Focal segmental glomerulosclerosis in mild IgA nephropathy: a clinical-pathologic study

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Abstract

Background. The significance of focal segmental glomerulosclerosis (FSGS) in mild IgA nephropathy is uncertain.

Methods. All consecutive renal biopsies performed between 1996 and 2005 in adults with a diagnosis of mild IgA nephropathy (Lee Grade 1 or 2) at St Paul’s Hospital, Vancouver, Canada, were reviewed.

Results. Seventy-five patients were included, 26 (35%) with IgA nephropathy and FSGS (FSGS+ group) and 49 (65%) with IgA nephropathy without FSGS (FSGS− group). The mean follow-up was 3 years. At the time of renal biopsy the FSGS+ group had a lower eGFR (60 versus 73 mL/min, P = 0.02), lower serum albumin (38 versus 41 g/l, P = 0.02), higher mean arterial pressure (103 versus 97 mmHg, P = 0.03) and greater protein excretion (3.0 versus 1.3 g/day, P < 0.01) than the FSGS− group. On histology, the FSGS+ group had a higher percentage of obsolete glomeruli (23.4% versus 12.7%, P < 0.01), and 31% of FSGS+ biopsies had ≥25% tubular atrophy/interstitial fibrosis while this was not observed in the FSGS− group (P < 0.01). The primary outcome measure, ΔGFR, was −2.56 mL/min/year in the FSGS+ group and +1.14 mL/min/year in the FSGS− group, difference: 3.70 mL/min/year (P = 0.03) (univariate). In the multivariate model, the FSGS+ group declined at 0.19 mL/min/year (−14.16, 13.78) and the FSGS− group improved at 2.85 mL/min/year (−11.64, 17.34), difference 3.04 mL/min/year, P = 0.18.

Conclusions. Our study suggests that the focal segmental glomerulosclerosis lesion and associated clinical and pathologic findings in patients with mild IgA nephropathy are associated with a worse renal outcome.

Keywords: focal segmental glomerulosclerosis; glomerular filtration rate; IgA nephropathy; outcomes

Introduction

Focal segmental glomerulosclerosis (FSGS) has been observed concurrently with primary glomerular diseases such as membranous glomerulonephritis (GN) [1–4] and IgA nephropathy [5], and is part of the spectrum of minimal change disease (MCD) [6]. Focal segmental glomerulosclerosis occurring concurrently with membranous GN is associated with poor renal outcomes [2,4]. Likewise, FSGS found on subsequent renal biopsy in patients with minimal change disease is associated with steroid resistance and inferior renal outcomes [7]. While FSGS has been shown to be a significant predictor of outcome in moderate IgA nephropathy [8], in mild IgA nephropathy the occurrence of an FSGS lesion is rare, and studies to date demonstrate mixed results in regard to renal prognosis [5,9–11]. This has led to confusion in the clinical arena as to the significance of this lesion.

In addition, there continues to be controversy regarding the co-existence of FSGS and mild IgA nephropathy, and whether it is the result of two primary renal disorders occurring simultaneously, one (FSGS) secondary to the other (glomerular injury and/or hypertension in the setting of IgA nephropathy), or alternatively if the pathological presence of IgA staining on immunofluorescence is simply an epi-phenomenon and thus potentially misleading. Histologically, FSGS like mild IgA nephropathy has at most a mild increase in mesangial hypercellularity and can only be distinguished from primary FSGS on the basis of mesangial IgA deposits on immunofluorescence [5].

Given the relative uncertainty about the importance of this unusual pathologic variant, we aimed to describe the renal outcomes of the FSGS lesion in mild IgA nephropathy in a cohort of patients in order to determine the impact of the presence of this lesion.

Subjects and methods

The Renal Pathology Laboratory at St Paul’s Hospital is the receiving laboratory for all renal biopsies done in British Columbia, Canada, with the exception of Vancouver Island,
for an estimated population of 4 million persons. We performed a retrospective cohort study by reviewing the biopsy logbooks between 1 January 1996 and 31 December 2005 to identify all native renal biopsies with a diagnosis of IgA nephropathy (Lee Grade 1 or 2) [12]. For each potential participant, the case folder, computer database and patient chart were reviewed.

