Focal segmental glomerulosclerosis plays a major role in the progression of IgA nephropathy. II. Light microscopic and clinical studies

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It is well known that lesions morphologically identical with focal segmental glomerulosclerosis (FSGS) may appear in IgA nephropathy (IgAN). Capsular adhesions without underlying abnormalities in the tuft, often the first sign of FSGS, are frequent in IgAN. In this retrospective study, a new cohort of 128 adult patients with IgAN was used to validate the new Oxford classification system of IgAN, and shown to have highly significant associations with clinical and outcome parameters. We then used these patients to determine the extent to which IgAN could be accounted for in terms of FSGS. Some form of lesion consistent with FSGS, notably hyalinosis and collapsing glomerulopathy, was found in 101 of these patients. No glomerular lesions were found in 16 patients, and 11 had mild lesions not definable as FSGS. Those with FSGS had significantly worse renal survival at 80 months than those without. Comparison of pure forms of FSGS (excluding collapsing glomerulopathy) 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 at 80 months following diagnosis. Importantly, patients with pure FSGS had relatively poor survival even without other superimposed glomerular abnormalities. Thus, the majority of cases of IgAN can be interpreted as representing one or another variant of FSGS. Hence, interpreting IgAN in terms of FSGS emphasizes the role that podocyte lesions may play in the pathogenesis and progression of this disease.

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From the time of its first description,[1,2] IgA nephropathy (IgAN) has been considered to be an immune complex disease, whose immunoglobulin moiety is now known to represent, in large part, mesangial and capillary wall deposits of an abnormal IgA1 with defects in its hinge region.[3–5] Much effort has been directed toward elucidating the mechanisms of interaction of the complexes with mesangial cells and the mechanisms of complement activation leading to mesangial and intracapillary proliferative lesions.[6–8] Our thinking has been molded in no small part by the often-striking resemblance of IgAN to the lesions of lupus nephritis, a prototypical immune complex disease.

However, it has long been known that lesions morphologically identical with focal segmental glomerulosclerosis (FSGS) may appear in IgAN,[3,9–13] and FSGS was included as a separate class in an earlier classification of IgAN.[10] FSGS is a histological pattern resulting from a variety of mechanisms, hereditary, infectious, toxic, and adaptive responses to reduced functioning renal mass.[14] All have in common damage to and/or loss of podocytes, thus qualifying as podocytopathies.

Several considerations prompted us to explore further, in a series of 128 patients, the question as to the extent to which the glomerular lesions in IgAN might be considered as representing the results of FSGS. First, in addition to the studies cited above, we found in preliminary analysis of our cases that nearly half had typical FSGS with hyalinosis or collapsing glomerulopathy. We were also struck, as others have been,[15–17] by the high frequency of glomerular capsular adhesions in IgAN, often accompanied by evident epithelial changes. Such adhesions are extremely common in FSGS, and Kriz[18,19] has referred to them as the 'first committed step' in FSGS. Finally, there is evidence for podocyte loss in IgAN, first in terms of the number of podocytes/glomerulus,[20] and second urinary loss of podocytes,[21] both of which correlate with disease progression. We indeed found that the majority of cases of IgAN can be interpreted as representing one or another of the variants of FSGS. This observation suggests

that the immune complexes of IgAN must be acting in a significant part on the podocytes, and evidence is beginning to accumulate as to the mechanisms by which IgA1 may exert its effects on podocytes.[22–27]

RESULTS

A total of 128 (87 males, 70.7%) were included in this retrospective study. There were 118 (92.2%) Caucasians, 10 (7.8%) Asians, and no blacks. Mean age was 38.7 years (range 18–78). Mean proteinuria was 2.43 g/day (s.e.m. 0.25), with only 6 patients presenting with no measurable proteinuria, and 97 patients (73.1%) having proteinuria >0.5 g/day. Renal insufficiency was frequent, with 73 patients (57%) presenting with serum creatinine (SCr) >120 μmol/l, of whom 35 had SCr >200 μmol/l. Mean glomerular filtration rate (GFR) was 52.1 ml/min per 1.73 m^2 (s.e.m. 2.9). All the patients except one (who was pregnant) received angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, or both for hypertension and/or persistent proteinuria. Only one patient had received corticosteroid therapy during the 6 months before diagnosis, and none had steroid therapy subsequent to diagnosis. No patient had other immunosuppressive therapy, either before or subsequent to diagnosis.

Morphologic lesions and clinical correlations
Morphologic lesions will be discussed first in terms of the new Oxford classification[15,16] and of immunofluorescence results. Following this, they will be described in terms of their interpretation as lesions of FSGS.

Oxford classification
The four Oxford criteria[15,16] (Table 1) were analyzed in our material and all were found to correlate extremely well with clinical and outcome parameters (Table 2). Several comments about each should be made.

Mesangial hypercellularity. Using the criterion of ≥4 nuclei/glomerular lobule as indicative of hypercellularity, we found 42 patients with mesangial hypercellularity in >50% of glomeruli (Figure 1a). However, mesangial hypercellularity occurred almost exclusively in the context of lesions interpretable as FSGS (40/42 cases), particularly FSGS with hyalinosis (22 cases).

Segmental glomerulosclerosis. Segmental glomerulosclerosis as used in the Oxford classification includes all segmental scars, including capsular adhesions in this category. The term should not be taken as synonymous with FSGS, for it also includes scars of indeterminate origin (see below and Figure 2). It occurred to some degree in 91 (72.8%) patients, a percentage similar to that in the Oxford study (76%; Figure 1b).

Endocapillary lesions. Endocapillary lesions with obstruction of capillary lumens by infiltrating cells, generally focal in distribution, were found in 31 patients (24.7%; Figure 1c). Once again, 29/31 examples occurred in a context interpretable

Table 1 | Definitions of Oxford criteria for IgA nephropathy and of the Columbia classification of FSGS as applied to IgA nephropathy

Oxford criteria for IgA nephropathy

Term	Definition
Mesangial hypercellularity	>4 to 5 mesangial cells/mesangial area in >50% of glomeruli
Segmental glomerulosclerosis	Any amount of the tuft involved in sclerosis, but not involving the entire tuft or the presence of an adhesion, in ≥1 more glomeruli
Endocapillary hypercellularity	Hypercellularity due to increased number of cells within glomerular capillary lumina causing narrowing of the lumina, segmental or diffuse in at least one glomerulus, graded as present/absent from biopsy
Tubular atrophy/Interstitial fibrosis	Percentage of cortical area involved by tubular atrophy or interstitial fibrosis, whichever is greater T0, 0–25%; T1, 26–50%; T2, >50%[a]

Columbia classification of FSGS in the context of IgA nephropathy

Variant	Inclusion criteria	Exclusion criteria
FSGS, NOS	At least 1 glomerulus with segmental increase in matrix obliterating the capillary lumina, or segmental glomerular capillary collapse, *associated with hyalinosis lesions and/or epithelial hypertrophy/hyperplasia*[b]	Exclude perihilar, cellular, tip, and collapsing variants
Perihilar variant	At least one glomerulus with perihilar hyalinosis, with or without sclerosis. >50% of glomeruli with segmental lesions must have perihilar sclerosis and/or hyalinosis	Exclude cellular, tip, and collapsing variants
Cellular variant	At least one glomerulus with segmental endocapillary hypercellularity occluding lumina, with or without foam cells and karyorrhexis, *with hyperplasia of overlying epithelium*[c]	Exclude tip and collapsing variants
Tip variant	At least one segmental lesion involving the tip domain (outer 25% of tuft next to origin of proximal tubule). The tubular pole must be identified in the defining lesion. The lesion must have either an adhesion or confluence of podocytes with parietal or tubular cells at the tubular lumen or neck. Tip lesion may be cellular or sclerosing	Exclude collapsing variant and any perihilar sclerosis
Collapsing variant	At least 1 glomerulus with segmental or global collapse and overlying podocyte hypertrophy and hyperplasia	None

Abbreviations: FSGS, focal segmental glomerulosclerosis; NOS, not otherwise specified.
[a]T-grades used only in Table 1. In other analyses, the actual percentages of tubular atrophy/interstial fibrosis are used.
[b]Added to exclude segmental scars of possible non-FSGS origin.
[c]Added to exclude endocapillary hypercellularity of possible non-FSGS origin.

