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Case Series

Clinical heterogeneity in biopsy-proven adult focal segmental glomerulosclerosis

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ABSTRACT

Focal segmental glomerulosclerosis (FSGS) is a histopathological pattern of podocyte injury and a major cause of nephrotic syndrome in adults. Despite a common histopathological diagnosis, patients may exhibit considerable variability in clinical presentation, disease severity, therapeutic response, and renal outcomes. This case series highlights the diverse clinical spectrum of biopsy-proven adult FSGS encountered in routine clinical practice.We report three adult female patients with biopsy-proven focal segmental glomerulosclerosis managed at a rural tertiary care teaching hospital. The first patient presented with long-standing nephrotic syndrome complicated by severe hypoalbuminemia, generalized edema, gross ascites, liver cirrhosis, and poor treatment adherence. The second patient developed relapsing nephrotic syndrome with persistent nephrotic-range proteinuria despite corticosteroid therapy, requiring treatment escalation and emergency hospitalization. The third patient presented predominantly with progressive acute kidney injury and deteriorating renal function in the presence of multiple comorbidities, representing an atypical clinical presentation of FSGS. Renal biopsy established the diagnosis in all three patients and guided individualized management.This case series demonstrates the marked clinical heterogeneity of biopsy-proven adult FSGS despite a common histopathological diagnosis. The findings emphasize the importance of timely renal biopsy, comprehensive clinicopathological correlation, and individualized therapeutic strategies for accurate diagnosis and optimal management.

Keywords: Focal segmental glomerulosclerosis FSGS, Nephrotic syndrome, Proteinuria, Renal Biopsy, Case series

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is a clinicopathological entity marked by segmental scarring of the glomeruli that follows podocyte injury, and it is one of the leading causes of nephrotic syndrome in adults. Rather than a single disease, FSGS covers a heterogeneous group of disorders with distinct causes, clinical presentations, treatment responses, and long-term renal outcomes. According to the KDIGO 2021 Glomerular Diseases Guideline, FSGS is classified into primary, secondary (adaptive or maladaptive), genetic, infection-associated, drug-induced and undetermined causes. Accurate classification is essential because treatment and prognosis differ substantially among these entities.[1-3]

Adult FSGS varies markedly in how it presents. Many patients have classical nephrotic syndrome, but others show hypertension, progressive renal dysfunction, acute kidney injury, or sub nephrotic proteinuria despite similar biopsy findings. This variability often complicates diagnosis and treatment decisions and calls for comprehensive clinicopathological correlation and individualized management.[2-4] The epidemiology, pathogenesis, and treatment outcomes of FSGS have been studied extensively, but reports describing the range of clinical presentations seen in routine practice are still fairly

limited, particularly in resource-constrained settings. We present three biopsy-proven adult cases of FSGS with distinct presentations, disease severity and treatment courses, to show why early recognition, renal biopsy and individualized management matter for patient outcomes.

CASE SERIES

Case 1

A 24-year-old woman with biopsy-proven focal segmental glomerulosclerosis (FSGS) presented with progressively worsening generalized swelling, facial puffiness, bilateral pedal edema and abdominal distension. Generalized edema had been present for one year, with worsening pedal edema and abdominal distension over the preceding month. She had hypertension and nephrotic syndrome secondary to FSGS, with a history of poor treatment adherence and previous default from therapy. There were no documented family history or clinical features suggestive of hereditary nephropathy. However, genetic testing was not performed because of financial constraints and limited patient resources. On examination, she was conscious, oriented, and hemodynamically stable. Pallor, facial puffiness, bilateral pitting pedal edema, generalized edema, and moderate ascites were noted, while cardiovascular, respiratory, and neurological examinations were unremarkable.

Laboratory investigations demonstrated anaemia (hemoglobin 9.3 g/dl), severe hypoalbuminemia (1.48 g/dl), reduced total serum protein (3.68 g/dl), and nephrotic-range proteinuria. Serum creatinine was mildly elevated (1.25 mg/dl) with preserved electrolyte balance. Autoimmune evaluation was negative, and hepatitis C serology was non-reactive. Ultrasonography revealed a coarse nodular liver with gross ascites, while both kidneys were normal in size without hydronephrosis. Echocardiography demonstrated preserved left ventricular systolic function (ejection fraction 65%), excluding a primary cardiac cause of edema.

A previous renal biopsy demonstrated focal segmental glomerulosclerosis of the not otherwise specified (NOS) variant, with segmental sclerosis involving 2 of 20 glomeruli (10%) and minimal tubular atrophy and interstitial fibrosis (<10%). Direct immunofluorescence showed only segmental IgM entrapment, with negative staining for IgA, IgG, C3, C1q, kappa, and lambda light chains, supporting the diagnosis of primary FSGS (Figure 1).