We included adults >18 years with mild IgA nephropathy on renal biopsy (see definitions below) and a minimum of two serum creatinine measurements over a 6-month period (at least one measurement pre-renal biopsy and one 6 months post-biopsy). We excluded patients with concurrent acute tubular necrosis, Henoch-Schönlein purpura, diabetes mellitus and systemic lupus nephritis, an inadequate biopsy specimen (<10 viable glomeruli for histologic exam) and incomplete patient data.

**Histologic data**

The renal biopsies were processed for light microscopy, direct immunofluorescence and electron microscopy. Tissue for histology was fixed in B5 or 10% formalin and embedded in polyglycol methacrylate. Two-micron-thick sections were cut from both the methacrylate and paraffin blocks. The methacrylate sections were stained with haematoxylin–eosin (H&E), toluidine blue and periodic acid-silver methenamine (PASM) while the paraffin-embedded ones were stained with H&E, periodic acid-Schiff (PAS), PASM and trichrome.

For electron microscopy, the tissue was fixed in buffered 2% glutaraldehyde and embedded in a polybed-araldite mixture. Ultra-thin sections were stained with uranyl acetate and lead citrate and examined with either a Zeiss EM 109 or a LEO 906E transmission electron microscope.

The material for immunofluorescence was snap-frozen in liquid nitrogen. Six-micron sections were stained with fluorescein-conjugated (FITC) rabbit antibodies specific for human IgG, IgM, IgA, C1q, C3, kappa and lambda light chains and fibrin (DAKO, Carpinteria, CA, USA).

All biopsy slides were re-reviewed by one author (A.M.) without knowledge of clinical outcomes. If the patient had more than one biopsy recorded in the database during the period of study, we included the first biopsy only. The biopsies were graded according to the scheme of Lee et al. that is similar to that of Haas [9]. In Grade 1 IgA nephropathy, the glomeruli are histologically normal or minimally hypercellular with no more than three mesangial cells per segment (Figure 1a). In Grade 2 IgA nephropathy, <50% of the glomeruli show mild mesangial hypercellularity (4–6 cells per segment) (Figure 1b). The FSGS lesion (Figure 1c) was typed according to the newly proposed pathologic classification for this disease [13]. The degree of tubular atrophy/interstitial fibrosis (TA/IF) was estimated in a semiquantitative way as follows: 0 = no TA/IF, + = up to 25% of the cortex showing TA/IF, ++ = 25–50% of cortex with TA/IF, +++ = >50% of cortex with TA/IF.

Definitions for purposes of this study: controls: FSGS− group, Grade 1 (≤3 mesangial cells per segment) or Grade 2 (4–6 mesangial cells per segment); cases: FSGS+ group, Grade 1 or Grade 2 with FSGS lesion.

**Clinical data**

We collected the following data at the time of renal biopsy: age, gender, weight, ethnicity, duration of symptoms prior to biopsy, clinical features [microhaematuria and proteinuria, microhaematuria only, macrohaematuria only, nephrotic syndrome (definition: at least three of the following present or reported: oedema, hyperlipidaemia with LDL >2.5 mmol/L, nephrotic range proteinuria with 24-h protein >3.5 g, hypoalbuminaemia with serum albumin <35 g/L, and lipiduria), acute renal failure and chronic kidney disease] defined as a calculated glomerular filtration rate (GFR) <60 mL/min, number of anti-hypertensives used, and angiotension-converting enzyme inhibitor and/or angiotension receptor blocker use.

Clinical and laboratory values obtained at renal biopsy and every 6 months thereafter were mean arterial pressure (MAP), albumin, lipid profile and 24-h protein excretion. GFR was calculated using the modified MDRD formula [14]. We also recorded if the patient received fish oil or immunosuppressive medications at any time after renal biopsy.

