

# Focal segmental glomerulosclerosis in IgA nephropathy with regard to Oxford classification: Does it matter?

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## ■ ABSTRACT

**Background:** The lesions resembling focal segmental glomerulosclerosis (FSGS) are frequently found concurrently with IgA nephropathy (IgAN). However, there is controversy regarding the significance of this co-existence. In this study, we sought to determine the significance of FSGS-like lesions in a group of IgAN patients, especially with regard to the Oxford classification. **Patients and Methods:** The FSGS lesions were typed according to the Columbia classification and correlated with clinico-pathological parameters including Oxford classification criteria. Individual lesions suggesting FSGS were also evaluated. IgAN lesions were classified according to the Oxford classification. **Results:** Of 114 patients, 80 (70.2 %) were male. The mean age of patients was  $37.7 \pm 13.6$  years. Of 35 patients with co-existent IgAN and FSGS, 50% had classic variant (not otherwise specified; NOS), 30% had tip and 20% perihilar variant of FSGS. None of the patients had collapsing or cellular variants. A significantly positive association of FSGS with M ( $p = 0.001$ ), S ( $p = 0.001$ ) and T ( $p = 0.001$ ) variables of Oxford classification was found. No significant difference of FSGS, hyalinosis, capsular adhesions and podocytopathy was found between males and females ( $p > 0.05$ ). However, a significantly positive association of proteinuria ( $p = 0.037$ ) and renal dysfunction ( $p = 0.026$ ) with podocytopathy, and of serum creatinine and renal dysfunction with the presence of FSGS ( $p = 0.027$ ,  $p = 0.001$ , respectively) was seen. **Conclusion:** In conclusion, the concurrence of FSGS-like lesions with IgAN is associated with the established poor clinical and pathological prognostic factors of this disease and the lesions appear to be of prognostic significance. The presence of such lesions should be sought diligently on renal biopsy examination.

**Key-Words:** Columbia classification focal segmental glomerulosclerosis; IgA nephropathy; Oxford classification; proteinuria; renal failure.

## INTRODUCTION

A nephropathy (IgAN) is a very common form of primary glomerulonephritis and occurs worldwide<sup>1-5</sup>. The reported frequency varies from 2 to 52% of all renal diseases in various studies from different parts of the world<sup>6-13</sup>. Morphological lesions resembling focal segmental glomerulosclerosis (FSGS) have been found concurrently with some of the primary glomerular diseases such as membranous glomerulopathy or IgAN<sup>14-16</sup>. Various pathologic processes, which affect the podocytes, lead to one of the histologic subtypes of FSGS<sup>15,19</sup>. According to the new Oxford classification of IgAN, segmental glomerulosclerosis is defined as a segmental increase in the mesangial matrix with obliteration of capillary lumens and/or adhesion of the tufts with Bowman's capsule (synchiae)<sup>19-22</sup>. There are mainly two mechanisms by which segmental sclerotic lesions develop. They may be secondary to an initial segmental proliferative or necrotizing lesion of a glomerular disease or these may be a primary disease as a result of podocyte injury, termed podocytopathy<sup>14-18</sup>. Segmental glomerulosclerosis (S) is also a morphologic variable included in the Oxford classification developed for IgAN, and is an adverse prognostic indicator for this classification<sup>1-5</sup>. It is well known that lesions morphologically identical with FSGS may appear in IgAN too<sup>15-18</sup>. However, there is controversy regarding the significance of this co-existence, and whether this concurrence is the result of two primary renal disorders occurring simultaneously or FSGS represents a "final common pathway" in the evolution of IgAN<sup>18-22</sup>. Indeed, some studies suggest that FSGS is secondary to another glomerular injury and/or hypertension in the background of IgAN, or alternatively, they are both due to primary podocyte injury<sup>19-23</sup>. It was shown that loss of podocytes with denudation of the underlying glomerular basement membrane (GBM) is followed by an adhesion to Bowman's capsule and, thus, the formation of a sclerotic lesion<sup>14,15</sup>. In various cases of primary FSGS, there is evidence for a circulating toxin that damages the podocytes, while in other settings the podocyte damage may be secondary to haemodynamic changes as a response to loss of functioning nephrons<sup>14-18</sup>. In the Oxford classification of IgAN, the presence of S lesion was one of the four morphologic variables that were found to predict an adverse outcome. The other variables consisted of mesangial hypercellularity (M), endocapillary hypercellularity (E), and tubular

atrophy/interstitial fibrosis (T)<sup>2-5, 17-26</sup>. In this study, we sought to study the significance of sclerotic lesions resembling idiopathic FSGS in a group of IgAN patients. We secondly aimed to find the association of FSGS lesions with morphologic variables of Oxford classification in our patients.