The patient was managed with diuretics (torsemide, metolazone, and spironolactone), Olmesartan, and continued cyclosporine therapy, along with calcium, vitamin D supplementation, and gastroprotection. Diagnostic paracentesis was performed for evaluation of ascites. Her edema improved with optimized medical therapy, and she was discharged with advice regarding strict medication adherence, dietary salt restriction, and regular nephrology follow-up.

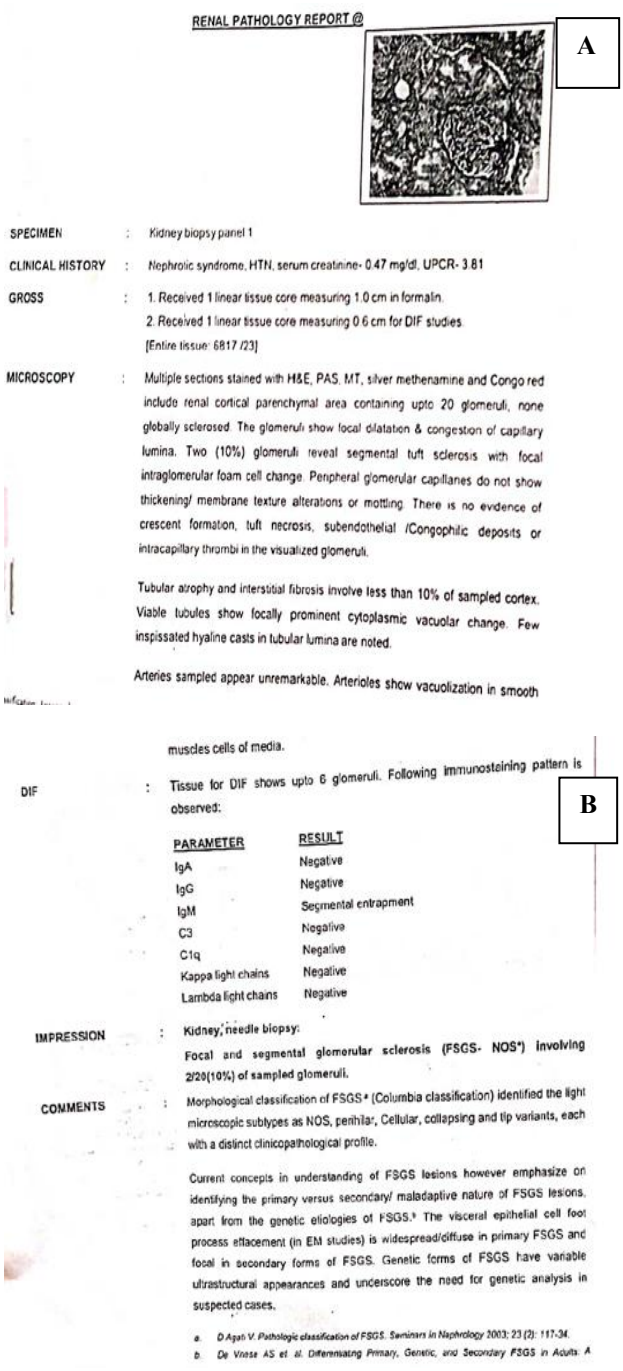

Figure 1: (A) Light microscopic examination of the renal biopsy demonstrated focal segmental glomerulosclerosis, not otherwise specified (NOS) variant, with segmental sclerosis involving 2 of 20 sampled glomeruli (10%), focal foam cell change, and minimal tubular atrophy and interstitial fibrosis (<10%). (B) Direct immunofluorescence showed segmental IgM entrapment with negative staining for IgA, IgG, C3, C1q, kappa, and lambda light chains. The overall findings were consistent with primary focal segmental glomerulosclerosis (FSGS).

Case 2

A 40-year-old woman with biopsy-proven focal segmental glomerulosclerosis (FSGS) presented with generalized body swelling, facial puffiness, bilateral pedal edema, progressive breathlessness, and generalized weakness. She had been diagnosed with nephrotic syndrome four months earlier following an episode of acute nephrotic-nephritic syndrome and was receiving oral corticosteroids, telmisartan, dapagliflozin, and diuretics under regular nephrology follow-up. Despite initial improvement, she developed recurrent edema that progressively worsened over the following weeks, culminating in breathlessness one day before presentation and requiring emergency hospitalization. The current episode represented a clinical relapse of biopsy-proven FSGS.

