Renal Failure

ISSN: 0886-022X (Print) 1525-6049 (Online) Journal homepage: informahealthcare.com/journals/irnf20

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To cite this article: Sevdegul Mungan, Ercan Turkmen, Makbule Cisel Aydin, Arzu Emine Saglam & Dilek Ertoy Baydar (2015) Tip lesion variant of primary focal and segmental glomerulosclerosis: clinicopathological analysis of 20 cases, Renal Failure, 37:5, 858-865, DOI: 10.3109/0886022X.2015.1033635

To link to this article: https://doi.org/10.3109/0886022X.2015.1033635

Published online: 10 Apr 2015.

RENAL FAILURE

http://informahealthcare.com/rnf
ISSN: 0886-022X (print), 1525-6049 (electronic)

Ren Fail, 2015; 37(5): 858–865
 DOI: 10.3109/0886022X.2015.1033635

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CLINICAL STUDY

Tip lesion variant of primary focal and segmental glomerulosclerosis: clinicopathological analysis of 20 cases

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Abstract

The glomerular tip lesion (GTL) is a distinctive histopathologic lesion which is regarded as a variant of focal and segmental glomerulosclerosis (FSGS). The prognostic significance of GTL among other FSGS variants has been disputed. In order to define the clinical features and outcome of GTL, we retrospectively reviewed the presenting clinical features, laboratory and biopsy findings and surveillance in our cohort of GTL, which consisted of 20 adults with native kidneys (mean age 46 years) with follow-up data ranging from 3 to 137 months. At presentation, mean urine protein, serum albumin and cholesterol levels were 5.17 g/d, 2.6 g/dL and 312.9 mg/dL, respectively, and none had renal insufficiency. Microscopic hematuria was detected in five patients. At biopsy, glomerular segmental lesions consisted of GTL without perihilar or collapsing lesions. GTL was observed in a variable proportion of glomeruli from 2.6% to 100%. Mesangial proliferation was seen in nine cases, at a moderate degree in two and mild in the rest. Three biopsies showed mild, two showed moderate interstitial fibrosis/tubular atrophy. Eleven patients received steroids alone and eight received sequential therapy with steroids and a cytotoxic agent. At a mean follow-up of 40.6 months, 17 patients (85%) achieved complete remission of nephrotic syndrome, 15% had partial remission. Four of 17 suffered from recurrences. No patient progressed to end-stage renal disease. Serum albumin at diagnosis was the only predictor of a recurrence ($p = 0.037$). Microscopic hematuria correlated with incomplete remission ($p = 0.045$). Our study demonstrates a clearly favorable prognosis in patients with FSGS-GTL variant.

Keywords

Focal segmental glomerulosclerosis, nephrotic syndrome, pathology, renal insufficiency, tip lesion

History

Received 21 December 2014
Revised 2 February 2015
Accepted 18 March 2015
Published online 10 April 2015

Introduction

Focal and segmental glomerulosclerosis (FSGS) is a glomerular disease characterized by scarring of portions (or segments) of some glomerular tufts. This disorder is mostly associated with nephrotic range proteinuria. Fahr and Rich were the first who described this lesion as a new pathologic finding.[1,2]

Columbia classification recognizes five histologic variants of FSGS: glomerular tip lesion (GTL), cellular, perihilar, collapsing and NOS (not otherwise specified).[3] Tip variant is defined as ''the presence of at least one segmental lesion involving the tip domain (outer 25% of the glomerular tuft next to the origin of the proximal tubule) with either adhesion between the tuft and Bowman's capsule at the tubular origin or neck, or the confluence of podocytes with parietal or tubular epithelial cells''. Perihilar or collapsing type sclerotic lesions in any glomerulus must be excluded for the diagnosis of tip lesion variant.[4] Recognition of the variants may have prognostic value in individuals with primary focal segmental glomerulosclerosis. GTL variant has low rate of progression to end-stage renal disease in most patients with an excellent response to steroids as in minimal change disease.[5–7] Yet, some FSGS-GTL patients show similar course to that of patients with other types of FSGS with unfavorable response to treatment.[8–10]

The aim of this study was to conduct a retrospective analysis in our series of 20 adult patients with biopsy-proven primary FSGS-tip lesion variant to determine the clinical features and outcome in this disease and to investigate whether demographics, laboratory parameters or microscopy can distinguish benign players from worse ones.