Table 2 | Evaluation of variables of Oxford classification in terms of clinical parameters

	Mesangial hypercellularity			Segmental glomerulosclerosis		
	Present	Absent	*P*-value	Present	Absent	*P*-value
	42 patients	82 patients		105 patients	47 patients	
Systolic BP$_{dx}$	150 (135–170)	133 (120–150)	0.0004	144 (129–164)	125 (120–137)	0.006
Diastolic BP$_{dx}$	90 (80–102)	80 (70–93)	0.007	84 (70–100)	80 (70–89)	NS
Malignant HTN	11/42=26.1%	8/82=6.1%	0.017	15/105=15.2%	1/20=5.0%	NS
SCr$_{dx}$	219 (156–450)	108 (90–167)	0.000001	160 (106–248)	106 (91–161)	0.00006
GFR$_{dx}$	31.3 (13.1–43.3)	62.1 (40.9–84)	0.000001	43 (26–66)	66.3 (44–84.6)	0.0003
Proteinuria$_{dx}$	2.9 (2.0–5.5)	1.0 (0.5–2.4)	0.000001	2.0 (0.9–3.3)	0.4 (0.1–1.1)	0.00003
SCr$_{end}$	219 (156–450)	111 (90–176)	0.0001	149 (107–279)	97 (83–105)	0.0008
GFR$_{end}$	0 (0–32.6)	55 (30–81)	0.000001	34 (0–61)	75.1 (55.0–100.3)	0.00003
Bad outcome[a]	25/41=61.0%	15/79=19.0%	0.0000	40/99=40.4%	1/19=5.3%	0.0012
Dialysis	21/39=53.8%	13/78=16.7%	0.0000	34/99=34.3%	1/19=5.3%	0.0051

	Endocapillary proliferation			Tubular atrophy/interstitial fibrosis		
	Present	Absent	*P*-value	T2 (>50%)	T0 (<25%)	
	31 patients	95 patients		29 patients	66 patients	
Systolic BP$_{dx}$	144 (130–170)	136 (121–180)	NS	170 (152–2010)	130 (120–148)	0.000000
Diastolic BP$_{dx}$	83 (70–102)	84 (70–97)	NS	104 (90–120)	80 (70–88)	0.000002
Malignant HTN	8/31=25.8%	9/95=9.5%	NS[b]	14/29=44.8%	0/46=0%	0.0000
SCr$_{dx}$	198 (145–1710)	124 (91–195)	0.001	450 (236–823)	100 (81–126)	0.000000
GFR$_{dx}$	34.4 (13.1–48.5)	54.3 (34.1–82.7)	0.0008	12.9 (5.7–27.9)	72.6 (53.6–90.0)	0.000000
Proteinuria$_{dx}$	3.0 (2.3–5.1)	1.2 (0.6–2.4)	0.000004	3.0 (2.1–4.8)	1.0 (0.4–1.7)	0.000002
SCr$_{end}$	210 (133–533)	115 (90–196)	0.003	480 (197–751)	107 (88–118)	0.000005
GFR$_{end}$	14.1 (0.0–35.8)	51.5 (7.6–75.1)	0.0005	0.0 (0.0–24.4)	66.8 (51.1–88.4)	0.000000
Bad outcome[a]	15/29=51.7%	24/89=27.0%	NS[b]	21/29=72.4%	3/64=4.7%	0.0000
Dialysis	13/29=44.8%	22/89=24.7%	NS[b]	19/28=67.9%	2/64=3.1%	0.0000

Abbreviations: BP, blood pressure; dx, diagnosis; GFR, glomerular filtration rate; HTN, hypertension; NS, not significant; SCr, serum creatinine.
Values expressed as median (25–75th quartiles) or as percentages. Probabilities calculated using Mann–Whitney *U*-test or Fisher's exact test, as appropriate.
[a]Bad outcome defined as doubling of SCr or need for dialysis.
[b]As corrected by Holm–Bonferroni method to minimize type 1 statistical error (α=0.05).

as FSGS. Differences in clinical and outcome parameters, although significant, were not as impressive as for the other Oxford criteria (Table 2).

Tubular atrophy/interstitial fibrosis. It was evident here that our cases were more advanced than those in the Oxford study[15,16] (Figure 1d). Although roughly 10% of cases in each study showed no significant fibrosis, ~48% of cases in the Oxford study showed interstitial fibrosis graded at ⩽10 versus 22% in this study. As might be expected, this criterion translated into the most highly significant difference for clinical and outcome parameters of any of the parameters (Table 2).

Other lesions. *Glomerular necroses* were present in 9 patients (8.5%), compared with 2.2% in the Oxford study (Figure 2a). Interestingly, they had no pejorative effect on outcome with none having a bad outcome.

Extracapillary proliferation occurred in 31 (24.2%) of our cases, a lower percentage than in the Oxford study (45%), but as in that study generally only involving a limited number of glomeruli. All of these occurred in cases interpretable as FSGS, including the cellular variant of FSGS (12 cases) and collapsing glomerulopathy (8 cases), and in that context the majority would be regarded as representing pseudocrescents (see below). There was no difference in the frequency of glomerular necroses between those with extracapillary

proliferation (2/31 = 6.5%) and those without (7/97 = 7.2%). Cases with extracapillary proliferation had more severe morphologic, clinical, and outcome parameters than those without, with 46.7 versus 23.9% finishing on dialysis (*P* = 0.05).

Immunofluorescence results

All cases in our series showed glomerular positivity for IgA as the predominant immunoglobulin. Deposits were predominantly mesangial, with some cases showing subendothelial deposits and occasionally subepithelial deposits, as in most series.[3] However, one aspect that has been little commented upon was the presence in a number of cases of IgA-positive droplets positive in podocytes and parietal epithelial cells (PECs), often to the exclusion of other immunoglobulins (Figure 1e and Supplementary Figure S3 online). These droplets appear to correspond to the bright red 'resorption' droplets seen on light microscopy in many cases (Figure 1f and Supplementary Figure S4 online).