## PATIENTS AND METHODS

After publication of the Oxford classification of IgAN, in 2009<sup>25, 26</sup>, we applied it in this study for the classification of IgAN.

### Definition of IgAN

The pathologic diagnosis of IgAN requires the demonstration of IgA-dominant mesangial or mesangial-capillary immune deposits through immunofluorescence (IF) microscopy. The immune deposits were semi-quantitatively assessed as 0 to 3+ positive bright. The definition of IgAN needs the presence of diffuse and global IgA deposits that are more than trace in positivity<sup>26-29</sup>. The renal biopsies from July 2009 to July 2012 were sent to a reference laboratory. None of the patients was treated before the biopsy. Biopsies with less than 8 glomeruli were excluded from the study. None of the patients was diagnosed as primary IgAN, having history of collagen vascular diseases, diabetes and liver cirrhosis, based on a questionnaire filled at the time of biopsy admission, laboratory data in patients' records and a brief history provided by referee physicians at the time of biopsy admission. The study was approved by the institutional ethical review committee and written informed consent was obtained from all patients at the time of biopsy. Strict adherence to Declaration of Helsinki was observed during the study.

### Histologic data

All kidney biopsies were prepared for light and direct IF microscopy. Tissue was fixed in 10% formalin for histologic sectioning. Each renal biopsy was prepared by cutting paraffin blocks into 3  $\mu$ m sections and staining 2 slides with periodic acid-Schiff (PAS), 2 slides for haematoxylin and eosin (HE), 1 slide for Jones methenamine silver (JMS) and 1 slide for

trichrome. Each slide contained 2-3 sections. Materials used for IF were snap-frozen in liquid nitrogen. Sections (6 $\mu$ m in thickness) were stained for IF study with fluorescein isothiocyanate (FITC)-conjugated antibodies specific for human IgG, IgM, IgA, C1q, C3 and fibrin (DAKO, Produktionsvej 42, DK-2600 Glostrup, Denmark)<sup>26-29</sup>. IF slides were reported in a scale of 0 to 3+ intensity. IF review was performed without information on patients' data and before reviewing the slides for light microscopy. After IF diagnosis of IgAN, histopathology glass slides were reviewed to define the morphologic variables, which were applied in Oxford-MEST classification method. We also assessed the presence of other individual glomerular lesions commonly found in IgAN, such as extracapillary proliferation (cellular, fibro-cellular or fibrous crescents) or segmental glomerular necrosis. All slides were reported by a single nephropathologist (HN), thus ensuring consistency of the results. Tissue for electron microscopy (EM) was saved for future study. EM analysis was not performed in this study.

### ■ Definitions of morphologic variables of IgA nephropathy; MEST (Oxford classification)

Total number of glomeruli and the number of glomeruli with global sclerosis were recorded for each biopsy. The presence of mesangial hypercellularity (**M**), endocapillary proliferation (**E**), segmental glomerulosclerosis (**S**) and the proportion of tubular atrophy and interstitial fibrosis; IF/TA (**T**) were estimated as published for Oxford-MEST classification<sup>25,26</sup>.

### ■ Definitions of Variants of FSGS

These were adapted from the Columbia classification of FSGS with some modifications as proposed by El Karoui *et al.*<sup>17, 22</sup>. Briefly, the presence of mesangial sclerosis accompanied by podocyte hyperplasia/hypertrophy and intracapillary hyalinosis was assumed as the presence of classic variant of FSGS (not otherwise specified, NOS)<sup>14-23</sup>, as illustrated in Fig. 1. Note that this definition of FSGS is not synonymous with the "S" variable of Oxford classification, as described in detail in the figure legend. For the cellular variant also the presence of podocyte alterations was considered mandatory for the

