Original Article

Morphological Sub-classification of Focal Segmental Glomerulosclerosis and Their Clinio-pathological Correlation: Experience From a Tertiary Care Centre

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ABSTRACT

Background: The word focal segmental glomerulosclerosis (FSGS) is used to describe the common morphologic pattern occurring due to various progressive renal diseases and also to describe the primary idiopathic lesion of FSGS. Here, we are documenting the distribution of various types of FSGS and associated morphological lesion in the renal biopsy which may help to define the underlying cause of FSGS

Methods: Total 47 cases of FSGS were retrieved from the archives and classified according to Agati's classification. Acid Fuchsin Orange G (AFOG) stain was done to look for immune deposits. Direct immunofluorescence (DIF) was done in few cases.

Result: FSGS - NOS (Not otherwise specified) was most common variant followed by perihilar and cellular variant. Focal segmental mesangial cell proliferation and GBM thickening were commonly found in NOS variant. Interstitial non caseating granulomas and mononuclear cell infiltrate admixed with neutrophils were more frequent in perihilar FSGS. Many cases earlier diagnosed as perihilar or tip lesion, latter turned out to be NOS variety on serial sections. AFOG stain revealed mesangial deposits in 70.22% cases, suggesting immunological aetiology of the disease instead of primary FSGS. DIF was performed in seven cases and all showed predominant IgM deposits in mesangium.

Conclusion: Typing of FSGS should be done on the serial sections, especially of tip lesion. Most of FSGS cases turned out to be secondary to other glomerular disease instead of idiopathic variant. So, FSGS appear to be a morphological descriptor of various chronic renal diseases instead of being a separate entity.

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Introduction

Focal segmental Glomerulosclerosis (FSGS) presents as proteinuria of mostly nephrotic range with hypertension, microscopic hematuria and progressive deterioration of renal function. In the beginning, it was considered to be a form of minimal change glomerlonethritis (MCGN) but later, it has been identified as a separate entity because it differed from MCGN due to greater steroid resistance and rapid progression to renal failure.[1] Histologically, it shows focal segmental scarring with obliteration of glomerular capillaries and deposits of IgM and C3 on direct immunofluorescence study. Electron microscopy shows stratification and effacement of foot process.[1,2] FSGS is seen in 10 to 15% cases of children as well as young adults with nephrotic syndrome, in the age range of 20 to 30 years and 40 to 60% patients develop end stage renal disease in a course of 10 to 20 years.[1-3]

FSGS may be Primary or secondary to various diseases like HIV infection, drugs, intravenous drug abuse, thrombosis, obesity, sickle cell disease, cyanotic congenital heart disease, Alport syndrome, hypoxic damage to kidney, reflux nephropathy, focal cortical necrosis and post nephrectomy.[4-6] Exact pathogenesis of secondary FSGS is not clear. But it seems to be due to structural and functional adaptation mediated by intrarenal vasodilatation, increased glomerular capillary pressure and plasma flow rate.[6] In familial FSGS, mutations or polymorphism of various genes encoding podocin (NPHS2), nephrin (NPHS1)[7,8], α actinin-4 (ACTN4) [9] and transient receptor potential cation channel subfamily C member 6 (TRPC6)[10-12]–and phospholipase CE1 (PLCE1)[13] are present. These genes encode podocyte specific proteins which are responsible for the normal function of podocytes. Non podocyte protein genes such as CD2 associated protein (CD2AP), Wilm's tumour gene (WT1), coenzyme Q2 (COQ2) and β4 integrins (ITG β4)[11,14] etc are also involved in familial FSGS. Of these, the NPHS2 gene mutation has been noticed in many familial and childhood FSGS who are resistant to steroids. None of our patients were sibling or progeny to each other which signified rarity of familial FSGS in our population.

D'Agati et al. proposed morphological classification of FSGS and have described 5 morphological subtypes of FSGS, named Not otherwise specified (NOS), perihilar, cellular, tip and collapsing variants. He also found distinct correlation among these subtypes with clinical and laboratory findings.[15] Here we are analysing 47 cases of FSGS and aim of this study is to know the incidence of various types of FSGS in our population. In addition, we also have tried to find out other histological and laboratory findings which may be associated with secondary FSGS (Secondary to chronic renal diseases).