Our primary outcome measure of interest was change in GFR over time (ΔGFR). Secondary outcome measures included MAP, albumin, lipid profile and 24-h protein...
excretion at 1 year. These secondary outcomes, in addition to assessing novel/persisting differences between groups, can be used as an indirect marker of the medical care the subjects received. We also aimed to make a statement regarding the probability that these two disease entities are primary renal disorders occurring concurrently, or otherwise.

Institutional ethics approval was obtained for this study.

Statistics

Differences between groups were compared using the non-parametric Wilcoxon signed-rank test for continuous data and the χ² test for categorical data. Values are reported as mean ± SD. GFR was calculated using the modified MDRD equation. Change in GFR over time (ΔGFR) was calculated using a linear mixed effects regression model. This model assigns greater weight to those subjects with more GFR measurements, and estimates an ‘average’ slope for ΔGFR over time. The multivariate linear mixed effects regression model was adjusted for age, gender, baseline MAP, eGFR and protein excretion. The ΔGFR between groups were compared using the Mantel–Cox log-rank test for differences. We also performed the same analysis (a) after excluding those with crescents on renal biopsy, (b) in cases and controls with Grade 1 IgA nephropathy only and (c) in cases (FSGS+ group) comparing those with and without TA/IF. All analyses were carried out using SAS 9.1.2. (SAS Institute, Cary, NC, USA). Differences were considered significant for P < 0.05.

Results

Histology

All biopsies in the renal biopsy database performed between 1 January 1996 and 31 December 2005 with a diagnosis of IgA nephropathy either Grade 1 or 2 according to the grading scheme of Lee [12] were retrieved and reviewed (n = 113). Twenty-six of these biopsies meeting inclusion criteria demonstrated focal segmental glomerulosclerosis (FSGS+ group); of the remaining patients, 49 without FSGS on biopsy met inclusion criteria and comprised the FSGS− group. Thirty-eight patients were excluded for inadequate patient data; none of these showed FSGS on biopsy. All biopsies demonstrated mesangial staining for IgA and C3 without peripheral capillary deposits, and IgA was the dominant immunoglobulin in the deposits. There was no staining for C1q. Lesser amounts of IgG and IgM were observed in 6 (23%) and 11 (42%) FSGS+ biopsies and in 18 (37%) and 23 (47%) FSGS− biopsies, respectively.

The mean number (±SD) of viable glomeruli per biopsy available for histologic examination was 15 (±4) for the FSGS+ group and 16 (±5) for the FSGS− group. The mean percentage of obsolete glomeruli (±SD) was significantly higher in the FSGS+ group (23.4 ± 16.8) than that in the FSGS− group (12.7 ± 10.4) (P < 0.01). The percentage of FSGS+ biopsies with ++ or +++ TA/IF (31%) was significantly greater than that of the FSGS− group (0%) (P < 0.01). The number of biopsies that demonstrated segmental endocapillary hypercellularity was not significantly different: 3/49 (FSGS−) and 1/26 (FSGS+), both in 1–3 glomeruli (P = 0.68).

In the FSGS+ group, 6 (23%) biopsies were Grade 1 while 20 (77%) were Grade 2, while in the FSGS− group, 10 (20%) had Grade 1 while 39 (80%) had Grade 2 disease. The distribution of the variants of FSGS in the FSGS+ biopsies was as follows: perihilar variant in 7 (27%), tip variant in 1 (4%) and not otherwise specified variant in 18 (69%). Focal effacement of foot processes was observed on electron microscopy in 21 of the FSGS+ biopsies. Diffuse effacement of foot processes was present in one of the FSGS+ biopsies (perihilar variant), and three of the biopsies from this group showed intact foot processes. No glomeruli were available for EM in one FSGS+ biopsy. Electron microscopy was done in 25 of the FSGS− biopsies. Foot process effacement was focal in all but five of the biopsies. In four, the foot processes were intact while in one there was extensive effacement.