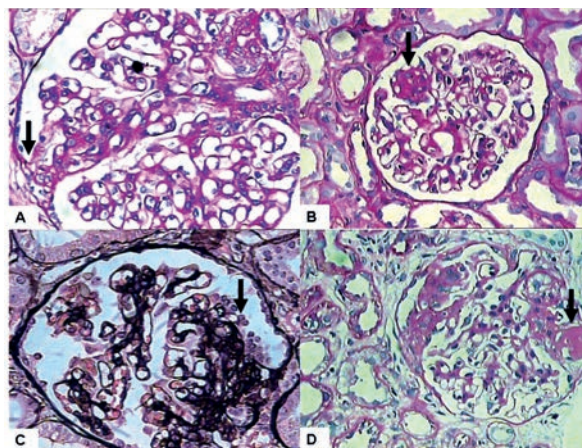
diagnosis in the context of IgAN. For other three variants of FSGS (perihilar, collapsing and tip variants), the definitions of Columbia classification for FSGS were applied directly<sup>17, 22</sup>. Also, we studied the presence of individual histological features suggesting FSGS, such as intracapillary hyalinosis, tuft-capsule adhesion (synechia), presence of podocytic hyperplasia/hypertrophy and/or podocytic capping<sup>14-23</sup> separately from FSGS variants and correlated these with various clinicopathological parameters.

### ■ Clinical Studies and Laboratory Data

The medical records of patients were reviewed to obtain various demographic, clinical and laboratory information at the time of biopsy. Data gathered at

**Figure 1**

Defining morphological features adapted for segmental glomerulosclerosis of Oxford classification and focal segmental glomerulosclerosis (FSGS) of Columbia classification. A. This glomerulus shows segmental adhesion formation (arrow) without any significant abnormality in the underlying tuft. Although this lesion is classified as segmental glomerulosclerosis in Oxford classification, we did not include it as a lesion resembling primary FSGS. (PAS,  $\times 400$ ) B. Another glomerulus showing segmental mesangial sclerosis (arrow) without any intracapillary hyalinosis or podocyte hypertrophy and/or hyperplasia. According to Oxford classification, this lesion also merits classification as segmental glomerulosclerosis, but not according to the Columbia classification. (PAS,  $\times 400$ ) C. This glomerulus shows segmental glomerulosclerosis associated with podocyte hyperplasia and hypertrophy (arrow). We have included cases showing such lesions as representing FSGS in IgA nephropathy (IgAN). (Silver stain,  $\times 400$ ) D. This glomerulus shows segmental glomerulosclerosis associated with intracapillary hyalinosis (arrow). We have included these lesions as representing FSGS in IgAN. (PAS,  $\times 400$ ).



the time of biopsy included gender, age, serum creatinine and proteinuria (based on a 24-hour urine collection). Renal dysfunction at the time of biopsy was defined as serum creatinine  $> 1.2$  mg/dl in females and  $> 1.4$  mg/dl in males.

## Statistical analysis

Results for categorical variables were expressed as numerical values and percentages. Continuous variables were expressed as mean or median values and standard deviations, and statistical significance of the differences between groups was calculated using independent-samples T test, Mann-Whitney U test and Chi-square tests depending on the nature of variables. A computer program (SPSS version 16.0, Chicago, IL, USA) was used for statistical analysis.  $P < 0.05$  was considered statistically significant.

## RESULTS

This is an observational study, conducted on IgAN patients. A total of 114 biopsies were enrolled to the study. In this survey of 114 patients, 80 (70.2 %) were male. The mean age of all patients was  $37.7 \pm 13.6$  years (for males,  $39 \pm 14.3$  years and for females,  $35 \pm 11.7$  years). The main demographic, clinical and laboratory features of this cohort are summarized in Table 1. The mean value of proteinuria was  $1.74 \pm 1.32$  g/day (median = 1.5 g/day). The mean of serum creatinine was  $1.6 \pm 1.5$  mg/dL (median = 1.2 mg/dL). Renal insufficiency at the time of biopsy

**Table 1**

Patient demographics, clinical and laboratory findings in all patients of IgA nephropathy at the time of biopsy.

Total number of patients	114
Males, n (%)	80 (70.2)
Females, n (%)	34 (29.8)
M:F ratio	2.3:1
Age, mean $\pm$ SD (years)	$37.7 \pm 13.6$
Serum creatinine, mean $\pm$ SD (mg/dl)	$1.6 \pm 1.5$
Proteinuria, mean $\pm$ SD (g/24 hours)	$1.74 \pm 1.32$
Renal dysfunction, n (%)	43 (37.7)
Males, n (%)	39 (90.6)
Females, n (%)	4 (9.3)

was quite common, found in 37.7% of cases. The majority of cases (90.6%) occurred in males.