Materials and Methods

A total of 47 cases were included in this study which were diagnosed in a period of 2 years between 18th June 2008 to 17th June 2010 .Cases were taken from outpatient as well inpatient division from the Department of Nephrology of our Institute and clinical findings were collected. All blood & urine related laboratory investigations were done by standard methods. Kidney biopsies were preserved in 10% buffered formalin for preparation of paraffin blocks. Thin serial sections of about 3 micron were cut from these blocks and three main stains including Hematoxylin and Eosin (H&E), Periodic acid schiffs (PAS) and Acid Fuchsin Orange G (AFOG) were performed. AFOG stain was done to see Immune deposits. In 7 cases, direct immunofluorescence (DIF) was also performed to see pattern and type of deposits. All the stains were done by methods described by Zolliger & Mihatsch et.al.[16]

Results

In our study, 31 patients (65.94%) were males and 16 patients (34.05%) were females. Age wise analysis showed that most patients were between the age ranges of 16 to 30 years. About 67.82% males and 68.75% females affected by FSGS were in the age group of 10 years to 30 years with a mean age of 20 years (Table-1).

Most common clinical manifestation was swelling of the face (72.34%) followed by lower limb edema (21.27%). Oliguria was seen in 16 patients (34.04%) and three patients (6.38%) complained of gross hematuria, 15 to 30 days prior to their first hospital visit. One patient presented with pain in bilateral knee joints along with photosensitivity & oral ulcer. Two patients (5.44%) had severe breathlessness along with edema of feet. The last three cases turned out to be cases of SLE after complete laboratory check up but histopathology of their renal biopsies showed features of FSGS. One patient had headache for several months and one patient had on & off burning micturition for several years. Two patients reported pain only in flank (Table-II).

Majority of the patients had nephrotic range proteinuria (68.08%) and others had non nephrotic range proteinuria (31.91%). Microscopic hematuria was present in 20 (42.85%) cases and leucocyturia was noted in around half (51.06%) of the patients. All the cases showed hyaline or granular casts in the urine. The biochemical findings revealed a rise in blood urea & serum creatnine in 29 cases (61.70%), anaemia in 33 cases (70.12%)(Table-III). Serum autoantibody analysis showed ANA to be positive in 3 cases and anti ds-DNA in 2 cases. These were clinically suspected to be SLE due to the associated features of malar rash, joint pains & breathlessness and finally diagnosed as SLE.

Table I: Age and sex distribution of FSGS

Age Groups (in Years)	No. Of Cases 'n' (%)	Males 'n' (%)	Females 'n' (%)
‹16	8 (17.02)	3 (9.67)	5 (31.25)
16-30	24 (51.06)	18 (58.05)	6 (37.5)
31-50	8 (17.02)	5 (16.12)	3(18.75)
›50	7 (14.86)	5 (16.12)	2 (12.5)

Table II : Clinical manifestations of FSGS

Symptoms	No. Of cases affected	Percentage
Facial Puffiness	34	72.34
Swelling of lower feet	10	21.27
Pain in knee joint, Photosensitivity, Oral ulcer	1	2.12
Breathlessness	2	4.24
Oliguria	16	34.04
Ascitis	1	2.12
Gross Hematuria	3	6.38
Pain in Flank	2	4.24
Fever	2	4.24
Frothy Urine	1	2.12
Headache	1	2.12
Burning Micturition	1	2.12

Table III: Important Urinary, Biochemical & Immunological findings in FSGS

Laboratory findings(n=47)	No. of cases involved (%)
Nephrotic range Proteinuria	32 (68.08)
Non-nephrotic range Proteinuria	15 (31.91)
Microscopic Hematuria	20 (42.85)
Increased leucocytes in urine	24 (51.06)
Hyaline and/or Granular casts	47(100)
Raised serum Creatinine & blood urea	29 (61.70)
Anaemia	33 (70.21)
ANA Positive	03 (6.38)
ds DNA Positive	02 (4.25)

Histopathological examination of kidney biopsies (Table-IV) revealed FSGS of NOS type (Figure 1a & 1b) in majority (65.95%) of the patients which showed segmental sclerosis in the perihilar, peripheral as well as in central areas. Next common type was the perihilar type (19.14%) where sclerosis was confined to the hilar region (Figure 2a & 2b) in more than 50 % of the involved glomeruli. This was followed by the cellular type (12.77%) where endocapillary proliferation was associated with segmental sclerosis (Figure 2d). The collapsing variant was very uncommon and was seen in only one case (2.12%). We could not find any pure tip variant of FSGS. Occasional tip type lesions were seen but all were associated with mixed perihilar and peripheral sclerosis hence all those were labelled as NOS type. Examination of serial sections of apparently perihilar, peripheral or a tip type lesion revealed mixed pattern of segmental sclerosis and hence was finally classified as NOS type. Age wise analysis showed that in all the age groups NOS variant was most common followed by perihilar and tip variant (Table-IV).