On examination, she was conscious and hemodynamically stable, with facial puffiness, generalized anasarca, bilateral pitting pedal edema, and mild ascites. Her pulse rate was 106 beats/min, blood pressure was 130/90 mmHg, and oxygen saturation was 98% on room air. Cardiovascular and respiratory examinations were otherwise unremarkable.

Laboratory investigations demonstrated persistent nephrotic syndrome with severe hypoalbuminemia and nephrotic-range proteinuria. Serum albumin improved only marginally (1.76 to 2.38 g/dl), while the urine protein-to-creatinine ratio remained persistently elevated (7.14-7.69). Serum creatinine improved from 1.76 to 0.87 mg/dL with treatment, although heavy proteinuria persisted. Hypercholesterolemia and hypertriglyceridemia were consistent with active nephrotic syndrome. Autoimmune evaluation showed a low-titre positive antinuclear antibody without evidence of systemic autoimmune disease. Ultrasonography demonstrated mildly increased bilateral renal cortical echogenicity with preserved corticomedullary differentiation and mild ascites.

Renal biopsy demonstrated focal segmental glomerulosclerosis of the not otherwise specified (NOS) variant, with segmental sclerosis involving three of twenty glomeruli, mild tubular atrophy and interstitial fibrosis (8–10%), and features of acute tubular injury. Direct immunofluorescence was negative for immunoglobulin and complement deposits, supporting the diagnosis of primary FSGS. Electron microscopy was recommended but could not be performed because of financial constraints and limited patient resources.

Following histopathological confirmation, antiproteinuric therapy was optimized, and oral prednisolone was increased to 50 mg daily while telmisartan, dapagliflozin, and torsemide were continued. Although renal function improved, persistent nephrotic-range proteinuria and recurrent generalized edema indicated an incomplete therapeutic response.

The patient subsequently experienced another clinical relapse requiring emergency hospitalization for management of anasarca, highlighting the variable treatment response and relapsing course of adult FSGS.

Case 3

A 50-year-old woman presented with a one-month history of generalized weakness, multiple joint pains, chronic abdominal pain, and bilateral pedal edema. Unlike the preceding two patients, she presented with progressive renal dysfunction rather than classical nephrotic syndrome, posing a diagnostic challenge. Her medical history was significant for poorly controlled type 2 diabetes mellitus and serological evidence suggestive of rheumatoid arthritis. There was no documented family history of renal disease. She was admitted for evaluation of worsening renal function.

On examination, she was conscious, oriented, and hemodynamically stable. Pallor and bilateral pedal edema were present, while cardiovascular, respiratory, and neurological examinations were unremarkable. Laboratory investigations demonstrated progressive acute kidney injury, with serum creatinine rising from 2.13 to 4.08 mg/dL, accompanied by hyperkalaemia, compensated metabolic acidosis, normocytic anaemia, and persistent hypoalbuminemia.

Glycemic assessment revealed poorly controlled diabetes mellitus (HbA1c 8.0%). Autoimmune evaluation showed positive anti-cyclic citrullinated peptide antibodies with negative antinuclear antibody testing, while extensive infectious work-up was negative. Cardiac evaluation demonstrated preserved cardiac function.

Renal biopsy confirmed focal segmental glomerulosclerosis of the not otherwise specified (NOS) variant, establishing the diagnosis despite the absence of a classical nephrotic presentation. Electron microscopy was recommended but could not be performed because of financial constraints and limited patient resources. The biopsy findings, interpreted in conjunction with the clinical, serological, and biochemical profile, supported FSGS as the underlying cause of the patient's renal impairment.

The patient received supportive management, including correction of electrolyte abnormalities, treatment of metabolic acidosis, optimization of glycemic control, and close monitoring of renal function. Despite treatment, renal function continued to deteriorate during hospitalization, reflecting an aggressive disease course. She was discharged with advice for close nephrology follow-up, serial monitoring of renal function, and continuation of disease-specific therapy according to biopsy findings and subsequent clinical response.

This case illustrates that biopsy-proven FSGS may present predominantly as progressive acute kidney injury rather

than classical nephrotic syndrome, emphasizing the broad clinical spectrum of adult FSGS. The clinical characteristics, biopsy findings, treatment, and short-term outcomes of the three cases are summarized in Table 1.

Table 1: Summary of clinical characteristics and outcomes of the three biopsy-proven FSGS cases.