Clinical

The average length of follow-up was 3 years. Table 1 compares the demographics and historical features of the cases and controls at the time of renal biopsy. The two groups were quite similar at baseline; however, there was a trend towards more patients in the FSGS− group reporting macrohaematuria, and the FSGS+ group having a higher
reported nephrotic presentation. There was a higher proportion of patients in the FSGS+ group with impaired kidney function defined as eGFR < 60 mL/min at the time of biopsy.

Table 2 presents the clinical features at time of biopsy. The FSGS+ group had a higher MAP, lower GFR, lower serum albumin concentration and a higher degree of protein excretion at the time of biopsy. The two groups were similar in regard to anti-hypertensive use, including percentage on an ACE-I or ARB and lipid profiles.

Follow-up clinical data 1 year after biopsy are presented in Table 3. The majority of differences that existed between the two groups at the time of renal biopsy were no longer present, and both groups had a similar MAP, serum albumin concentration and protein excretion rate. The FSGS+ patients were on a higher number of anti-hypertensive medications, and while the use of ACE-I and ARB increased in both groups, a higher percentage of the FSGS+ group were on these drugs at follow-up. Twenty-three percent of the FSGS+ group were prescribed fish oil compared to 29% in the FSGS− group (P = 0.78). Overall, there were few people on immunosuppressive therapy: 15% in the FSGS+ group (all prednisone) and 10% in the FSGS− group (3 prednisone, 1 cyclophosphamide, 1 combination therapy) (P = 0.71).

For the FSGS+ group in the univariate model, the ΔGFR declined at 2.56 mL/min/year (−5.26, 0.14) while the FSGS− group improved at 1.14 mL/min/year (−0.89, 3.17), difference 3.70 mL/min/year (P = 0.03). This in the univariate model. This difference was no longer significant in the multivariate model: the FSGS+ group declined at 0.19 mL/min/year (−14.16, 13.78) and the FSGS+ group improved at 2.85 mL/min/year (−11.64, 17.34), difference 3.04 mL/min/year, P = 0.18. After excluding those with crescents on biopsy (n = 2 and n = 7, respectively), the FSGS+ group declined at 2.67 mL/min/year (−5.60, 0.26) and the FSGS− group improved at 1.40 mL/min/year (−1.00, 3.80), difference 4.07 mL/min/year, P = 0.03 (univariate). In the multivariate model (with crescents excluded), the FSGS+ group improved at 0.34 mL/min/year (−14.56, 15.24) and the FSGS− group improved at 3.51 mL/min/year (−12.27, 19.29), difference 3.17 mL/min/year (P = 0.22). In those with Grade 1 IgA nephropathy, the ΔGFR (univariate) declined at 3.92 mL/min/year in the FSGS+ group (−10.42, 2.58), and improved at 5.61 mL/min/year in the FSGS− group (0.63, 10.59), for a difference of 9.53 mL/min/year (P < 0.01). Finally, in those FSGS+ patients with +++ to ++++ TA/IF on biopsy (n = 7), the ΔGFR declined at 6.63 mL/min/year (−13.02, −0.24), while in those without this degree of TA/IF (n = 19), the GFR declined at 1.00 mL/min/year (−5.62, 3.62), for a difference of 5.63 mL/min/year (P = 0.08).