Materials and methods

Case selection

Inclusion criteria

This was a retrospective analysis of adult (>20 years of age) patients who were diagnosed as having primary FSGS-tip lesion variant via renal needle biopsy, presented to our

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institution from 1999 to 2013. The diagnosis was based on the criteria of the FSGS Columbia classification described by D'Agati et al.[3] as

> ''the presence of one or more segmental lesions involving the outer 25% of the glomerular tuft next to the origin of the proximal tubule, in the absence of perihilar sclerosis or collapsing FSGS''.

The identification of proximal tubular pole in the glomerular capillary tuft was strictly required before defining the segmental sclerosis as tip lesion.

Exclusion criteria

Patients in whom at least 3 month clinical follow-up was not available, those who received renal transplant, those whose renal biopsy contained inadequate sample (fewer than 10 glomeruli), and those with secondary FSGS (e.g., chronic hypertension, reflux nephropathy, HIV, morbid obesity, intravenous drug abuse, unilateral renal agenesis or renal atrophy, Alport or other genetic diseases with predisposition to FSGS) or other glomerular disease with sclerotic lesions were excluded.

Clinical data

Hospital medical records of the patients were used to obtain clinical and laboratory information at the time of renal biopsy and at each follow-up. The details included age, gender, past medical history, presenting clinical features, findings of physical examination, degree of proteinuria (24-h urinary protein), presence of hematuria, serum creatinine, albumin, total protein, total triglyceride, total cholesterol and low density lipoprotein (LDL) levels. Administered treatment regimens were noted for each case.

Definitions

A complete remission (CR) was defined as proteinuria <0.3 g/24 h with a stable serum creatinine concentration. A partial remission (PR) was defined as proteinuria between 0.3 and 2.0 g/24 h with at least 50% reduction in proteinuria from baseline and a stable serum creatinine concentration. A relapse was defined as a proteinuria >3 g/24 h after prior reduction of the proteinuria to <2.0 g/24h.

Histomorphological analysis

Renal biopsies were processed for light microscopy (LM) and immunofluorescence microscopy (IFM) according to standard techniques. Electron microscopic studies were available in one case. For LM, 10 glass slides, each containing 3–4 tissue sections (2 μm thickness), were stained with hematoxylin and eosin, periodic acid-Schiff (PAS), Masson's trichrome, Jones methenamine silver (JMS), periodic acid methenamine silver (PAMS) and Congo red stains. Routine IFM was performed on 4 μm thick cryostat sections using polyclonal fluorescein isothiocyanate conjugated antibodies to IgG, IgM, IgA, C3c, C4c,C1q, lambda and kappa light chains (Dako Corporation, Carpenteria, CA). The glass slides of the renal biopsy specimens retrieved from pathology archives were reviewed by the pathologists (D.E.B. and S.M.) who were blinded to the clinical data. The numbers of glomeruli were counted, and proportions of global sclerosis and segmental sclerosis (i.e., tip lesions) in each biopsy were calculated. The extent of interstitial fibrosis/tubular atrophy was semiquantitatively scored on a scale of 0–3 + depending on the renal cortical area affected (0, 0–5%; 1+, 6–25%, 2 + 26–50% and 3 + >50%). Arteries and arterioles were evaluated semiquantitatively for global estimation of arteriosclerosis taking into account arterial intimal fibrosis on a scale of 0–3 + (0, none; 1+, intimal sclerosis with ≤25% luminal occlusion; 2+, 26–50% occlusion; 3+, >50% occlusion) and hyaline deposits in arteries and arterioles on a scale of 0–2 + (0, absent; 1, present, small, non-occlusive of lumen; 2, present, extensive, and/or impinging on lumen). The presence of interstitial inflammatory cell infiltration was noted. IFM was negative in all cases except nonspecific IgM and/or C3 deposition in tip lesions when included in the frozen sections.

Statistical analysis

Kolmogorov–Smirnov test was used to test normal distribution of interval variables. Student's *t*-test and Mann–Whitney's test were utilized to analyze numeric data, with normal and non-normal distribution, respectively. One-Way ANOVA test was utilized to test the differences between three groups (complete remission, remission with recurrence and partial remission). Pearson Chi-square test was applied for categorical variables. For the comparison of the clinical and laboratory characteristics among patients with different clinical outcomes, the Fisher exact test was used for categorical data and the Wilcoxon rank-sum test for continuous data. Continuous data are reported as mean ± SD and median (range). Throughout, p-value < 0.05 was considered as the level of statistical significance. The analysis was performed using SPSS version 15.0 for Windows (SPSS Inc., Cambridge, MA).