The mean number of total glomeruli in all renal biopsies was  $14.8 \pm 7.2$ . The mean number of globally sclerosed glomeruli was  $2.4 \pm 2.9$  (median = 1). The segmental glomerulosclerosis (S) as a morphologic variable of MEST classification was present in 72 (63.2%) patients, but the segmental sclerotic lesion in favour of FSGS was found in 35 (30.7%) patients. Of 35 patients with co-existence of IgAN and FSGS, 50% were classic variant (not otherwise specified; NOS), 30% had tip variant and 20% the perihilar variant of FSGS. None of the patients had collapsing or cellular variants of FSGS. A correlation of various demographic, clinical, laboratory and the MEST variables with the presence of FSGS is presented in Table 2. Regarding individual histological lesions that suggest FSGS, segmental glomerulosclerosis was found in 72 (63.2%) patients, synechiae formation in 71 (63.3%) patients, and some form of podocytopathy in 18 (15.8%) patients. We also found intracapillary hyalinosis in 13 (11.4 %) patients. The association of these individual lesions of segmental glomerulosclerosis, intracapillary hyalinosis, tuft-capsule adhesion and podocytopathy with FSGS is summarized in Table 3. All of these except podocytopathy correlated strongly with the presence of FSGS ( $p = 0.001$ ). Finally, a correlation of these four features with some demographic, clinical and laboratory features is shown in Table 4. In this study, no significant difference of FSGS, intracapillary hyalinosis, tuft-capsule adhesion and podocytopathy was found between males and females ( $p > 0.05$ ). However, a significantly positive association of podocytopathy with proteinuria ( $p = 0.037$ ) and renal dysfunction ( $p = 0.026$ ), and of serum creatinine and renal dysfunction with the presence of FSGS ( $p = 0.027$ ,  $p = 0.001$ , respectively) was seen. In this study also, a significant positive association of FSGS with M ( $p = 0.001$ ), S ( $p = 0.001$ ) and T ( $p = 0.001$ ) variables of Oxford classification was also found. No significant association of FSGS with E variable of Oxford classification was seen ( $p = 0.061$ ).

## Amyloid Type Identification

According to immunohistochemical identification, the most prevalent type of amyloidosis was AA, corresponding to more than half of the patients

**Table II**

A comparison of some demographic, clinical, laboratory and pathological variables of Oxford classification among focal segmental glomerulosclerosis (FSGS) positive and FSGS negative subgroups of IgA nephropathy.

Parameters	FSGS + (n = 35)	FSGS - (n = 79)	p - value
Demographic and laboratory variables			
Age (years)	36.7 ± 13	38.16 ± 3.8	0.61
Gender (M/F)	25/10	55/24	0.84
Proteinuria (g/d)	1.99 ± 1.37	1.63 ± 1.29	0.17
Serum creatinine (mg/dL)	2.24 ± 2.26	1.33 ± 0.94	0.02
Renal dysfunction, %	60	27.8	0.001
Oxford variables, n (%)			
Mesangial hypercellularity			
M0	5 (14.3)	36 (45.6)	0.001
M1	30 (85.7)	43 (54.4)	
Endocapillary hypercellularity			
E0	20 (57.1)	59 (47.7)	0.06
E1	15 (42.9)	20 (25.3)	
Segmental glomerulosclerosis			
S0	3 (8.6)	39 (49.4)	0.001
S1	32 (91.4)	40 (50.6)	
Tubular atrophy/interstitial fibrosis			
T0	8 (22.9)	51 (64.6)	0.001
T1	12 (34.3)	23 (29.1)	
T2	15 (42.9)	5 (6.3)	

(58.8%, n = 60), followed by AL in about one fifth (20.6%, n = 21). The ratio AA/AL was 2.9 to 1. The subtype of light chain in AL amyloidosis was  $\lambda$  in two thirds of patients. Two different types of amyloid deposits – light chain  $\lambda$  and serum amyloid A – were present in one patient. Immunostaining disclosed a predominant pattern for light chain  $\lambda$  deposition and small patchy deposits for serum amyloid A at different sites. AFib was the most frequent type of hereditary amyloidosis contributing to 3.9% (n = 4) of the cases. ATTR was identified in two (2.0%) patients, AApoAI in one (1.0%), and ALys in one (1.0%). The type of amyloidosis remained unclassified in 12 (11.7%) patients, mostly due to negative immunohistochemistry.