Focal mesangial cell proliferation was seen in 70.9% of NOS variety (Figure 1), 100% of the cellular variety (Figure 2d) and 11.11% of the perihilar variety. Focal GBM thickening was seen in only 29.03% cases of NOS

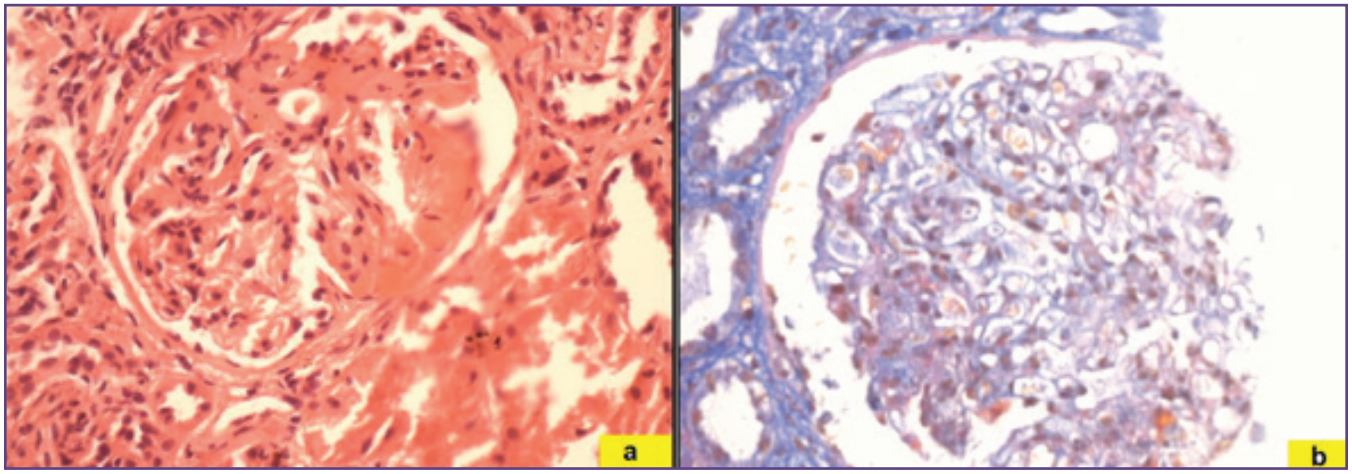

Fig. 1: NOS variant of FSGS:- Segmental sclerosis in perihilar, peripheral and central region along with hyalinosis in tip area. Focal mesangial proliferation is also noticed (Figure 1a, H&E X400). AFOG stain highlights sclerosis in various locations (Figure 1b, AFOG X400).