### Table 2. Baseline clinical data at the time of renal biopsy

<table>
<thead>
<tr>
<th></th>
<th>FSGS+ (n = 26)</th>
<th>FSGS− (n = 49)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>103 (10)</td>
<td>97 (14)</td>
<td>0.03</td>
</tr>
<tr>
<td>Anti-HTN/patient</td>
<td>0.8 (0.8)</td>
<td>1.0 (1.0)</td>
<td>0.69</td>
</tr>
<tr>
<td>ACEI and/or ARB (%)</td>
<td>46 (0.8)</td>
<td>47 (0.9)</td>
<td>0.95</td>
</tr>
<tr>
<td>eGFRa (mL/min)</td>
<td>60 (21)</td>
<td>73 (26)</td>
<td>0.02</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>38 (4)</td>
<td>41 (6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Lipid profile (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5.8 (1.7)</td>
<td>5.3 (1.3)</td>
<td>0.42</td>
</tr>
<tr>
<td>LDL</td>
<td>3.1 (1.1)</td>
<td>3.2 (0.9)</td>
<td>0.62</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.4 (0.5)</td>
<td>1.3 (0.4)</td>
<td>0.31</td>
</tr>
<tr>
<td>TG</td>
<td>2.1 (1.6)</td>
<td>2.1 (1.3)</td>
<td>0.73</td>
</tr>
<tr>
<td>Protein excretion (g/day)</td>
<td>3.0 (2.5)</td>
<td>3.1 (1.1)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Protein excretion quintiles (g/day) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.5</td>
<td>0.0</td>
<td>24.4</td>
<td></td>
</tr>
<tr>
<td>&gt; 0.5 and ≤ 1.0</td>
<td>20.8</td>
<td>24.4</td>
<td></td>
</tr>
<tr>
<td>&gt; 1.0 and ≤ 2.0</td>
<td>20.8</td>
<td>33.3</td>
<td></td>
</tr>
<tr>
<td>&gt; 2.0 and ≤ 3.5</td>
<td>33.3</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>&gt; 3.5</td>
<td>25.0</td>
<td>4.4</td>
<td></td>
</tr>
</tbody>
</table>

FSGS+: cases; FSGS−: controls.
Results presented as means (SD) or percentage where indicated.
aeGFR calculated with modified MDRD equation.

### Table 3. Follow-up clinical data 1 year after biopsy

<table>
<thead>
<tr>
<th></th>
<th>FSGS+</th>
<th>FSGS−</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAPb (mmHg)</td>
<td>99.6</td>
<td>92.1</td>
<td>0.12</td>
</tr>
<tr>
<td>Anti-HTN/patientc</td>
<td>1.5</td>
<td>1.1</td>
<td>0.04</td>
</tr>
<tr>
<td>ACEI and/or ARB (%)c</td>
<td>84.6</td>
<td>67.3</td>
<td>0.11</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>40.5</td>
<td>40.1</td>
<td>0.91</td>
</tr>
<tr>
<td>Protein excretiond (g/day)</td>
<td>1.1 (1.2)</td>
<td>1.0 (1.0)</td>
<td>0.80</td>
</tr>
<tr>
<td>Protein excretion quintiles (g/day)</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>≤ 0.5</td>
<td>37.5</td>
<td>36.0</td>
<td></td>
</tr>
<tr>
<td>&gt; 0.5 and ≤ 1.0</td>
<td>31.2</td>
<td>36.0</td>
<td></td>
</tr>
<tr>
<td>&gt; 1.0 and ≤ 2.0</td>
<td>12.5</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>&gt; 2.0 and ≤ 3.5</td>
<td>12.5</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>&gt; 3.5</td>
<td>6.2</td>
<td>4.0</td>
<td></td>
</tr>
</tbody>
</table>

FSGS+: cases, FSGS−: controls.

Results presented as means (SD), or percentage where indicated.

*a n = 20 in the FSGS+ group and n = 38 in the FSGS− group had 1 year of follow-up; however, not all patients had investigations on a routine basis.

*b n = 18 FSGS+ and n = 33 FSGS− had data available for MAP at 1 year.

c Data carried forward from last visit before study end, initiation of renal replacement therapy or loss to follow-up; n = 26 FSGS+, n = 49 FSGS−.

### Discussion

In this study, we describe a faster decline in GFR in those with focal segmental glomerulosclerosis in association with mild IgA nephropathy than those with mild IgA nephropathy alone.

The proportion of Grade 1 IgA nephropathy was similar in both the FSGS+ and FSGS− groups. However, the FSGS+ group had a significantly more chronic change in the form of obsolete glomeruli and TA/IF than did the FSGS− group. This suggests that the chronic lesions were less likely to be a result of the IgA nephropathy and more likely to be associated with the FSGS component in view of the relative mildness of the glomerular lesion attributable to IgA nephropathy in these cases. The distribution of structural variants of FSGS was similar to that reported in a recent publication [15].