### Hereditary Forms and their Amyloidogenic Variants

Molecular diagnosis of hereditary forms disclosed the point mutations *FGA* p.Glu545Val in all AFib cases and *TTR* p.Met51Val in the two cases of ATTR. Sudden death of the ALys positive patient did not allow genetic study. In the AApoAI case pathogenic changes were not detected in the encoding region (exons 2 to 4) and exon-intron respective transitions of the *APOA1* gene.

### Underlying Disease

In our series, systemic AA amyloidosis patients showed mainly chronic infectious complications of

**Table III**

A comparison of some individual histopathological features suggestive of focal segmental glomerulosclerosis (FSGS) among FSGS positive and FSGS negative subgroups of IgA nephropathy.

Parameters	FSGS + (n = 35)		FSGS - (n = 79)		p - value
	Present	Absent	Present	Absent	
Hyalinosis	12 (34.3)	23 (65.7)	1 (1.3)	78 (98.7)	0.000
Synechiae	31 (88.6)	4 (11.4)	40 (50.6)	39 (49.4)	0.000
Podocytopathy	9 (25.7)	26 (74.3)	9 (11.4)	70 (88.6)	0.053
Segmental sclerosis*	32 (91.4)	3 (8.6)	40 (50.6)	39 (49.4)	0.000

\*This refers to the S variable of Oxford classification.



**Table IV**

A comparison of some demographic, laboratory and clinical features among some of the individual histological lesions which suggest a diagnosis of focal segmental glomerulosclerosis (FSGS).

	Segmental sclerosis*			Tuft capsule adhesion		
	Present	Absent	p – value	Present	Absent	p – value
	72 patients	42 patients		71 patients	43 patients	
Age (years)	37.8 ± 12.4	37.61 ± 15.8	0.944	37.3 ± 12.9	38.4 ± 14.9	0.691
Gender (M/F)	57/15	23/19	0.006	50/21	30/13	0.941
Proteinuria (g/d)	1.86 ± 1.36	1.53 ± 1.24	0.211	1.72 ± 1.14	1.77 ± 1.6	0.849
Serum creatinine (mg/dL)	1.92 ± 1.83	1.07 ± 0.40	0.004	1.71 ± 1.67	1.43 ± 1.26	0.348
Renal dysfunction, n (%)	37 (51.4)	6 (14.3)	0.001	33 (46.5)	10 (23.3)	0.014
	Podocytopathy			Intracapillary hyalinosis		
	Present	Absent	p – value	Present	Absent	p – value
	18 patients	96 patients		13 patients	101 patients	
Age, mean±SD (years)	38.44 ± 16.54	37.6 ± 13.15	0.812	33.07 ± 8.11	38.33 ± 14.14	0.193
Gender (M/F)	14/4*	66/30	0.444	9/4*	71/30	0.937
Proteinuria (g/d)	2.54 ± 1.73	1.6 ± 1.18	0.037	2.32 ± 1.55	1.66 ± 1.28	0.092
Serum creatinine (mg/dL)	2.6 ± 2.6	1.42 ± 1.0	0.115	1.66 ± 0.85	1.6 ± 1.6	0.902
Renal dysfunction, n (%)	11 (61.1)	32 (33.3)	0.026	7 (53.8)	36 (35.6)	0.204

\*This refers to the S variable of Oxford classification.

pulmonary tuberculosis (Table III). A familial AA associated to Muckle-Wells syndrome was unequivocal in one patient. AL amyloidosis was related to monoclonal gammopathy of undetermined significance (MGUS) in 10 (47.6%) and multiple myeloma in eight (38.1%) patients, whereas the diagnosis was unknown in three (14.3%). The combined AL and AA amyloidosis patient had multiple myeloma light chain lambda and a previous history of syphilis. One of the four patients with AFib and the AApoAI patient also had MGUS. The ALys patient had rheumatoid arthritis.