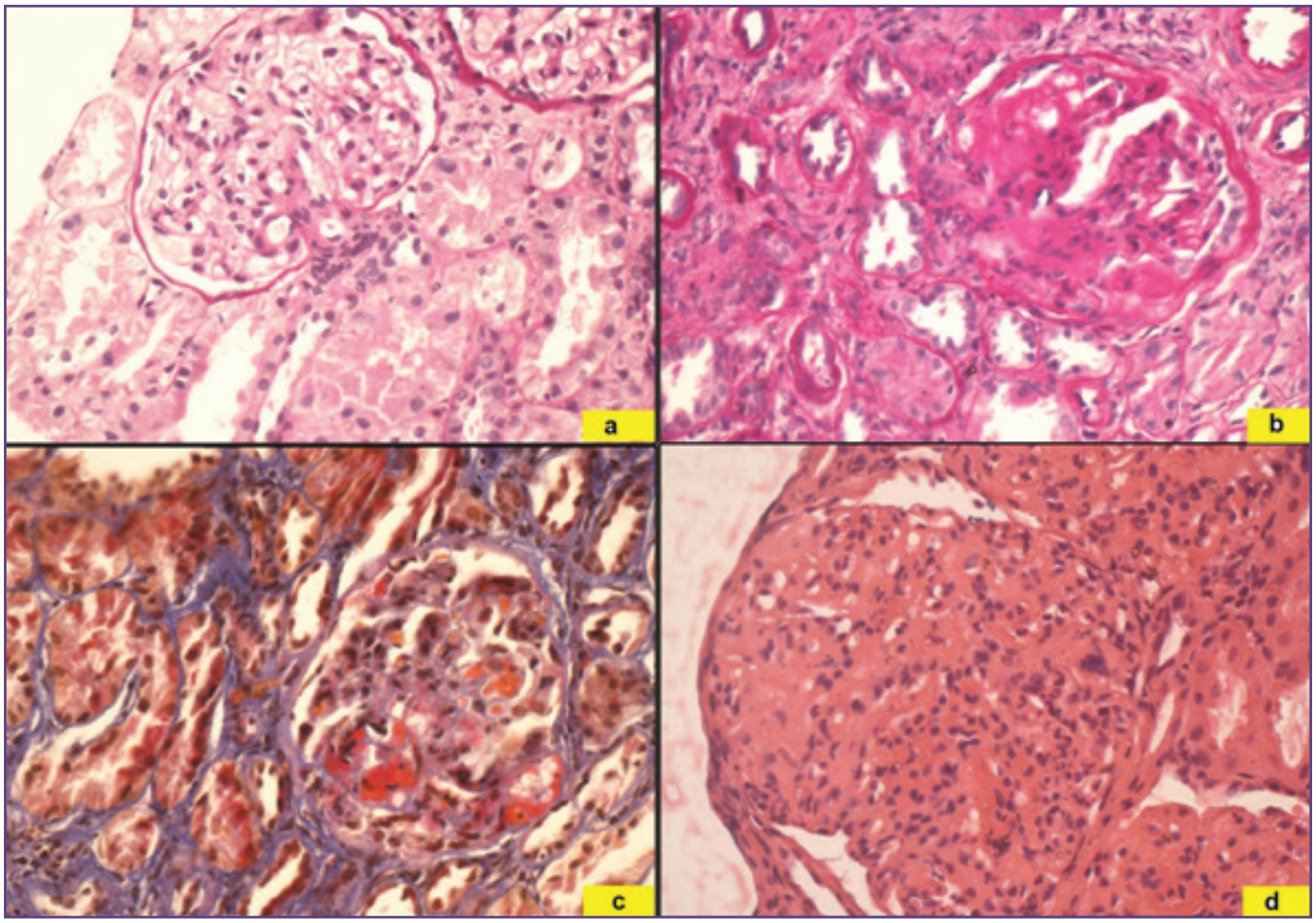

Fig. 2: Perihilar (a,b,c) & Cellular variant (d) of FSGS:- Segmental hyalinosis in perihilar area (Figure 2a, H&E,X400). One of the glomerulus showing moderate perihilar sclerosis along with tubular atrophy, interstitial mononuclear infiltrate and fibrosis (Figure 2b, H&E, X400). AFOG stain show deposits in sclerosed area and foam cells (Figure 2c, AFOG, X400). Cellular variant of FSGS show diffuse endocapillary proliferation and segmental sclerosis (Figure 2d, H&E, X400).

Table IV: Distribution of various types of FSGS in different age groups

AGE (IN YEARS)	TOTAL NUMBER OF CASES	TYPES OF FSGS							
		NOS		PERIHILAR		CELLULAR		COLLAPSING	
		No	%	No	%	No	%	No	%
<16	8	5	62.5	2	25	1	12.5	0	0
16-30	24	15	62.5	4	16.67	4	16.67	0	0
31-40	4	3	75.0	1	25.0	0	0	0	0
41-50	4	3	75.0	1	25.0	0	0	0	0
>51	7	5	71.43	1	14.29	1	14.29	0	0
	47	31	65.90	9	19.15	6	12.77	1	2.13

type. Hyaline thrombi in the capillary loops were seen in 33.33% cases of Perihilar type, 19.43% of NOS and 16.66% of cellular types respectively. Interstitial lymphoid aggregates were seen in 22.22% of perihilar type and 9.74% cases of NOS type. Non- caseating epithelioid cell granulomas were also seen in 8 cases (17.02%) and these were more common in Perihilar type (22.22%) followed by cellular (16.66%) and NOS (16.12%) types. Interstitial fibrosis was more common in perihilar type (77.77%, Figure 2b) followed by NOS type (61.21%) and cellular type (16.66%). Hyaline thickening of small & medium sized blood vessels were mostly seen in NOS (61.21%) and perihilar type (44.44%). Vasculitis was most commonly seen in NOS variant (12.88%)(Table-V).