Results

Clinical data

A total of 20 cases of primary FSGS-tip variant that met the inclusion criteria were identified in the study period. No patients had other primary glomerular diseases, such as IgA nephropathy, membranous nephropathy, pauci-immune glomerulonephritis, lupus nephritis or hereditary nephritis that may lead to secondary FSGS.

There was a wide age range, from 21 to 72 years (mean age 46 years). Twelve (60%) patients were females (1:1.5 male-to-female ratio). Of the 20 patients, 14 presented with pedal edema or anasarca (70%), while others had nonspecific symptoms of polyuria, dysuria, palpitation, flank pain and headache. Two patients (10%) were receiving antihypertensive agents at initial presentation. Past medical history revealed chronic B viral hepatitis, pemphigus vulgaris, ankylosing spondylitis, hyperuricemia, thalassemia trait and polycystic ovary syndrome, each in one patient. Physical examination documented hypertension in 11 patients.

Serum creatinine at the time of biopsy ranged between 0.46 and 1.37 mg/dL (mean 0.9 mg/dL). All patients had significant detectable proteinuria on dipstick urine examination,

with a mean 24-h urinary protein excretion of 5167.35 mg/d (median 3.9 g/d). Serum albumin levels ranged between 1.1 and 4.9 mg/dL (mean 2.6 g/dL). Microscopic hematuria was detected in five patients. The main clinical and biochemical parameters are summarized in Table 1.

Histopathological features

The median number of glomeruli was 30, with a range of 11–80. Global glomerulosclerosis was noted in a median of 10% glomeruli (range: 0–31%). FSGS-tip lesion (segmental sclerosis at the tubular pole of the capillary tufts) was seen in a variable number of glomeruli, constituting a median value of 20% (range: 2.6–100%) of the total number of nonobsolescent glomeruli. Morphology of the segmental sclerotic lesions was variable. In 10 cases, they were cellular with endocapillary foamy cells (Figure 1); in the others they were in the form of simple capillary tuft—capsule, or podocyte—parietal cell or tubular epithelial cell adhesion at the tubular pole (Figure 2). Six biopsies revealed hyalinosis (hyaline protein globules) in the areas of sclerosis (Figure 3). Nine biopsies showed segmental mesangial hyperplasia in addition to tip lesions, usually mild (seven cases), but also focally moderate in two cases (Figure 4).

The chronic tubulo-interstitial changes (interstitial fibrosis and tubular atrophy) were grade-1 in three and grade-2 in two biopsies; no significant tubulointerstitial alteration was observed in the rest. Mild (1+) and moderate to severe (2+) hyaline arteriolosclerosis was noted in five and one biopsies, respectively. Fibrous thickening of the intima of the arteries was evident in 12 cases, two being moderate (2+) and the rest being mild (1+). The histological features are summarized in Table 2.

Table 1. Clinical and laboratory features of the 20 cases of FSGS-GTL.

Number of patients (male / female)	8/12
Age at biopsy (mean ± SD) years	46 ± 14.1
Edema as presenting symptom (*n* (%))	14 (70)
Microscopic hematuria (*n* (%))	5 (25)
Protein in urine (mean ± SD, g/24 h)	5167.35 ± 3975.1
Serum creatinine (mean ± SD, mg/dL)	0.9 ± 0.3
Serum albumin (mean ± SD, g/dL)	2.6 ± 1.0
Total cholesterol (mean ± SD, mg/dL)	312.9 ± 109.1
LDL (mean ± SD, mg/dL)	200.7 ± 78.8
Triglycerides (mean ± SD, mg/dL)	226.7 ± 165.4

Note: SD, standard deviation.

Follow-up data

Consequent to the biopsy diagnosis of FSGS-GTL, all patients except one were given immunosuppressive treatment with steroids ranging from 4 weeks to 1 year. Angiotensinogen-convertase inhibitors (ACE inhibitor) or angiotensin receptor blockers (ARB) were added to the therapeutic regime. Eight patients received one or two cytotoxic agents in addition to steroids. One patient was treated conservatively with RAS blockade only and did not receive steroids or other forms of immunosuppressive therapy. Follow-up data were available in all patients, with a mean follow-up period of 46 months (range 3–137 months). Of these, three showed