Lesions considered in terms of FSGS

Definition of diagnostic criteria for FSGS in the context of IgAN. We wished to apply the Columbia 2004 classification of FSGS[14] as nearly as possible to our cases of IgAN. For collapsing glomerulopathy, the tip, and perihilar variants of
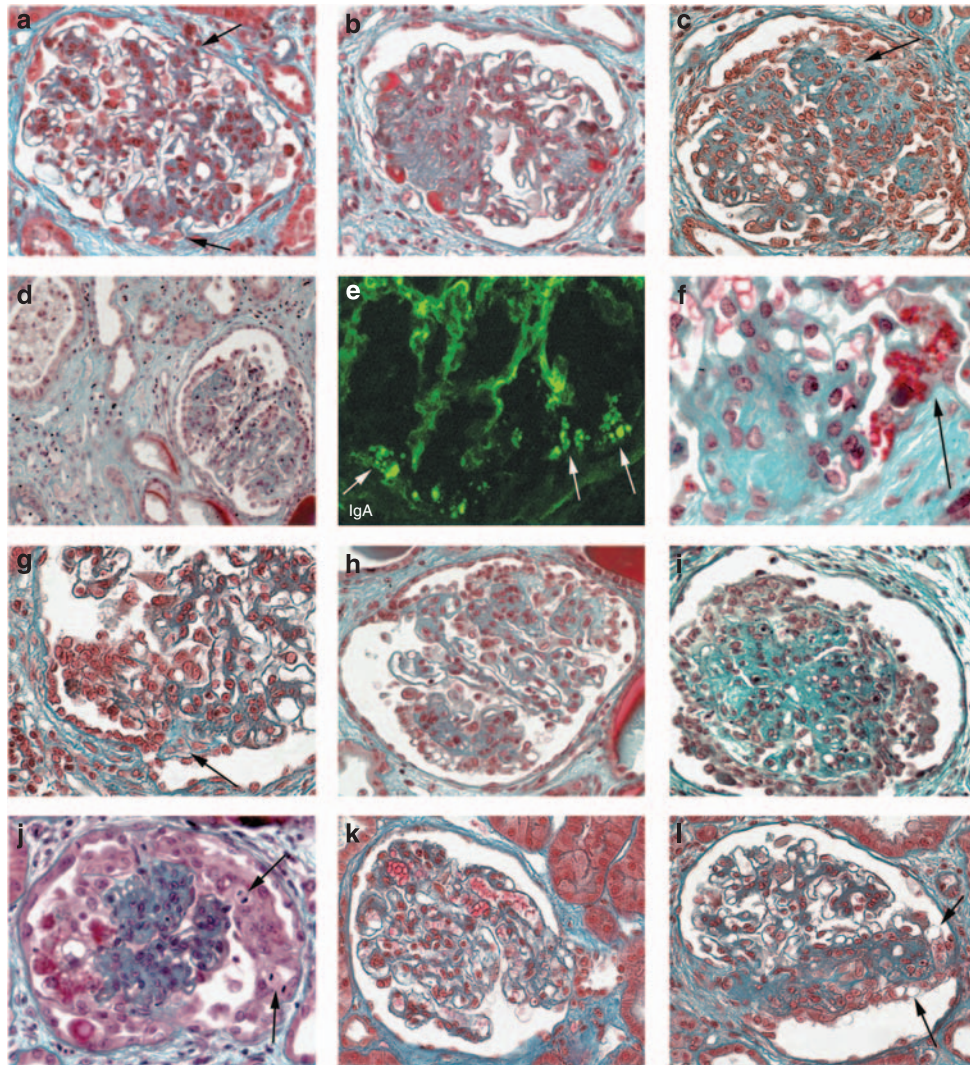
Figure 1 | Lesions of FSGS in IgA nephropathy. (a) Oxford criterion—mesangial hypercellularity. Multiple lobules show mesangial hypercellularity with >4 cells/lobule. Note also capsular adhesions (arrows) and reactive epithelial cells (right). Masson trichrome (MT), original magnification ×400. (b) Oxford criterion—segmental glomerulosclerosis. In this instance, several hyalinosis lesions in nonhilar positions are seen. MT, original magnification ×450. (c) Oxford criterion—endocapillary hypercellularity. Several lobules show marked endocapillary hypercellularity with occlusion of capillary lumens. The hyperplastic epithelial cells and the zone of lighter staining collagen (arrow) are consistent with the cellular variant of focal segmental glomerulosclerosis (FSGS). MT, original magnification ×350. (d) Oxford criterion—tubular atrophy/interstitial fibrosis. Advanced tubular atrophy and interstitial fibrosis. In this field they surround a glomerulus showing collapsing glomerulopathy, with numerous tubules showing vacuolated macrophagic cells. MT, original magnification ×250. (e) Immunofluorescence for IgA. Diffuse mesangial staining with small clusters of droplets (arrows) in epithelium adjacent to Bowman's capsule. original magnification ×600. (f) Hyaline droplets in epithelium, adjacent to segmental scar. Droplets (arrow) are predominantly in cells identifiable as parietal epithelial cells (PECs) but also in cells overlying tuft. MT, original magnification ×850. (g) Parietal epithelial cells at adhesion. Here growing along an adhesion (not in this plane of section) onto the glomerular tuft. Light-staining matrix (arrow) suggests that the adherent lesion was a form of FSGS. MT, original magnification ×450. (h) Cellular variant of FSGS. Note continuity of PECs from capsule onto glomerular tuft. Elsewhere, the epithelium is tall and vacuolated; such epithelium stains as being of PEC origin immunohistochemically. MT, original magnification ×350. (i) Collapsing glomerulopathy. The collapsed capillary loops are covered with a layer of hyperplastic epithelial cells. Vacuolization is only modest in this instance. MT, original magnification ×320. (j) Pseudocrescent in collapsing glomerulopathy. Proliferating epithelial cells, with evident mitoses (arrows), fill much of Bowman's space but do not obliterate it. Note abundant hyaline droplets in the epithelial cells. MT, original magnification ×550. (k) Tip lesion. Cellular lesion at tubular pole, with foamy macrophage in lumen and adhesion to Bowman's capsule. Remainder of the glomerulus shows only modest mesangial proliferation. MT, original magnification ×350. (l) Segmental scar with overlying epithelial prominence. The segmental scar is adherent to Bowman's capsule. The overlying epithelium is tall and often vacuolated (arrow). MT, original magnification ×400.

FSGS, it was possible to apply the Columbia criteria directly. However, in the instance of the FSGS not otherwise specified (NOS), we were forced to use more stringent

criteria. In primary FSGS,[14] the NOS category was defined as a 'segmental increase in matrix obliterating capillary lumina, also segmental collapse without overlying podocyte

hyperplasia.' As the diagnosis of primary FSGS is predicated on the absence of diffuse glomerular immunoglobulin deposition or of any other primary glomerular disease, it is reasonable to attribute any segmental scars in that situation to FSGS. In IgAN, however, there are diffuse glomerular IgA deposits, mesangial hyperplasia, and focal glomerular necroses (8.5% in our series) that may heal with segmental scars, complicating the situation. A simple segmental scar, although possibly representing FSGS, might also represent healing of a segmental necrosis (Figure 2a and b). Therefore, we required that such segmental scars have, in addition, either overlying epithelial proliferation or hyalinosis lesions in order to be diagnosed as FSGS NOS (Figure 2e–h and Table 1).

A second adaptation of the Columbia classification was that for the diagnosis of cellular FSGS in the context of IgAN, we required the presence of hyperplastic epithelium overlying the areas of endocapillary cellularity, to separate such lesions from possible endocapillary hypercellularity of other causes (Table 1).

The Oxford criteria define *segmental glomerulosclerosis* as 'any amount of the tuft involved in sclerosis, but not involving the whole tuft, or an adhesion' (Figure 2). This definition would include the simple segmental scars discussed above, which were inadequate for diagnosis of FSGS in the absence of added hyalinosis or epithelial proliferation. We also took the conservative view that simple capsular adhesions without evident lesions in the underlying tuft, with (Figure 2d) or without (Figure 2c) accompanying epithelial proliferation, although possibly representing early FSGS, were inadequate to establish that diagnosis.