### ■ Clinical Findings at Kidney Biopsy

The clinical features at kidney biopsy are listed in Table II. The 102 patients included 51 (50.0%) females and 51 (50.0%) males. The mean age at time of kidney biopsy for the entire group was 53.3 ± 14.9 years. AA patients were younger and had a better renal function than AL and AFib. CKD-EPI estimated glomerular filtration rate was 62.5 ± 43.9 mL/min./1.73m<sup>2</sup> for AA, 51.7 ± 34.6 mL/min./1.73m<sup>2</sup> for AL and 29.4 ± 22.8 mL/min./1.73m<sup>2</sup> for AFib patients. Nephrotic syndrome was the first sign of renal involvement in 83 (81.4%) patients with a similar frequency for all types of amyloidosis. The presence of hypertension was associated with AFib (100% for AFib, 38.1% for AL and 35% for AA).

The mean age of the patients at diagnosis of the underlying disorder was 36 ± 20 years for AA (data available for 53 patients) and 63 ± 9 years for AL (data available for 18 patients). The mean duration between the onset of the underlying disorder and the diagnosis of AA amyloidosis (data available for 53 patients) was 13.9 ± 12.3 years and for AL amyloidosis (data available for 18 patients) was 1.4 ± 1.5 years.

### ■ DISCUSSION

Focal segmental glomerulosclerosis is one of the common histopathological patterns underlying idiopathic nephrotic syndrome (INS), which initially affects a part of some but not all glomeruli associated with the tubulointerstitial and vascular damage of the kidney<sup>15-18</sup>. It is not a specific disease entity but rather represents a descriptive morphological diagnosis. The clinical diversity and varied histologic features of FSGS contribute to the complex nature of the lesion<sup>15-23</sup>. Lesions morphologically identical to idiopathic FSGS have been found in association with other primary glomerulopathies, such as membranous nephropathy and IgAN. Some authors have suggested that FSGS serves as a “final common pathway” in the evolution of other primary glomerular

diseases. Still others think that IgAN may be better considered as a variant of FSGS<sup>22</sup>. The co-existence of IgAN with FSGS has been found to have an adverse effect on the outcome of IgAN<sup>30-34</sup>. Histologically, FSGS-like IgAN has at most a mild increase in mesangial hypercellularity and can only be distinguished from primary FSGS on the basis of diffuse mesangial IgA deposits on IF. In the case of co-existence of IgAN and FSGS, some other morphologic variables like podocytopathy (podocytic cobblestoning or podocytic capping) or intracapillary hyalinosis could suggest the presence of FSGS in addition to IgAN<sup>16-23</sup>. The lesions of FSGS may occur in pure form or be superimposed by other glomerular lesions, such as segmental necrosis, and/or extracapillary proliferation. Patients with pure FSGS have been shown to have relatively poor survival even without other superimposed glomerular lesions<sup>19-23</sup>. However, there is scant data in published literature regarding the significance of FSGS-like lesions in the setting of IgAN.

This study is an attempt to determine the significance of FSGS-like lesions in a cohort of IgAN patients of racially uniform population of Iran. Of four morphologic variables of Oxford classification, three (M, S and T) had significantly positive association with the presence of FSGS ( $p = 0.001$  each), while E variable had also a partially positive association ( $p = 0.06$ ). Regarding individual lesions, the lesions of podocytopathy showed significant association with all four morphological variables (MEST) of Oxford classification. Furthermore, intracapillary hyalinosis had significantly positive association with T variable of IgAN classification. Regarding clinical and laboratory parameters, there was no significant difference of age, gender and proteinuria between FSGS+ and FSGS- subgroups of IgAN. Serum creatinine at presentation was significantly higher in the FSGS+ group and renal dysfunction was also significantly more common in the former subgroup as compared with the FSGS- group. We found a significantly positive association of proteinuria and renal dysfunction with podocytopathy.