AFOG stain showed red deposits in the mesangium in 33 cases (70.21%, Figure 2c). DIF was done in 7 cases only. Heavy IgM with weak C3 mesangial deposit in 4 cases and weak IgM & C3 mesangial deposit in 3 cases were noted. In addition, weak mesangial Ig A deposit in 4 cases, focal IgG deposit in 2 cases and scanty C4 deposit in 1 case were also identified.

Discussion

FSGS is a leading cause of nephrotic syndrome and histologically characterised by demonstration of segmental sclerosis in a glomerulus. FSGS could be either primary or secondary. Primary FSGS occur due to molecular defects in various genes, leading to disturbance in podocytic and non podocytic protein, [10-14] however exact pathogenesis of secondary FSGS is not fully understood. Ferrario et al. proposed that all the three intrinsic cells of glomerulus, like epithelial cells, mesangial cells and endothelial cells take part in sclerosis.[17] According to their hypothesis epithelial cells get hypertrophied and produce proteinuria as well as adhesions, and proliferated mesangial cells secrete more extracellular matrix (ECM) and decrease ECM catabolism which is responsible for glomerulosclerosis. An injury to the endothelial cell also leads to platelet and fibrin deposition and also stimulates mesangial cell proliferation with subsequent fibrous tissue formation.

Histologically, FSGS has been classified into five subtypes and there are various studies which have documented the incidence of the FSGS subtypes and their association with clinical features & prognosis. Similar to our study, Nada et al. also noted a male predominance in a ratio varying from 2.08:1 to 6:1 in various histological types of FSGS except perihilar variant where males and females were equally affected.[18] Das et al found nephrotic range proteinuria varying from 62.5% to 75% and hematuria ranging from 44.8% to 66% in various types of FSGS.[19] Almost similar to this, we also found nephrotic range proteinuria in 68.93% cases but microscopic hematuria was present in only 42.8% cases. None of the above two Indian studies mentioned about pyuria, while in present series 51.06% patients had pus cells in urine which was more than 6 per high power field. Some of the patients (10.63%) had even higher urinary pus cells up to 12/HPF.

In the present series, most common histological type of FSGS was NOS type (65.95%) followed by Perihilar (19.14%), Cellular (12.77%) and collapsing (2.12%) types. We did not find pure tip lesion variant since it was associated with NOS type of FSGS. Frequency of various types of FSGS varies in different reported series. Nada et al[18] from India found high frequency of NOS (72.5%) followed by tip lesion (13.5%), cellular variant (8%), Perihilar (4%) and collapsing (2%) in a study of 210 cases within a period of 4 years. Another study from India by Das et al[19] have reported a lower frequency with NOS type being 44.6% followed by Perihilar 24.6%, collapsing 13.8%, tip lesion 12.3% and cellular type 4.6%. Reports from other countries also showed almost similar findings. Shi et al, from China have found the NOS type being most common type which formed 55.9% cases. Interestingly, the tip lesion was next common type in their study with an incidence of 37% followed by cellular type 25.5%, Perihilar 69% and tip lesion 4.8%.[20]

Table V: Histological findings of Renal biopsies of FSGS

Types of FSGS (number of cases)	Glomeruli							Interstitium			Blood vessels			
	Mesangial proliferation (%)	Endocapillary proliferation (%)	Focal GBM thickning (%)	Crescents (%)	Hyaline clumps/ thrombi	Focal collapse	Periglomerular Fibrosis	Lymphoid Collection	Granulomas	Mononuclear cell infiltrate & Neutrophils	Focal fibrosis	Hyaline thickening	Fibromuscular hyperplasia	Vasculitis
NOS 31 (65.9)	22 (70.96)	–	9 (29.03)	–	6 (19.43) + 0	6 (19.34)	1 (3.22)	3 (9.74)	5 (16.12)	11 (35.48)	19 (61.21)	19 (61.21)	13 (41.27)	4 (12.88)
Perihilar 09(19.15)	1 (11.1)	–	–	1(11.1)	3 (33.33)	–	1 (11.11)	2 (22.22)	2 (22.22)	4 (44.44)	7 (77.77)	4 (44.44)	1 (11.11)	0
Cellular 06(12.77)	6 (100%)	6 (100%)		–	1 (16.66)	1 (16.66)	1 (16.66)	–	1 (16.66)	1 (16.66)	1 (16.66)	3 (50)	3 (50)	1 (16.66)
Collapsing 01(2.13)	0	0	0	–	0	0	0	0	0	1 (100)	0	1 (100)	0	0