Classification of IgAN cases in terms of FSGS types. We attempted to classify our cases of IgAN according to the 2004 pathologic classification of FSGS.[14] For the most part, this attempt worked well. It was possible to classify 103 of 128 (80.5%) cases among the 5 subtypes of FSGS (Table 3). Of the remainder, 11 cases (8.6%) had glomerular lesions not definably FSGS (7 with capsular adhesions only, 3 with capsular adhesions with epithelial response, and 2 cases of glomerular necroses, 1 having associated glomerular capsular adhesions). Finally, there were 18 cases with no lesions on light microscopy aside from mild mesangial prominence in some. Common to all of the types of FSGS were capsular adhesions that served as a bridge along which PECs grew inward to cover the glomerular tuft (Figure 1g and h).

FSGS with classic hyalinosis lesions was found in 46 (35.1%) patients. The lesions were invariably adherent to Bowman's capsule. Interestingly, the majority of hyalinosis lesions (37/46 = 80.4%) were in nonhilar locations (Figure 1b).
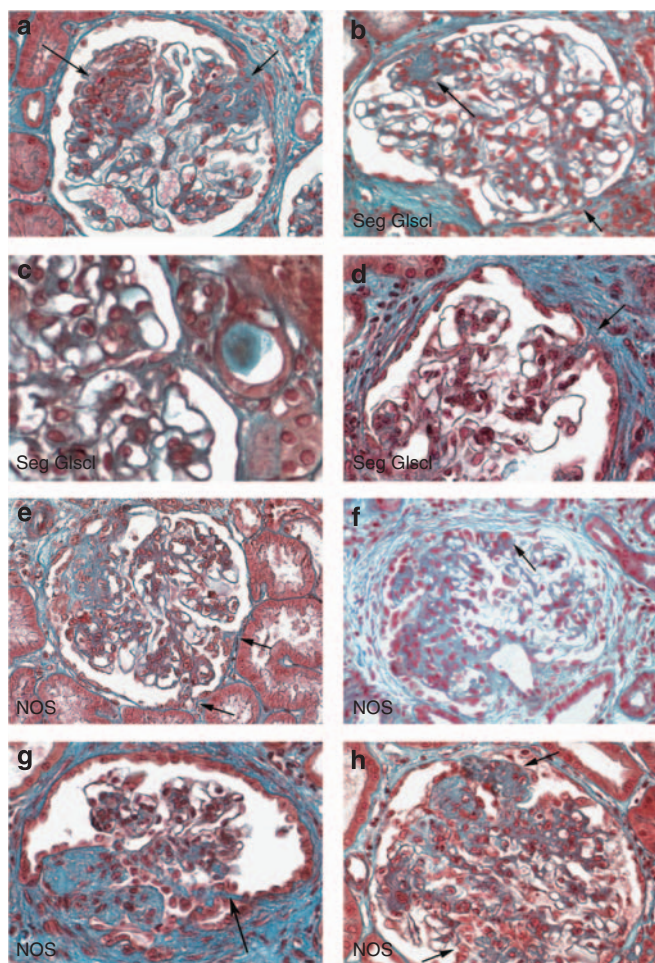

Figure 2 | Distinctions between segmental glomerulosclerosis and focal segmental glomerulosclerosis, not otherwise specified (FSGS, NOS). (**a**) Segmental necrosis and segmental glomerulosclerosis. Lobule on left shows segmental necrotic lesion, without significant overlying epithelial hyperplasia. On right is a segmental scar adherent to the capsule with only minimal epithelial prominence. Masson trichrome (MT), original magnification × 400. (**b**) Segmental glomerular scar. The scar, without associated epithelial hyperplasia, is regarded as representing simply segmental glomerulosclerosis, not FSGS. MT, original magnification × 400. (**c**) Capsular adhesion. This capsular adhesion qualifies as segmental glomerulosclerosis under the Oxford criteria, but has neither associated epithelial hyperplasia nor lesions in the underlying lobule, and hence is not regarded as FSGS under our definitions. MT, original magnification × 550. (**d**) Capsular adhesion with associated epithelial hyperplasia. This lesion qualifies as segmental glomerulosclerosis under Oxford criteria, but in the absence of lesions in the underlying tuft was considered insufficient for diagnosis of FSGS. MT, original magnification × 475. (**e**) FSGS, NOS. There is a segmental scar, upper left, with adherence to Bowman's capsule and overlain by reactive epithelium. Two capsular adhesions, one with epithelial response, are seen at lower right (arrows). MT, original magnification × 400. (**f**) FSGS, NOS. In addition to segmental scars with overlying epithelial prominence, there is a small hyalinosis lesion (arrow) at top. MT, original magnification × 300. (**g**) FSGS, NOS. Segmental scar at lower left with extensive hyperplasia of Bowman's epithelium, and an additional adhesion (arrow) along which epithelium, presumably of parietal epithelial cell (PEC) origin, is growing. MT, original magnification × 400. (**h**) FSGS, NOS. Segmental scars with capsular adherence in one location, with a small hyalinosis lesion (top arrow). The scarred areas are overlain by hyperplastic and sometimes vacuolated epithelium. Epithelial prominence is widespread (lower arrow). MT, original magnification × 350.

Table 3 | Lesions of IgA nephropathy interpreted in terms of FSGS classification

	No lesions	GI lesions, not definably FSGS[a]	Focal segmental glomerulosclerosis type				
			Tip lesion	Perihilar hyalinosis	FSGS, NOS	FSGS, cellular variant	Collapsing glomerulopathy
	16 patients	11 patients	4 patients	7 patients	52 patients	27 patients	11 patients
% Tubular atrophy/interstitial fibrosis	5 (0–12.5)	15 (10–20)	10 (7.5–10)	**30 (20–40)**	**20 (10–40)**	**40 (20–60)**	**70 (40–90)**
Interstitial inflammation	0 (0–0)	1 (0–3)	0.5 (0–1.0)	**2 (1–2)**	**1 (0–2)**	**2 (0–2)**	**1 (1–2)**
Arteriosclerosis	1 (1–2)	1.5 (1–3)	1 (1–1.5)	**3 (2–3)**	2 (1–3)	2 (1–3)	2 (2–3)
Arteriolar lumen caliber	3 (2.5–3)	3 (2–3)	3 (3–3)	3 (2–3)	2.5 (2–3)	**2 (2–3)**	**2 (1.5–2)**
Thrombotic microangiopathy	2/16=12.5%	2/11=18.2%	1/4=25%	**6/7=85.7%**	**29/52=57.7%**	**19/27=70.4%**	**10/11=90.9%**
Systolic BP$_{dx}$	122 (113–135)	134 (120–156)	125 (119–140)	**157 (136–180)**	**140 (127–161)**	**150 (130–170)**	**160 (130–197)**
Diastolic BP$_{dx}$	77 (68–89)	80 (63–93)	83 (74–93)	90 (80–110)	80 (70–97)	90 (80–102)	90 (70–120)
SCr$_{dx}$	99 (84–113)	126 (97–161)	106 (101–108)	147 (91–190)	126 (89–193)	**211 (158–498)**	**450 (298–1316)**
eGFR$_{dx}$	82 (65–87)	79 (50–91)	52 (51–71)	50 (34–68)	54 (37–76)	**34 (13–44)**	**10.9 (4.3–20.9)**
Proteinuria$_{dx}$	0.28 (0.09–0.93)	**1.70 (0.5–4.0)**	0.97 (0.65–1.54)	**1.60 (0.88–2.82)**	**1.45 (0.8–2.62)**	**2.63 (1.69–4.65)**	**3.99 (2.84–6.30)**
Serum albumen	42.3 (36.5–47.3)	38.0 (34–41)	35.8 (32.6–39.0)	37.5 (36.5–41.5)	37.8 (35.0–40.0)	**33.7 (28.7–39.1)**	**34.4 (31.0–38.8)**
Hx. gross hematuria	7/13=53.8%	5/10=50%	1/3=33.3%	2/5=40%	14/43=32.6%	4/22=18.2%	0/11=0%
eGFR$_{end}$[b]	75 (61–100)	70 (50–91)	50 (22–64)	51 (34–61)	**43 (7–67)**	**5 (5–32)**	**5 (5–5)**
Bad outcome[c]	0/16=0%	1/10=10%	1/4=25%	1/7=14.3%	14/50=28%	**14/24=58.3%**	**9/10=90%**
Hemodialysis	0/16=0%	1/10=10%	1/4=25%	0/7=0%	11/50=22%	**14/24=58.3%**	**9/10=90%**