A few investigators have previously attempted to determine the prognostic value of lesions of FSGS in IgAN patients. To find the significance of FSGS in mild IgAN, renal biopsies performed, between 1996 and 2005, in adults with a diagnosis of IgAN were reviewed by Weber *et al.*<sup>16</sup>. A total of seventy-five

patients, 26 (35%) with IgAN and FSGS (FSGS+ group) and 49 (65%) with IgAN without FSGS (FSGS- group) were included in the study. At the time of the renal biopsy, the FSGS+ group had a lower estimated glomerular filtration rate (eGFR), lower serum albumin, higher mean arterial pressure and greater protein excretion than the FSGS- group. On histology, the FSGS+ group had a higher percentage of totally sclerosed glomeruli and 31% of FSGS+ biopsies had  $\geq 25\%$  IFTA, while this was not observed in the FSGS- group. They concluded that, FSGS lesion and associated clinical and pathologic findings in patients with mild IgAN are associated with a worse renal outcome<sup>16</sup>. In the studies conducted by El Karoui *et al.* on a cohort of 128 adult patients with IgAN, some form of lesion consistent with FSGS, notably hyalinosis and collapsing glomerulopathy (CG) was found in 101 of their patients<sup>22</sup>. Those with FSGS had significantly worse renal survival at 80 months than those without. Comparison of pure forms of FSGS (excluding CG) with cases of FSGS having other glomerular lesions (mesangial hyperplasia, endocapillary hypercellularity, glomerular necroses, extracapillary proliferation) revealed that those with FSGS and other superimposed lesions did significantly worse than cases of pure FSGS<sup>22</sup>.

Our findings broadly support the findings of the previous studies but are not entirely concordant with those reported by El Karoui *et al.*<sup>22</sup>. In our study of 112 biopsies of IgAN, 35 patients had lesions typical of FSGS (*versus* 101/128 in the study by El Karoui *et al.*). Also none of our biopsies had lesions in favour of collapsing or cellular variants of FSGS. Moreover, intracapillary hyalinosis and podocytopathy were found in 11.4% and 15.5% of our biopsies, respectively. El Karoui *et al.* concluded that, the majority of cases of IgAN can be interpreted as representing one or another variant of FSGS<sup>22</sup>. They also concluded that interpreting IgAN in terms of FSGS emphasizes the role that podocyte lesions may play in the pathogenesis and progression of this disease<sup>22</sup>. Indeed, a remarkably high number of their patients, 101 of the total 128, had lesions termed 'consistent with FSGS', classified by this group as hyalinosis and CG<sup>22, 23</sup>. These differences may be due to variations in the presentation of IgAN around the world, possibly due to ethnic factors<sup>1-6</sup>. It is possible that, there are at least three ways by which segmental glomerulosclerosis may occur in the glomeruli in IgAN. First, by post-inflammatory scarring; second,

due to compensatory haemodynamic changes following nephron reduction, and finally by primary podocyte damage, perhaps due to mediators released from mesangial cells<sup>14-22, 24-36</sup>.

We believe that it is possible to distinguish objectively between the S variable of Oxford classification and the FSGS of the Columbia classification. Lesions of podocyte hypertrophy/hyperplasia and intracapillary hyalinosis favour the later over former and these should be looked for carefully when examining renal biopsies from patients with IgAN with segmental glomerular sclerosing lesions. We hypothesize that S variable of Oxford classification represents an early stage in the progression of glomerular lesions in IgAN and the FSGS lesion, the more advanced stage, which finally culminates in diffuse chronic sclerosing glomerulonephritis (GN) and end-stage renal disease (ESRD). We believe that the lesions of FSGS, as defined herein and Columbia classification, represent the morphological markers of progression in IgAN. We are of the view that the lesions of FSGS do not represent idiopathic FSGS superimposed on IgAN as two separate but concurrent diseases, rather these represent a morphological indicators of impending nephron loss and development of progressive renal failure.

Our study has some limitations too. These include the origin of the study from a single centre in Iran, its retrospective nature and the lack of clinical outcome data. However, we are following this cohort of patients actively and we plan to study the correlation of the MEST variables and FSGS lesions with clinical outcome in the near future. On the other hand, there are many strong points in our study. These include a racially homogeneous study population, a fair number of patients in the study, no use of pre-biopsy immunosuppressive therapy and the reporting of all biopsies by a single nephropathologist, thus ensuring uniformity of the diagnostic criteria.

In conclusion, our findings firstly corroborate the previous studies regarding the prognostic significance of the presence of FSGS lesions in IgAN. Secondly, to the best of our knowledge, this represents the first report which studies the association of FSGS of Columbia classification with the MEST variables of Oxford classification. Our findings indicate that the presence of FSGS-like lesions in the

background of IgAN is associated with the established poor clinical and pathological prognostic factors of this disease and the lesions appear to be of prognostic significance. The presence of such lesions should be sought diligently on renal biopsy examination.

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