Another study in African - American population has shown a predominance of NOS type of FSGS (44%) followed by cellular (32%) and Collapsing (24%) type. They did not find any cases of tip lesion or perihilar variant.[21] A multiethnic study done by two workers showed variable results. Strokes et al in their multiethnic study noticed that NOS type of FSGS to be more common (62.3%) followed by collapsing (23.7%), tip lesion (9.4%) and cellular (4.5%) variant. They did not find any case of Perihilar FSGS.[22] Contrary to it, another study done by Thomas et al in a multiethnic population found again higher prevalence of the NOS type followed by Perihilar (26%), tip lesion (17%) and collapsing (11%) type.[23]

Some of the very recent studies have shown more pronounced frequency of NOS type. A study of 291 cases have found NOS variety in 77 %, tip variety in 13.7%, perihilar in 4.8%, collapsing in 3.4% and cellular in 1%.[28] Like our study in their series most of the patients were also young adults with median age of 26 years and 25.4% patients were under 15 years of age.[24] In our study, 17% patients were below 16 years of age. A study conducted in Pakistan in children have shown again that 89% of FSGS is contributed by NOS type, 8% by collapsing type, 1.4% by tip variant, 0.7% by perihilar and 0.7% by cellular type.[25] Contrary to it, a study of 41 patients from Louisiana found low incidence of NOS (44%), followed by cellular (32%) and collapsing variant (24%).[21] Like us they also did not find any case of tip type of lesion.

Analysis of age wise distribution of various types of FSGS revealed that NOS variety was most frequent in all age group, followed by perihilar variant, but there was no significant variation in the frequency of various types of FSGS in different age groups. Like us, other study also did not find significant association of FSGS subtypes with age of the patients.[26] Contrary to it some worker found significant increase of NOS variety in children between 2 to 12 years.[27] These differences may be because of subjective interpretations. In our opinion, multiple serial sections needs to be examined because a perihilar or tip lesion present in single slide often turned out to be NOS type of FSGS due to appearance of other variants of FSGS on serial sections. Secondly, Agatie's classification system is not very clear about cellular type FSGS as similar lesion with endocapillary proliferation may be misdiagnosed as endocapillary GN in chronic phase rather than a pure cellular variety of FSGS.

In our study all cases had patchy mononuclear cell infiltration in which 23.40% had very severe inflammatory infiltrate in the interstitium. In addition, non-caseating epithelioid cell granulomas and neutrophil were also noted in 17.02% & 36.17% cases respectively. About 70.96% of glomerular lesions of NOS type and all the cases of cellular type revealed focal segmental mesangial cell proliferation. This may suggest that the glomerular lesions of FSGS in these cases are most likely due to sclerosis of proliferating lesions of chronic tubulo-interstitial nephritis which gives rise to secondary immune complex formation leading to focal mesangial cell proliferation and then scarring.

One of our earlier study (Usha et al, 2008) has found that about 10% renal biopsy shows mesangioproliferative GN[28] and other study have found that 20% biopsy diagnosed as MCGN show focal mesangial cell proliferation.[29] Probably these focal proliferative lesions got sclerosed and produce FSGS. Floege et al. proposed that glomerular cell proliferation and expression of platelet derived growth factor precedes FSGS.[30] Focal segmental mesangial cell proliferation is also found in IgM nephropathy. IgM and C3 have been demonstrated in segmentally sclerosed glomeruli of all types of FSGS by immunofluorescence study.[31,32] In present study, AFOG stain revealed mesangial deposits in

>70% cases and DIF showed IgM deposits in mesangium in all the seven cases.

Conclusion

Concluding our study, we found NOS type being most common variant of FSGS followed by perihilar in all the age groups. It is important to examine serial sections of each case before morphological subtyping of FSGS. There are various associated histopathological findings in different FSGS. In view of findings of various special stain including DIF, and interstitial inflammation, we may suggest that primary FSGS is not a distinct entity; instead it may be secondary to various chronic renal diseases like IgM nephropathy or mesangioproliferative GN or focal proliferative GN or may be secondary to chronic tubulointerstitial nephritis & pyelonephritis.

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Competing Interests

None declared

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