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; GI, glomerular; NOS, not otherwise specified; SCr, serum creatinine.
Values expressed as mean ± s.e.m. or as percentages. Probabilities calculated according to Mann–Whitney *U*-test or Fisher's exact test, as appropriate.
Values in bold are significantly different from the group with no lesions, after correction by Holm–Bonferroni method to minimize type 1 statistical error (α=0.05).
[a]Glomerular lesions included: 7 cases with glomerular capsular adhesions only; 3 cases with capsular adhesions with epithelial response; and 2 cases with focal glomerular necroses (1 having glomerular capsular adhesions as well).
[b]Patients on dialysis assigned an arbitrary eGFR=5 ml/min per 1.73 m^2.
[c]Bad outcome defined as doubling of SCr or need for dialysis.

These cases were subdivided into the Columbia classification as follows: 7 cases the perihilar variant of FSGS, 9 cases the cellular variant, with the remaining 30 cases relegated to the FSGS, NOS category.

Collapsing glomerulopathy. Collapsing glomerulopathy was found in 11 cases (Table 3). In its most distinctive form, glomeruli were retracted with obliterated capillary lumens surrounded by a halo of vacuolated cells, staining as PECs[28] (Figure 1c and i). Partial involvement of glomeruli was also seen with retracted lobules surrounded by a halo of tall vacuolated, reactive PECs (Supplementary Figure S2 online). Capillary collapse and obliteration rather than endocapillary proliferation is the primary feature distinguishing this lesion from the cellular variant (see below). In fact, in 9/11 cases with collapsing glomerulopathy, other glomeruli could be interpreted as the cellular variant, and 7/11 cases had more typical lesions of FSGS with hyalinosis, emphasizing the spectrum of lesions seen in these cases. Of 11 cases, 8 had associated extracapillary proliferation, interpreted as pseudocrescents (Figure 1j). All showed advanced parenchymal damage, with numerous vacuolated cells with the morphology of macrophages in the tubular lumens, (Figure 1d). Clinically, they presented with advanced renal insufficiency and heavy proteinuria, with half having malignant hypertension (Table 3). Of 10 patients with follow-up, 9 finished on hemodialysis, with the remaining patient having an estimated GFR (eGFR) of 31 ml/min per 1.73 m^2 at 22 months postbiopsy. (The eleventh patient was lost to follow-up shortly after biopsy.)

Perihilar variant. The 7 perihilar variant cases, characterized by hyalinosis lesions adjacent to the hilum, with or without hyalinosis lesions elsewhere in the tuft, had substantial proteinuria, and most were hypertensive, but had relatively good outcomes (Table 3).

Tip lesions. These lesions consist of expansion of the glomerular tuft at the tubular pole, the capillary lumens being filled with cells, often foamy macrophages, the overlying epithelium showing reactive changes and adhesions to the capsule or initial proximal tubular basement membrane (Figure 1k and Supplementary Figure S6 online). We had six examples of tip lesions, four in pure form and two associated with other lesions and classed as FSGS, NOS. The four 'pure' cases had minimal parenchymal lesions and modest proteinuria, but one nonetheless finished on dialysis (Table 3). It should be pointed out that the relative frequency of tip lesions in our series is lower than in primary FSGS, with lower values for proteinuria, both observations remaining unexplained for the present.

Cellular variant of FSGS. These lesions comprised lobules with substantial endocapillary hypercellularity, often with foam cells. As in primary FSGS, these hypercellular lobules were almost always overlain by a prominent layer of hyperplastic, often vacuolated PECs[28] (Figure 1c and j). Often it was possible to trace progression of these cells from the capsule down onto and over the affected tuft (Figure 1g).

In all, 27 patients in our series had lesions diagnosable as the cellular variant of FSGS (Table 3). In addition to the PECs overlying the cellular lesions, 12 biopsies had extracapillary
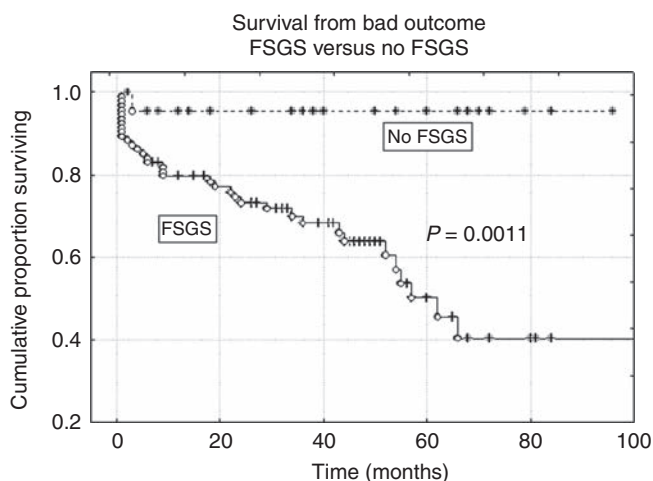
Figure 3 | Survival from bad outcome—all cases. Kaplan–Meier survival curves, comparing survival from bad outcome for all cases with focal segmental glomerulosclerosis (FSGS) compared with those without FSGS. Bad outcome is defined as doubling of serum creatinine (SCr) or need for dialysis.

proliferative lesions, usually centered around the endocapillary lesions (Supplementary Figure S8 online). Only one case showed glomerular necroses. We also found that 12/27 (44.4%) had FSGS lesions with hyalinosis in other glomeruli. Clinically, 24/27 (90.9%) presented with renal insufficiency, all having substantial proteinuria (3.41 ± 2.54 g per 24 h), with 58% finishing on dialysis.

FSGS, NOS. There were 52 cases qualifying as FSGS, NOS. In all, 11 cases had hyalinosis lesions, 23 cases segmental scars with overlying epithelial proliferation (Figure 1l), or both (10 cases). Two cases had glomerular necroses, 2 tip lesions, and 5 some form of extracapillary proliferation. Clinically, proteinuria was only moderate, but nearly 80% were hypertensive and 48% had renal insufficiency at presentation, with a quarter finishing in terminal renal insufficiency.