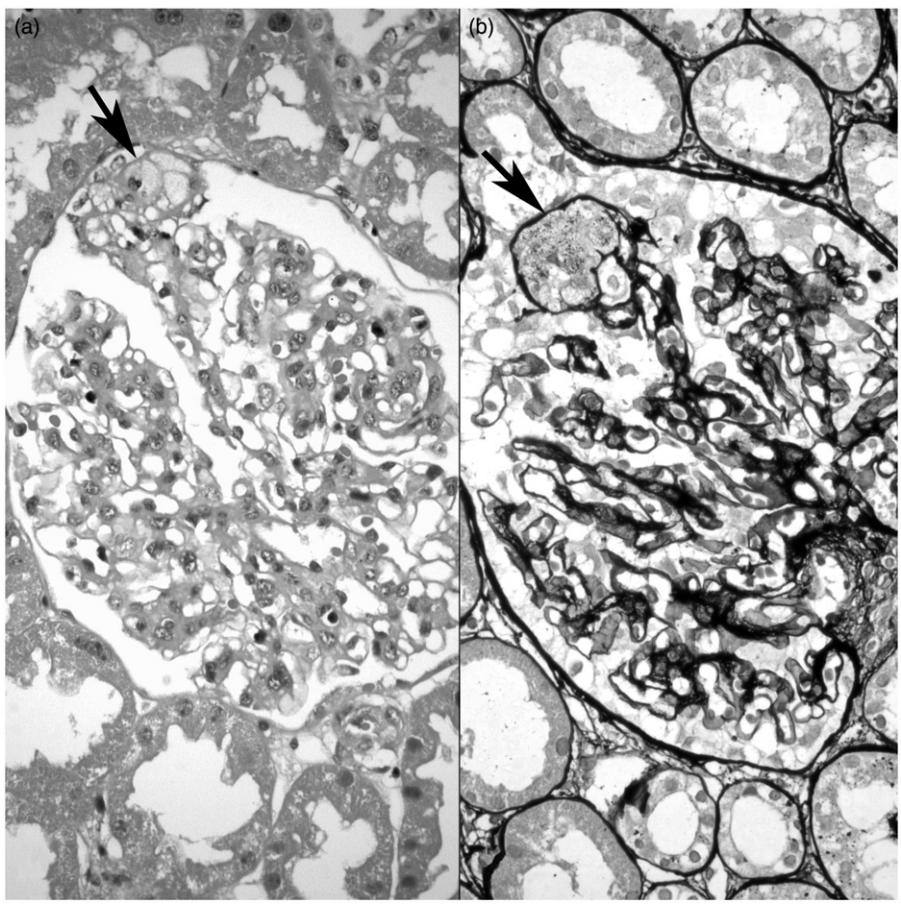

Figure 1. Sclerosed capillaries are occluded by foamy macrophages (arrows); the uninvolved parts of the glomeruli have patent capillary lumina, normal mesangium and cellularity (a: H&E × 400; b: Jones' methenamine silver × 400 (a and b depict the same glomerulus)).

