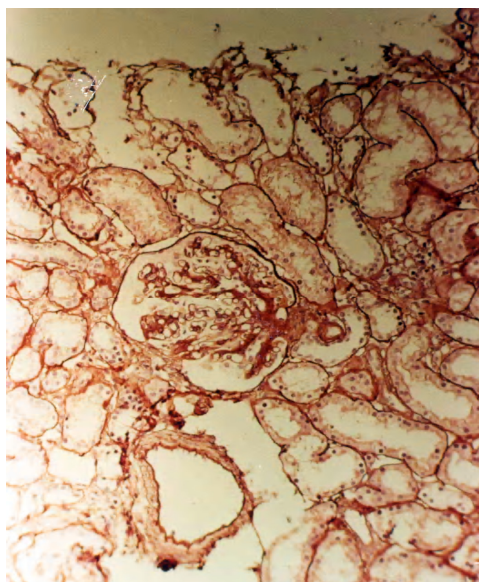


Fig. 8. Hilar affection in perihilar variant of FSGS

21 patient was diagnosed as perihilar variant of FSGS, aged $41,1 \pm 3,89$. DBP at biopsy was $100 \pm 1,98$ mmHg, serum creatinine levels of $140 \pm 13,43$ μ mol/l, plasmaproteins level of $66,21 \pm 1,24$ g/l and daily protein loss of $2,59 \pm 0,4$ g. Summary data of this group presented creatinine level > 120 μ mol/l and normal plasmaproteins. None of the patients responded to immunosuppressive treatment, and 5-year survival rate was 55%.

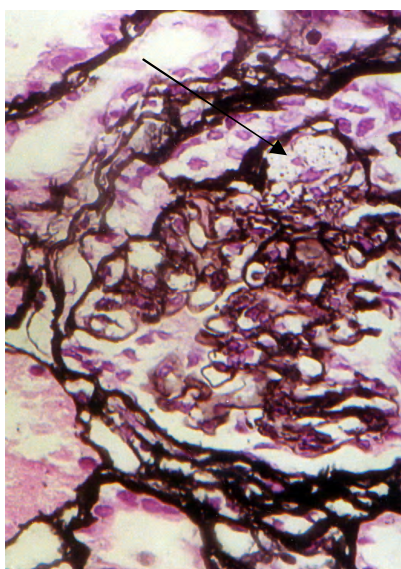


Fig. 9. Foam cells in cellular variant of FSGS

This group consisted of 28 patients, aged $36,2 \pm 2,06$. DBP was $96,12 \pm 1,95$ mmHg, plasma creatinine $108,9 \pm 7,94$ μ mol/l, plasmaproteins $57,6 \pm 1,92$ g/l and daily protein loss of $5,16 \pm 0,75$ g/d. Complete remission was noted in 3/28 and partial in 10/28 patients. 15 patients developed chronic renal failure during follow-up, but slow progressive and 5-year survival rate was the best: 67%.

NOS variant

8 patients were not classified in previous groups, but presented focal-segmental changes. They were aged $39,62 \pm 3,7$, with DBP at start of the study $99,37 \pm 5,54$ mmHg, serum creatinine $111,75 \pm 12,66$ μ mol/l, plasmaproteins $66,25 \pm 1,83$ g/l and daily protein loss of $1,7 \pm 0,33$ g/d. Only one patient (with nephrotic syndrome) responded partially to immunosuppressive treatment, the other 7 patients developed chronic renal failure during follow-up. The 5-year survival rate was 45%.

Analyzing clinical data of all groups, it can be seen that “tip” lesion patients was younger comparing to perihilar ($p=0,000$), cellular ($p=0,007$) and NOS lesion patients ($p=0,012$). DBP was the highest in perihilar variant, but the difference was significant comparing only to “tip” variant ($p=0,05$). There was not noted significant difference in serum creatinine levels at biopsy among different histopathological variants ($p=0,091$). Plasmaproteins level was significantly lower in collapsing and cellular variant compared to perihilar and NOS ($p=0,012$), and the difference among the daily loss of proteins of different patterns was also significant ($p=0,000$). We also noted different survival rates in different histopathological forms.

Discussion

We reviewed the presentation and clinical course of adult patients with primary FSGS to determine the significance of different forms of glomerular histopathological lesions. Glomerular changes were classified according to Columbia FSGS Classification [22]. We can conclude that there was no significant difference in renal function among the groups, nephrotic syndrome was characteristic for collapsing, cellular and tip lesion and hypertension for perihilar and NOS variant. Complete remission was rarely occurred in all groups, some patients with nephrotic syndrome responded to immunosuppressive treatment with partial remission [31,32]. But, partial remissions were more frequent in cellular and tip lesion, only two collapsing variant patients with severe nephrotic syndrome partially responded to therapy. Histopathological patterns with clinical presentation with nephrotic syndrome and more frequent partial and complete remissions (excluding collapsing variant) also presented better survival. It is well known that cellular, collapsing and tip lesion share clinical presenting features of heavier proteinuria, more frequent nephrotic syndrome and shorter duration of symptoms compared to NOS and perihilar variant of FSGS, suggesting that the first three variants reflect acute glomerular injury, or possibly a response to heavy proteinuria [22-28]. Literature data agree that morphologic variants of idiopathic FSGS display significantly different rates of remissions. The outcome is the worst for collapsing variant; this fact was also presented in our study [22-24]. “Tip” lesion patients presented the best outcome in the other series [22,26], they are on the second place in our material, after cellular variant. It is interesting that contrary to literature data cellular variant is frequent among our patients with FSGS, with severe

nephrotic syndrome as dominant clinical feature and the best survival. This difference may be due to the fact that tubular atrophy, interstitial fibrosis, interstitial edema, interstitial inflammation and vascular changes were not taken into consideration. The degree of podocyte hyperplasia and hypertrophy in each segmental lesion also was not graded. It is clear that inclusion of tubulointerstitial changes and quantification of glomerular changes may explain the difference in survival and different responses to treatment, but it will be the matter of the other study.

Conclusions

This study confirms that different histopathological variants of FSGS according to Columbia FSGS classification present different clinical features and different outcome of the disease.

Conflict of interest statement. None declared.

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