Factors predictive of bad outcome
Renal survival at 80 months was 32.6% for patients with FSGS versus 95.1% for those without (*P* = 0.00027; Figure 3). Univariate analysis of the factors associated with bad outcome is presented in Table 4. All of the expected clinical factors (hypertension, proteinuria, SCr, and eGFR at diagnosis) and parenchymal parameters (sclerotic glomeruli, tubular atrophy, and interstitial fibrosis) were highly associated with bad outcome. Morphologically, all three of the glomerular parameters in the Oxford classification (mesangial hypercellularity, endocapillary proliferation, and segmental glomerulosclerosis) were associated with bad outcome. Among FSGS types, collapsing glomerulopathy and cellular variant were also associated with bad outcome.

Interrelationships between lesions of FSGS and Oxford criteria parameters. All cases having lesions that we regarded as representing FSGS, with the exception of 1 NOS and 2 cellular variant cases, qualified as having segmental glomerulosclerosis under the Oxford criteria.[15,16] Similarly, 39/41

examples of mesangial hypercellularity and 29/31 cases with endocapillary proliferation occurred in the context of a form of FSGS. However, it was possible to compare 42 cases in which lesions of FSGS occurred alone with 47 cases in which there was superimposed mesangial hypercellularity (15 cases), endocapillary proliferation (9 cases), or both (15 cases), as well as glomerular necroses (5 cases) and/or extracapillary proliferation (22 cases). (Cases of collapsing glomerulopathy were excluded, so as to not unduly weight the analysis.) As might be expected, those with superimposed glomerular lesions were worse for most morphologic, clinical, and outcome parameters, although differences were not significant after application of the Holm–Bonferroni correction. Nevertheless, these differences, although not individually significant, translated into worse survivals for the group with superimposed lesions. By 80 months of follow-up, renal survival of those with superimposed glomerular lesions was 22.8 versus 49.2% for the 'pure' cases (*P* = 0.0417; Figure 4).

However, the reverse point should be stressed as well. That is, the cases with only FSGS had substantial morphologic lesions, all had proteinuria, most were azotemic, and 25% finished on hemodialysis The implication here is that FSGS lesions, of themselves, are associated with substantial declines in renal function and that the superimposed glomerular lesions simply aggravate an already parlous situation.

Comparison of predictive power of Oxford criteria versus FSGS. Table 5 compares analyses of the four Oxford criteria and of the different types of FSGS in terms of their association with Bad Outcome by Cox proportional hazards modeling and the rate of decline of renal function by multiple linear regression. (They cannot be compared directly in a single analysis because of the extensive multicolinearity between the parameters in the two systems.)

Examination of the univariate analysis of clinical and morphologic factors related to bad outcome (Table 4) reveals the remarkable strength of the clinical prognostic factors, notably hypertension, SCr, and the level of proteinuria at diagnosis. The morphologic factors, although significant, are not in the aggregate as strong as the clinical indicators, whether analyzed according to the Oxford criteria or by division according to FSGS type. These differences are reflected in Cox multiple hazards modeling (Table 5), in which eGFR sorts as significant in both models, but only mesangial hyperplasia among the morphologic factors sorts as significant. However, analysis of the rate of decline of renal function by multiple linear regression does show endocapillary proliferation and %tubular atrophy/interstitial fibrosis among the Oxford criteria, and the NOS, cellular, and collapsing variants among the FSGS types, to be significantly associated with rate of decline.

DISCUSSION
Our study completely confirms the Oxford criteria[15,16] in another adult cohort, this one with somewhat more advanced disease than in the Oxford study (Table 2). However, we feel

Table 4 | Univariate analysis of factors associated with bad outcome

Parameter	Bad outcome 41 patients	Preserved renal function 80 patients	P-value
Clinical parameters			
Systolic BP_{dx}	160 (140–180)	133 (121–150)	0.000002
Diastolic BP_{dx}	90 (80–110)	80 (70–91)	0.0002
HTN_{dx}	32/41=78.0%	30/80=37.5%	0.0000
$Systolic_{end}$	135 (123–154)	124 (111–130)	0.000001
Malignant HTN	14/41=34.1%	3/80=3.75%	0.0000
$Proteinuria_{dx}$	3.00 (1.73–5.50)	1.20 (0.50–2.47)	0.000004
$Proteinuria_{end}$	3.87 (2.26–5.01)	0.48 (0.10–1.07)	0.000001
Serum albumen	34.1 (29.5–38)	38.2 (35.2–42.0)	0.000004
SCr_{dx}	371 (195–743)	107 (87–160)	0.000000
GFR_{dx}	15.6 (8.4–34.1)	65.0 (44.2–83.8)	0.000000
TMA by laboratory criteria	8/39=20.5%	0/80=0%	0.0001
Morphologic parameters			
Oxford criteria			
Mesangial hypercellularity	25/40=62.5%	16/80=20.0%	0.0000
Endocapillary proliferation	17/41=36.6%	14/80=17.5%	0.0093
Segmental glomerulosclerosis	40/41=97.6%	1/80=1.3%	0.0000
Tubular atrophy/ interstitial fibrosis, %	60 (40–80)	15 (10–25)	0.000000
FSGS types			
FSGS, any variant	40/41=97.6%	51/80=63.8%	0.0000
FSGS, NOS	14/41=34.1%	35/80=43.8%	NS
FSGS, perihilar variant	1/41=2.4%	6/80=7.5%	NS
FSGS, cellular variant	14/41=34.1%	11/80=13.8%	0.0087
FSGS, tip lesion	1/41=2.4%	3/80=3.8%	NS
FSGS collapsing glomerulopathy	10/41=24.4%	1/80=1.3%	0.0001
Other morphologic parameters			
% Sclerotic glomeruli	71 (44–83)	16.7 (5.6–31.9)	0.000000
Extracapillary proliferation	17/40=42.5%	14/80=17.5%	0.0036
Glomerular necroses	0/41=0%	9/80=11.2%	0.027
Interstitial inflammation	2 (1–2)	0.5 (0–1)	0.000009
Microcystic change	14/38=36.8%	2/77=3.9%	0.0003
Arteriosclerosis	2 (2–3)	2 (1–2)	0.0044
TMA fibrinoid	23/41=56.1%	18/80=22.5%	0.0003
TMA organized	30/41=73.1%	28/80=35.0%	0.0001
Any TMA	35/40=85.4%	33/80=41.3%	0.0000

Abbreviations: BP, blood pressure; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; HTN, hypertension; NOS, not otherwise specified; NS, not significant; SCr, serum creatinine; TMA, thrombotic microangiopathy.
Values expressed as median (25–75th quartiles) or as percentages. Probabilities calculated using Mann–Whitney U-test or Fisher's exact test, as appropriate.

Figure 4 | Survival from bad outcome—cases from Table 3. Kaplan–Meier survival curves, comparing survival from bad outcome for the cases included in Table 3. Cases with 'pure' focal segmental glomerulosclerosis (FSGS) are compared with cases of FSGS with superimposed other glomerular (GI) lesions (mesangial hyperplasia, endocapillary hypercellularity, glomerular necroses, and/or extracapillary proliferation). Bad outcome is defined as doubling of serum creatinine (SCr) or need for dialysis.

IgAN.[10,11] Second, in another study[28] we have shown immunohistochemically that IgAN behaves basically identically to cases of primary FSGS, with progressive loss of normal podocyte markers (synaptopodin, GLEPP-1 (glomerular epithelial protein 1), nephrin, and vascular endothelial growth factor) and marked increase in PECs, as indicated by PAX2 and CK8, these latter proliferating inward along sites of capsular adhesion onto the tuft to have an important role in advanced lesions. Third is the presence of cytoplasmic droplets positive for IgA in podocytes and PECs. Such droplets are well recognized in collapsing glomerulopathy[29,30] and in florid FSGS,[31] but have not been previously described in IgAN.