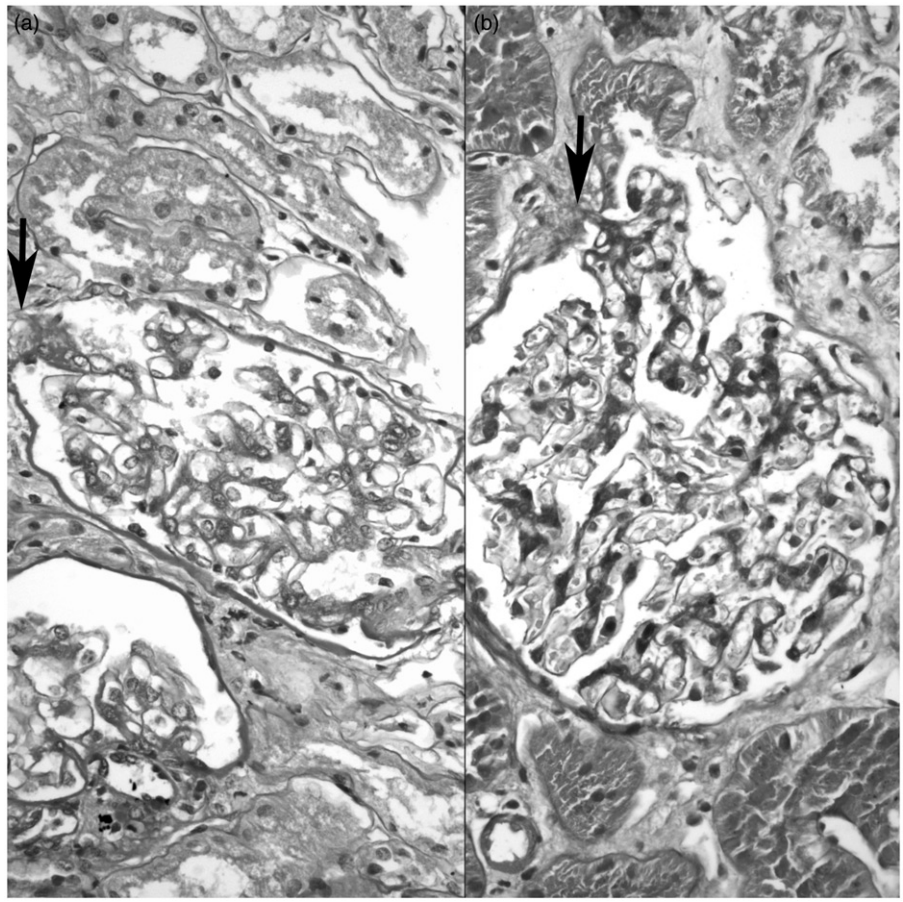

Figure 2. Sclerotic segment in each glomerulus is minute and is noted mainly by the adhesion of loop to Bowman's capsule (arrows) (a: PAS × 400; b: Masson trichrome × 400 (a and b depict the same glomerulus)).

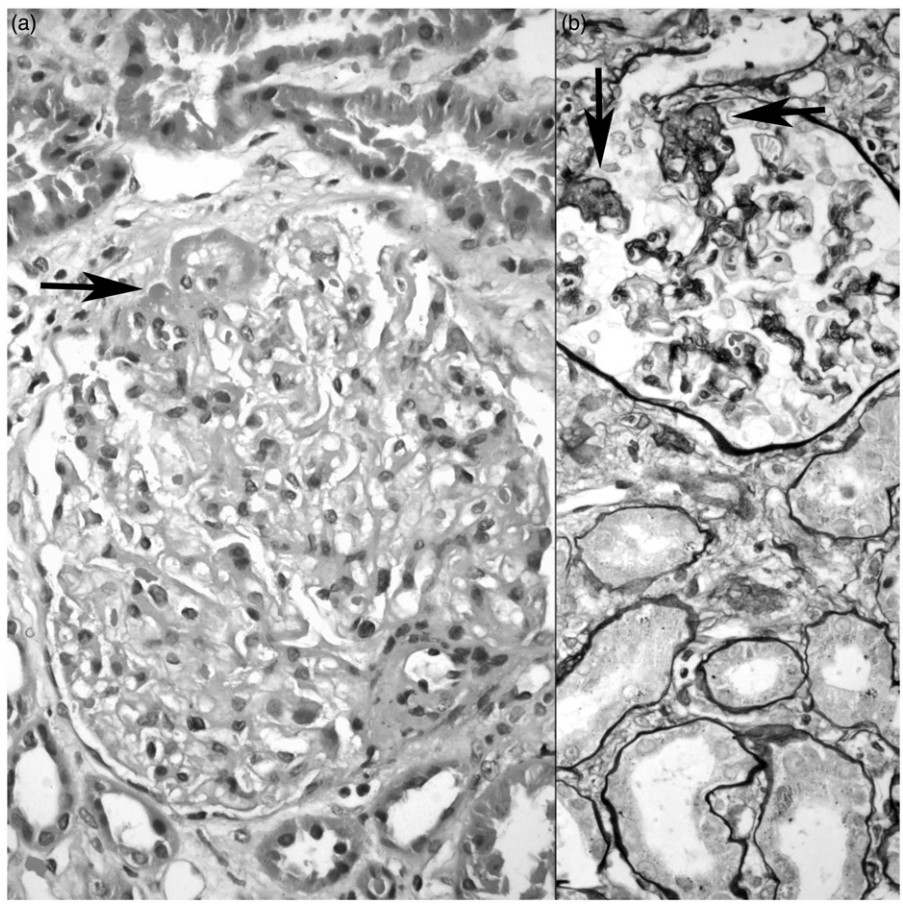

Figure 3. Tip lesions with hyalinosis (arrows) (a: H&E × 400; b: Periodic acid methenamine silver ×400 (a and b depict the same glomerulus)).