Our FSGS+ cohort had a ‘nephrotic-like’ presentation, higher MAP and more severely impaired kidney function at baseline. These clinical and laboratory factors have been
previously shown to be associated with progressive renal disease in IgA nephropathy [16]. Recently, it has been demonstrated that proteinuria exposure over time is the strongest predictor of renal function decline [17]. In the present study, differences in blood pressure and protein excretion no longer existed 1 year post-biopsy (Table 3). The improvements observed are likely due to a large percentage of patients in the FSGS+ group being prescribed ACEI and/or ARB’s at follow-up that have well-documented antiproteinuric effects in IgA nephropathy [18].

We demonstrated that the FSGS+ group had a significantly faster decline in renal function compared to the FSGS− group in the univariate model; in the fully adjusted model this difference was no longer present. It is likely that many of the variables (i.e. proteinuria, MAP, etc.) are co-linear with FSGS on biopsy and thus it is no longer an independent predictor. We did not include ++ or +++ TA/IF or percentage of obsolete glomeruli as the former was only present in the FSGS+ group, and the latter variable was likely co-linear with the presence of FSGS, as it occurred in a significantly higher percentage of FSGS+ biopsies. We observed similar results after excluding those with crescents on biopsy. Our findings are concordant with previous reports on mild IgA nephropathy and concurrent FSGS. A retrospective study by Packham et al. demonstrated that in patients with IgA nephropathy and normal baseline renal function at the time of biopsy (defined as creatinine <0.12 mmol/L), nephrotic range proteinuria and FSGS lesion on biopsy were associated with development of chronic renal failure or end-stage renal failure within 5 years [10]. A study published by the Southwest Pediatric Nephrology Study Group found that development of end-stage renal disease was common in children with IgA nephropathy and FSGS [11].

A cohort study published by Haas in 1996 reviewed the histologic and clinical features of 18 patients with mild IgA nephropathy (defined as ≤4 cells per mesangial area) and concurrent FSGS lesions on renal biopsy [5,9]. None of the 18 cases showed crescents, and all had <40% globally scarred glomeruli and <40% estimated tubular loss. In agreement with our study, he found that patients with concurrent FSGS lesions had a nephrotic-like picture at the time of renal biopsy [5]. He found no difference in renal survival (defined as ESRD requiring dialysis or transplant) between FSGS+ plus mild IgA nephropathy patients when compared to a contemporaneous cohort of primary FSGS patients (n = 33) or patients with IgA nephropathy of all histologic variants (n = 94). In his 1997 histologic classification system of IgA nephropathy, Haas Grade 1 (≤4 cells/mesangial area) and Haas Grade 2 (Haas Grade 1 plus FSGS) are grouped together as they were observed to have similar renal survival, albeit the number of patients and the duration of follow-up were small (1 of 11 Haas Grade 2 developed ESRD, while 0 of 16 Haas Grade 1 developed ESRD). In the present study, 2/6 of FSGS+ patients with Grade 1 IgA nephropathy (≤3 mesangial cells per segment) reached the same endpoint used by Haas, while none (0 of 10) in the FSGS− group did (P = 0.24); 3/20 in the FSGS+ and 0/39 in the FSGS− group with Grade 2 IgA nephropathy (4–6 mesangial cells per segment) reached this same endpoint (P = 0.09).

It should be noted that the FSGS+ group in the present study may not be exactly comparable to the group of patients with Haas Grade 2 in that the FSGS+ group contained some patients that may be considered Grade 3 (presence of crescents) and Grade 5 (degree of tubular atrophy) according to the Haas classification [9]. The outcome measure we used (∆GFR) is a more sensitive tool to detect progression of kidney disease that is not captured by evaluating renal survival only. When the analysis is limited to those we have assigned Grade 1 IgA only, a cohort similar to Haas Grade 2, those with FSGS experience a faster decline in renal function. It is possible that patients with Haas Grade 2 in the aforementioned study [9] may have experienced similar outcomes if observed for a longer period of time and the same outcome measure was used.