The question arises as to whether the FSGS is primary or secondary to advancing renal parenchymal damage. Some authors consider that FSGS is the final common pathway of various pathophysiological mechanisms[32,33] including the FSGS in IgAN.[34] Against this 'final common pathway' concept, however, we have shown that the lesions of FSGS in IgAN may occur very early. Of the 101 patients with frank FSGS, 31 had SCr $\leqslant 110\,\mu$mol/l and 28 had eGFR >60 ml/min per 1.73 m² at the time of biopsy, with correspondingly mild parenchymal lesions (Figure 1k). These observations argue against the idea that FSGS seen in IgAN might be due simply to nephron reduction. Furthermore, we have demonstrated loss of podocyte markers, such as GLEPP-1, in glomeruli that are still morphologically normal.[28] Thus, the phenotypic changes in podocytes precede recognizable glomerular lesions by light microscopy, suggesting that they are the cause rather than the consequence of the latter.

Capsular adhesions are associated with scarring or active lesions in the underlying tuft in many conditions. However, in IgAN they frequently occur in the absence of recognizable

that looking at IgAN in terms of variants of FSGS is a useful alternative manner of looking at the disease. It raises new questions regarding the pathogenesis of glomerular lesions in IgAN. The evidence supporting this approach is as follows: First, in this study we found 57 patients (44.5%) for whom there can be no doubt as to their diagnosis as a form of FSGS: 46 patients with clearcut hyalinosis lesions and 11 patients with collapsing glomerulopathy. An additional 44 patients (34.3%) had lesions that we interpret as FSGS on the basis of the criteria set forth in Table 1, for a total of nearly 80% of patients showing some form of FSGS. This is a much higher proportion of patients with FSGS than previously reported in
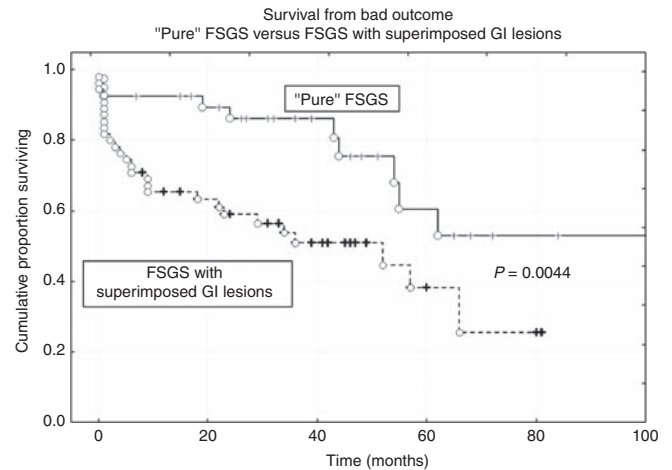
Table 5 | Analysis of rate of decline of renal function and outcome

	Oxford criteria model							
	Rate of decline of eGFR (ml/min per 1.73 m^2 per year) Multiple linear regression $F_{(7, 92)}=6.1047$, $P<0.00001$, $R^2=0.3172$				Factors associated with bad outcome[a] Cox proportional hazards modeling $\chi^2=106.01$, d.f.=7, $P=0.00000$			
	β	s.e. β	t-Value	P-value	β	s.e. β	t-Value	P-value
Mesangial hyperplasia	0.0923	0.1053	0.8765	0.38	0.8404	0.3819	2.2054	0.027
Segmental glomerulosclerosis	0.1198	0.0953	1.2561	0.21	0.4012	0.5354	0.7495	0.45
Endocapillary proliferation	0.2124	0.1093	1.9435	0.055	0.0747	0.3644	0.2051	0.84
% Tubular atrophy/interstitial fibrosis	0.5120	0.1351	3.7893	0.00026	0.0056	0.0106	0.5307	0.60
Proteinuria$_{dx}$	0.1479	0.1112	1.3468	0.18	−0.0352	0.0590	−0.5961	0.55
eGFR$_{dx}$	0.3586	0.1407	2.5481	0.012	−0.0908	0.0220	−4.1256	0.000037
Mean arterial pressure$_{dx}$	−0.0104	0.1097	−0.0946	0.92	0.0069	0.0085	0.8117	0.42
	FSGS model							
	Rate of decline of eGFR (ml/min per 1.73 m^2 per year) Multiple linear regression $F_{(8, 103)}=4.1988$, $P<0.00022$, $R^2=0.2459$				Factors associated with bad outcome Cox proportional hazards modeling $\chi^2=105.36$, d.f.=8, $P=0.0000$			
	β	s.e. β	t-Value	P-value	β	s.e. β	t-Value	P-value
Collapsing glomerulopathy	0.3147	0.1066	2.9509	0.0039	1.2614	1.0893	1.1580	0.25
FSGS, NOS	0.3033	0.1134	2.6746	0.0087	0.5847	1.0391	0.5627	0.57
Perihilar variant	0.0570	0.0974	0.5851	0.56	0.5486	1.4390	0.3812	0.70
Cellular variant	0.4384	0.1171	3.743	0.0003	1.3599	1.0401	1.3075	0.19
Tip lesion	0.1167	0.0910	1.2793	0.20	1.6460	1.3860	1.1872	0.24
Proteinuria$_{dx}$	0.2083	0.1044	1.9961	0.049	−0.0153	0.0648	−0.2367	0.81
eGFR$_{dx}$	0.0896	0.1113	0.8042	0.42	−0.0972	0.0173	0.9073	0.000000
Mean arterial pressure$_{dx}$	0.0744	0.1035	0.7064	0.48	0.0046	0.0078	1.005	0.55

Abbreviations: eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; NOS, not otherwise specified.
[a]Bad outcome defined as doubling of SCr or need for dialysis.

underlying lesions, as is true in FSGS.[28] Kriz[18,19] refers to this phenomenon as the 'first committed step' in the development of FSGS. However, adhesions in the absence of underlying lesions are rare in systemic lupus erythematosus, implying that IgAN in this respect behaves more like FSGS than a typical immune complex glomerulopathy.[28]

The causes of the podocyte lesion leading to FSGS are undetermined for the moment. The possibility of toxicity, either direct or indirect, of IgA1 on the podocyte is attractive. It has been shown that serum IgA1 from patients with IgAN leads to reduction of podocyte markers such as nephrin or ezrin on podocytes in culture,[22,35,36] as well as apoptosis of podocytes.[24] Furthermore, in children with IgAN, two types of autophagy in podocytes have been observed, one (type II) in which the ingested material is digested and disposed of in normal fashion, the other (type I) in which the ingested material persists undigested in the podocytes, and this type is associated with more aggressive histological lesions.[26] It is tempting to attribute the accumulation of IgA in large droplets in PECs and podocytes described above to this phenomenon.