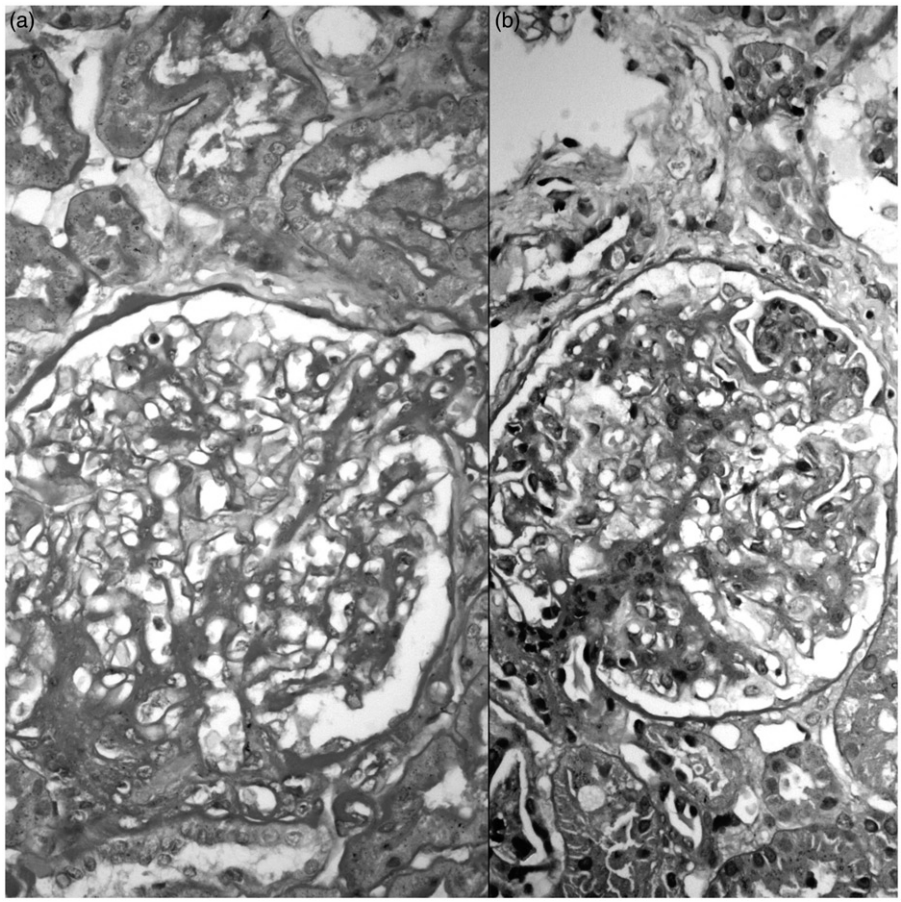

Figure 4. Glomeruli with mesangial expansion and cellularity in addition to tip lesion (a and b: PAS × 400).

Table 2. Histopathological findings in the renal biopsy specimens.

Number of glomeruli	
median (range)	30 (11–80)
Proportion (%) of global sclerosis	
median (range)	10 (0–31)
Ratio (%) of glomeruli with GTL	
median (range)	20 (2.6–100)
Mesangial hyperplasia	
n (%)	9 (45)
Interstitial fibrosis/tubular atrophy, *n* (%)	
Grade I	3 (15)
Grade II	2 (10)
Grade III	0
Arteriolar hyalinosis, *n* (%)	
Grade I	5 (25)
Grade II	1 (5)
Grade III	0
Arterial intimal fibrosis, *n* (%)	
Grade I	10 (50)
Grade II	2 (10)
Grade III	0

partial remission. The remaining 17 patients (85%) had completely resolved proteinuria. However, four of these had recurrence of disease (at 2nd, 3rd, 4th and 10th years) with the same complete response following treatment. In general, patients did well with no significant decline in renal function, both in the short and long term. None of the patients had end stage renal failure, serum creatinine ranged between 0.59 and 1.56 mg/dL at the last follow-up visit.