A number of histological changes have been found to be significant prognostic factors in IgA nephropathy. These include grade of glomerular lesion [9,12,19], extent of glomerulosclerosis [19–22] and TA/IF [19,20,22] and the presence of peripheral (capillary wall) immune glomerular deposits [23]. FSGS has been shown to be a significant predictor of outcome in moderate (Lee Grade 3) IgA nephropathy [8] and in combined groups of patients with all grades of IgA nephropathy [24–26]. In the present study, 31% in the FSGS+ group had ++ or +++ TA/IF, in contrast to none in the FSGS− group. In the FSGS+ group a trend towards a greater decline in GFR was observed in the patients with ++ or +++ TA/IF compared to those with no or TA. Of note, four of the five FSGS+ patients who required renal replacement therapy demonstrated TA/IF and >40% obsolete glomeruli on biopsy, indicating that those with more advanced histologic lesions experience inferior renal outcomes. It is important to keep in mind that our study did not specifically look at Haas Grade 2 patients but rather at those whose biopsies showed IgA nephropathy with mild or no mesangial disease with or without FSGS; thus these four FSGS+ patients are properly classified as Haas Grade 5 due to the degree of glomerulosclerosis.

Whether the FSGS and the IgA nephropathy in the FSGS+ patients are directly related is uncertain. FSGS is believed to result from podocyte injury [27]. If the IgA nephropathy were directly responsible for the podocyte injury, peripheral deposits along the glomerular basement membranes would likely be observed, which was not the case in the FSGS+ biopsies. Another possible mechanism whereby IgA nephropathy could lead to secondary FSGS is extensive nephron loss resulting in glomerular hyperperfusion and hypertension and FSGS. If this were the case in the present study, then one would have expected to observe a continuum with respect to the extent of glomerular obsolescence and TA/IF in the two groups. However, this was not seen. Thus, it is likely that the FSGS and IgA nephropathy are not directly related. However, the possibility of a subtle indirect relationship, perhaps as a result of the podocytes being more vulnerable to injury, cannot be excluded.

There are several limitations to our study. Firstly, the overall number of subjects in the FSGS+ group was small, a result of performing a single centre study of a rare pathologic entity. Due to the limited number of biopsies, Grade 1 and Grade 2 IgA nephropathy were combined for the analysis. This was justified as there was no significant
difference in ΔGFR between these two groups overall (data not shown). Secondly, we used a unique definition of mild IgA nephropathy, making a true comparison with the Haas cohort study and others difficult. Thirdly, the primary outcome measure, ΔGFR, was calculated with the modified MDRD formula from the serum creatinine value. Subjects tended to have bloodwork drawn at the same lab over time and therefore acted as their own ‘internal control’ for GFR calculations. Lastly and most importantly, as demonstrated in the present study, it is extremely difficult to discern what (additional) risk the FSGS lesion portends in mild IgA nephropathy or any other glomerular lesion, given that this lesion tends to have associated clinical and histologic characteristics (hypertension, proteinuria, impaired renal function, tubular atrophy/interstitial fibrosis and glomerulosclerosis) that are themselves strong predictors of inferior renal outcomes.

Conclusions

We conclude that in those patients with mild IgA nephropathy on biopsy, the presence of FSGS portends a worse renal outcome. Those with FSGS and mild IgA nephropathy had several associated clinical and histologic findings that are known predictors of inferior renal outcomes, and likely contributed to a faster decline in GFR in this group. Our findings suggest that IgA nephropathy and the FSGS lesion in mild IgA nephropathy may be distinct pathologic entities occurring simultaneously. This study highlights the fact that this pathologic entity should not be assumed to have a benign prognosis, and attention to the FSGS lesion, in particular, is essential.

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Conflict of interest statement. None declared.

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