Role of FSGS in the progression of IgAN

Our study is the first to attempt to class lesions as FSGS versus no FSGS and then to divide the FSGS group into the different subclasses of FSGS as currently classified.[27] We have shown that cases with FSGS have a much worse renal survival than do patients without FSGS ($P = 0.00027$; Figure 3). More importantly, if one dissects the cases with FSGS into those with 'pure' FSGS (excluding collapsing glomerulopathy) and compares them with cases of FSGS with superimposed other glomerular lesions (mesangial hyperplasia, endocapillary hypercellularity, glomerular necroses, or extracapillary proliferation), the cases of FSGS with superimposed other glomerular lesions do worse that those with 'pure' FSGS, as might be expected (Figure 4). But the differences are not terribly great and the important observation is the reverse one; that is, the cases with 'pure' lesions have a poor prognosis, with 49.2% survival from bad outcome at 80 months. The different types of FSGS in our IgAN series had outcomes broadly parallel to those in the literature for primary FSGS,[37–39] with collapsing glomerulopathy and the cellular variant having a particularly poor prognosis.

Our findings suggest that lesions consistent with FSGS should be sought systematically in evaluating cases with IgAN, as an aid in thinking about prognosis and management. This retrospective, observational study has the limitation that although treatment was similar in the vast majority of patients, there nonetheless remain differences with unknown impact on prognosis.

Finally, we have been able to explain a great deal of the progression of renal insufficiency in IgAN in terms of FSGS, and have been able to categorize the majority of cases in terms of the standard classes of FSGS. However, there remain aspects of IgAN that are not explained in terms of FSGS. Most notable is the near-universal presence of hematuria in IgA patients. Microscopic hematuria is indeed seen in FSGS, in roughly 30–60% of patients,[40,41] but macroscopic hematuria is rare. Second is the presence of glomerular necroses in IgAN.[3] In FSGS, only in the cellular form are lesions interpretable as segmental necroses seen, with cellular infiltration and nuclear fragments.[14] All of the glomerular necroses in our series fit this definition. However, in other series, frank fibrinoid necroses and cases with membranoproliferative appearance or widespread true crescents have all been described,[3] as well as IgA-dominant postinfectious glomerulonephritis.[42,43] Although all of these more florid lesions are infrequent in IgAN, they indicate that thinking of IgAN uniquely in terms of FSGS would be an oversimplification. Although we are persuaded that FSGS accounts for much of the progression of IgAN in patients considered overall, these other lesions undeniably have a role as well.

Finally, although we feel that, using the criteria laid out in Table 1, the basic diagnosis of FSGS in the context of IgAN should be readily reproducible, division into the various subtypes will be subject to considerable interobserver variability, and will almost certainly not be as reliable as the Oxford classification that was developed specifically and rigorously with the aim of reproducibility.[15,16]

Conclusion

We have shown in this study that IgAN may be associated with lesions of FSGS, similar to those of primary FSGS. When present in 'pure' form they carry a moderately poor prognosis, and when other glomerular lesions such as mesangial hyperplasia or endocapillary hypercellularity are superimposed the prognosis becomes yet worse. We suggest that such lesions should be sought in the evaluation of biopsies of IgAN for a better understanding of the pathophysiology of the disease. However, we do not see classification of lesions into FSGS types as a substitute for the Oxford classification but rather as a complement to it, offering different pathophysiological insights and perhaps in the future leading to different therapies.

Conceiving of IgAN as a disease with a substantial podocytic component serves to shift our thinking away from the traditional view of IgAN as an intratuft lupus-like process to a more global view in which all components of the glomerulus are actively affected by the immune complexes.

PATIENTS AND METHODS
Patients

All adult (>18 years) patients diagnosed with IgAN from January 2002 to January 2008 in the Georges Pompidou European Hospital Pathology Department were enrolled in this retrospective study. These biopsies came from four different medical centers. The diagnosis was based on the presence of predominant IgA and C3 deposits in the mesangium. Patients with systemic lupus erythematosus, Henoch–Schönlein purpura, chronic liver disease, or HIV infection were excluded, as well as patients whose renal biopsy specimen contained <8 glomeruli, and those without sufficient initial clinical data, leaving a total of 128 patients. Biopsies were performed for isolated hematuria in four cases, and all others were biopsied for some combination of hematuria, proteinuria, and/or elevated SCr. Mean follow-up was 44 ± 27 months. Among the 121 patients with complete follow-up, 41 patients (34%) met the criteria for bad outcome (doubling of SCr or need for dialysis), with 36 patients (29.7%) requiring dialysis, 16 of them within 3 months of diagnosis.

Clinical and laboratory data cited in this study included: age, sex, blood pressure, number of antihypertensive agents used, immunosuppressive therapy, proteinuria, hematuria, and SCr. The GFR was estimated (eGFR) with the simplified MDRD (Modification of Diet in Renal Disease) formula.[44]

These were collected at the time of renal biopsy, and at the end of follow-up (or institution of renal replacement therapy). The following definitions were used: hypertension: systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg or use of antihypertensive agents; malignant hypertension: marked elevation of blood pressure, associated with central nervous system symptoms (blurred vision, headaches, nausea, vomiting, or papilledema). Bad outcome was defined as doubling of SCr or renal replacement therapy at the end of follow-up.

Renal histopathology

The renal biopsies were processed for light microscopy, and direct immunofluorescence. Tissue for histology was fixed in acetic acid–formol–absolute alcohol, and processed and stained by standard methods. Sections (6 μm) were stained for immunofluorescence study with fluorescein isothiocyanate-conjugated antibodies specific for human IgG, IgM, IgA, C1q, C3, κ and λ light chains, and fibrin (DAKO, Carpinteria, CA). All biopsy slides were re-reviewed by two senior pathologists (DN and GH) without knowledge of clinical outcomes. The biopsies were graded according to the Oxford classification of IgAN.[15,16] Glomerular lesions were also evaluated in terms of possible lesions of FSGS using the proposed 2004 classification of FSGS,[14] as modified to apply to IgAN (Table 1). Thrombotic microangiopathy lesions were described as: (1) 'acute,' with fibrin deposits or (2) 'organized,' with evident fibrosis and recanalization. The severity of interstitial cell infiltration, interstitial fibrosis, and tubular atrophy was also semiquantitatively scored on a scale of 0–4 + ((0: none, 1: 0–25%, 2: 25–50%, 3: 50–75%, and 4: >75%). Arteries and arterioles were also evaluated semiquantitatively (0–4 +) for severity of arteriosclerosis and size of arteriolar lumen (with 3 taken as normal).

Statistical methods

Results were expressed as numerical values and percentages for categorical variables. Continuous variables are expressed

as median (25–75th percentile), because the majority had non-Gaussian distribution. Comparisons were based on the Fisher's exact test for categorical data and the Student's *t*-test for normally distributed continuous data. For non-Gaussian distributed parameters, we used the nonparametric Mann–Whitney *U*-test to compare continuous variables, and the Wilcoxon test to compare two paired groups.

The Oxford criteria and the FSGS variants were compared in two fashions: rate of decline of eGFR was evaluated by multiple linear regression. Cases reaching dialysis were assigned an arbitrary residual eGFR of 5 ml/min per 1.73 m^2. Outcome was evaluated by Cox proportional hazards models, with Bad Outcome defined as doubling of SCr or need for dialysis. Probability values of <0.05 were regarded as statistically significant.

DISCLOSURE
All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL
Figure S1. Capsular adhesions in IgAN.
Figure S2. Partial involvement by collapsing glomerulopathy.
Figure S3. Immunofluorescence for IgA.
Figure S4. Epithelial cytoplasmic droplets.
Figure S5. FSGS, perihilar variant.
Figure S6. Tip lesion.
Figure S7. Cellular variant and glomerulus with hyalinosis.
Figure S8. Extracapillary proliferation.
Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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