Statistical analysis

Patients who experienced recurrence in follow-up had significantly lower serum albumin ($p = 0.037$) at the time of first diagnosis (Table 3). Measurement of plasma albumin below 2 g/dL in patients that would and would not recur was 100% and 23.1%, respectively. Microscopic hematuria correlated with incomplete remission ($p = 0.045$). Two out of three patients (66.7%) with partial remission had hematuria, whereas this was observed in only one of 13 with non-recurring complete remission (7.7%). Prevalence of hematuria was 50% (two out of four) in CR patients who showed a relapse later ($p > 0.05$). Other clinical parameters including age at diagnosis of FSGS-GTL, gender, baseline serum creatinine or creatinine at current status, level of serum total cholesterol, LDL or triglycerides, degree of proteinuria or presence of hypertension did not correlate with the outcome. Histological features including percentage of global sclerosis, ratio of tip lesions, morphology of segmental sclerosis (association of foamy cells or hyalinosis in tip lesions), presence or degree of interstitial fibrosis/tubular atrophy and vascular changes also did not show any correlation with outcome.

Discussion

FSGS is a relatively common glomerulopathy that affects both children and adults. Patients typically present with heavy proteinuria or nephrotic syndrome. The effectiveness of therapeutic strategies has been poor in many patients as

Table 3. Characteristics of patients with FSGS-GTL and comparison between patients showing partial remission, complete remission with recurrence and complete remission without recurrence.

Characteristics	Complete remission without recurrence ($n = 13$)	Complete remission with recurrence ($n = 4$)	Partial remission ($n = 3$)	p Value
Male, *n* (%)	5 (38.5%)	2 (50.0%)	1 (33.3%)	0.659
Age (years)				
Mean ± SD	44.8 ± 14.7	41.0 ± 10.7	58.0 ± 12.5	0.264
Median	44.0	45.5	59.0	
Hypertension, *n* (%)	6 (46)	2 (50)	3 (100.0)	0.276
Hematuria, *n* (%)	1 (7.7)	2 (50.0)	2 (66.7)	0.045[a]
Serum creatinine (mg/dl)				
Mean ± SD	0.8 ± 0.3	1.0 ± 0.3	1.0 ± 0.1	0.452
Median	0.8	1.0	1.1	
Serum albumin (g/dl)				
Mean ± SD	2.9 ± 0.9	1.3 ± 0.2	2.6 ± 0.6	0.037[b]
Median	2.8	1.4	2.5	
Proteinuria (g/24 h)				
Mean ± SD	4420.4 ± 2246.3	4960.5 ± 5292.3	8680.0 ± 7456.7	0.256
Median	4082	3360	6440	
Total cholesterol (mg/dl)				
Mean ± SD	311.6 ± 109.5	368.0 ± 132.1	245.3 ± 44.0	0.356
Median	292.0	354.5	223.0	
LDL (mg/dl)				
Mean ± SD	181.6 ± 66.7	261.7 ± 118.5	202.0 ± 36.7	0.212
Median	178.0	238.5	210.0	
Triglyceride (mg/dl)				
Mean ± SD	241.1 ± 193.4	192.0 ± 106.2	211.0 ± 120.7	0.915
Median	176.0	187.5	220.0	
Total glomeruli				
Mean ± SD	29.1 ± 14.9	52.5 ± 20.6	16.7 ± 7.4	0.017[b]
Median	30	50	14	
Global sclerosis (%)				
Mean ± SD	10.2 ± 9.2	13.5 ± 4.4	18.3 ± 11.1	0.355
Median	8.0	12.5	14.0	
GTL (%)				
Mean ± SD	19.3 ± 15.0	28.2 ± 5.7	39.3 ± 52.5	0.358
Median	20.0	30.0	10.0	
Foamy cells in GTL, *n* (%)	5 (38.5)	4 (100)	1 (33.3)	0.081
Hyalinozis in GTL, *n* (%)	3 (23.1)	2 (50.0)	1 (33.3)	0.584
Mesangial proliferation, *n* (%)	6 (46.2)	2 (50.0)	1 (33.3)	0.822
IF/TA, *n* (%)	3 (23.1)	1 (25.0)	1 (33.3)	0.241
Arteriolar hyalinozis, *n* (%)	3 (23.1)	1 (25.0)	2 (66.7)	0.322
Arterial intimal fibrosis, *n* (%)	7 (54.8)	3 (75.0)	2 (66.7)	0.728

Notes: [a]Pearson chi-square; [b]One-way ANOVA.
IF/TA, interstitial fibrosis/tubular atrophy.

noted in early studies[11,12] and FSGS appears one of the most common causes of end-stage renal disease among the glomerular lesions.[13] The prognosis of FSGS correlates with the severity and persistence of proteinuria. The initial treatment of primary FSGS, usually with corticosteroids, results in remission of proteinuria only in about 25% of patients.[14–16] Prolonged prednisone therapy (mean 9 months) in adults resulted in complete and partial remission rates of 33% and 29%, in observational and uncontrolled trials, respectively.[17] About 60% of patients with persistent nephrotic-range proteinuria progress to end-stage renal disease within 5–10 years.[18] In the FSGS trial sponsored by the NIH (FSGS-CT, NCT00135811), Gibson et al. have reported the results of the treatment in steroid-resistant patients. At the end of the 52-week treatment period, the incidence of complete and partial remissions was only 33% in the mycophenolate mofetil + dexamethasone group and only 46% in the cyclosporin A group.[19]

A morphological classification of primary FSGS has been recently proposed and generally well accepted among the nephropathologists.[3] The main rationale for the classification is to provide standard definitions as well as to bring therapeutic and prognostic insights. The schema comprises five histologic variants of FSGS: NOS, cellular FSGS, collapsing FSGS, perihilar FSGS and GTL. In this study, we have explored the clinicopathological characteristics and outcome of FSGS-GTL variant in a cohort of 20 adult patients.

Howie and Brewer were the first authors who described the tip lesion in adult patients.[20] They propose the term ''tip change'' for the structural alteration of the glomerular tuft and the term ''tip lesion'' for the combination of tip change and minimal change nephrotic syndrome.[21] Some studies have shown a poor response to treatment in FGGS-GTL with a course similar to classic FSGS.[8–10,17,22] But many others have reported excellent reaction to steroids, similar to that seen in minimal change disease.[5–7,23–25] Thomas et al.[5] stated that tip lesion FSGS had the highest rate of complete remission (50%) and the highest rate of renal survival at 3 and 5 years (both 76%) among all FSGS variants. Our series has

confirmed favorable prognosis in FSGS-GTL. Of our 20 patients, 85% achieved complete remission of nephrotic syndrome at a mean follow-up of 46 months and no one lost renal function. In parallel with favorable outcome, renal biopsies of our patients had mild chronic histologic features.

Although FSGS-GTL seems to have favorable outcome, yet there are cases with incomplete response to treatment. This has been 15% (3 out of 20) in our cohort. The only clinical parameter that predicts incomplete remission in our patients has been the detection of microscopic hematuria at the disease presentation. About 66.7% of cases with partial response have microscopic hematuria in comparison with 17.6% among the complete responders ($p = 0.045$). Prevalence of hematuria in patients showing relapse in the follow-up after complete recovery is also frequent (50%), however this does not reach statistical significance.

GTL varies morphologically although the common denominator is the segmental sclerosis at the tip portion of glomeruli. Some lesions of segmental sclerosis are cellular and contain numerous foamy histiocytes. Some of these may contain nonspecific hyaline protein insudates. Tip lesions in the others are reflected in the form of simple adhesion between capillary tuft and Bowman's capsule or adhesion(s) between podocytes and parietal epithelial cells or tubular cells. The morphologic variations of GTL in our series did not correlate with disease outcome. Lack of correlation with outcome is also true when ratio of GTL or globally sclerotic glomeruli, tubulointerstitial or vascular changes is taken into account as parameters.

Similar to minimal change disease, proteinuria or nephrotic syndrome may relapse in FSGS-GTL. This has occurred in our four patients among 17 complete responders (23.5%). Deeper hypoalbuminemia has predicted relapse in our cohort ($p = 0.037$). All of our patients who relapsed had serum albumin below 2 g/dL and this increased the risk of disease recurrence four times ($p = 0.045$). No other clinical or histological parameters have been associated with the potential of relapse of nephrotic syndrome.

The main drawback of our study is the small case number owing to the constraints of enrolling from a single clinic. This limits the conclusions about the group and may have underpowered the value of some variables that can be important to foresee the disease recurrence or partial response to treatment. Documentation of more cases with follow-up is warranted to confirm and extend our findings. Multicenter studies will be beneficial to uncover those factors that might predict the outcome better in this rare entity.

In conclusion, FSGS-tip variant is a favorable subtype among other FSGS forms. Immunosuppressive treatment with steroids that may or may not include cytotoxic agents will resolve proteinuria in the majority of cases. As usual FSGS is an important cause of renal dysfunction, accurate detection of this variant will bring appropriate therapeutic approach. Other intense treatment modalities such as plasma exchange and immunoabsorption can be taken into consideration in unresponsive rare patients.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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