Characteristics	Case 1	Case 2	Case 3
Age in years/Sex	24/F	40/F	50/F
Initial presentation	Nephrotic syndrome with generalized edema and ascites	Relapsing nephrotic syndrome with anasarca	Progressive acute kidney injury with pedal edema
Major comorbidities	Hypertension, liver cirrhosis	None significant	Type 2 diabetes mellitus, rheumatoid arthritis
Serum creatinine (mg/dl)	1.25	1.76 → 0.87	2.13 → 4.08
Serum albumin (g/dl)	1.48	1.76 → 2.38	Hypoalbuminemia present
Proteinuria	Nephrotic-range	Persistent Nephrotic-range	Proteinuria present
Renal biopsy	FSGS (NOS variant)	FSGS (NOS variant)	FSGS (NOS variant)
Initial treatment	Cyclosporine, diuretics, ARB	Prednisolone, ARB, dapagliflozin, diuretics	Supportive medical management
Clinical course	Partial improvement; previous non-adherence	Persistent proteinuria with relapse	Progressive renal dysfunction despite supportive therapy
Key learning point	Poor adherence contributed to disease progression	Relapsing disease despite immunosuppressive therapy	FSGS may present predominantly as AKI

*AKI = Acute kidney injury; ARB = Angiotensin receptor blocker; FSGS = Focal segmental glomerulosclerosis; NOS = Not otherwise specified.

DISCUSSION

Focal segmental glomerulosclerosis (FSGS) is one of the leading causes of nephrotic syndrome in adults and reflects a histopathological pattern of podocyte injury rather than a single disease entity. Current KDIGO classification recognizes primary, secondary (adaptive), genetic, infection-associated, drug-associated, and undetermined forms of FSGS, each with distinct pathogenic mechanisms, treatment implications, and renal outcomes.[1-3] The Columbia classification adds to this picture by identifying distinct histological variants that may correlate with clinical behaviour and prognosis.[5]

The clinical picture in adult FSGS is highly variable. Nephrotic syndrome is the classical presentation of primary FSGS, but patients may show varying degrees of edema, hypertension, proteinuria, renal insufficiency, or acute kidney injury.[2,4,6,7] In this series, the first patient had long-standing nephrotic syndrome with severe hypoalbuminemia, generalized edema, and massive ascites complicated by poor treatment adherence. The second patient had relapsing disease with persistent nephrotic-range proteinuria despite corticosteroid therapy. The third patient presented mainly with progressive renal dysfunction and acute kidney injury rather than overt nephrotic syndrome. These findings show that identical histopathological lesions can produce markedly different clinical phenotypes, which calls for careful clinicopathological correlation.

Renal biopsy remains the cornerstone for diagnosing FSGS and excluding other glomerular diseases with overlapping clinical features. The KDIGO 2021 Glomerular Diseases Guideline recommends interpreting biopsy findings alongside clinical and laboratory parameters, since histopathology alone cannot reliably distinguish primary from secondary forms or predict treatment response.[1] Electron microscopy demonstrating diffuse podocyte foot-process effacement is particularly useful in distinguishing primary FSGS from maladaptive secondary forms and is recommended when available.[1,2,8] In all three patients, renal biopsy established the diagnosis and guided management, confirming its central role in adults with unexplained proteinuria or renal dysfunction.

Treatment outcomes in FSGS are similarly variable. Current guidelines recommend high-dose corticosteroids as first-line therapy for primary FSGS, while supportive measures-renin–angiotensin system blockade, blood pressure control, sodium restriction, edema management, and cardiovascular risk reduction-remain the backbone of care regardless of cause.[1,3,9] Disease progression depends on more than histopathology alone; treatment adherence, degree of proteinuria, baseline kidney function, and disease subtype all play a part.[3,9,10] In our series, poor treatment adherence likely contributed to persistent nephrotic syndrome in the first patient, while the second patient relapsed despite corticosteroid therapy, showing how unpredictable adult FSGS can be. The third patient's renal function worsened despite supportive management,

another example of how variable treatment response can be in practice.

According to the KDIGO 2021 Glomerular Diseases Guideline, complete remission is defined as reduction of proteinuria to <0.3 g/day (or urine protein-creatinine ratio <300 mg/g) with stable renal function, while partial remission is defined as a reduction in proteinuria of at least 50% from baseline to a value <3.5 g/day with stable kidney function. Relapse refers to recurrence of nephrotic-range proteinuria after achieving remission. Steroid-resistant primary FSGS is defined as failure to achieve complete or partial remission following an adequate course of high-dose corticosteroid therapy, typically after approximately 16 weeks of treatment.[1,8]

Persistent proteinuria is one of the strongest predictors of poor renal outcomes in FSGS. A reduction in proteinuria is linked to better renal survival and is increasingly used as a surrogate endpoint in clinical trials, while persistent nephrotic-range proteinuria predicts progression to chronic kidney disease and end-stage kidney disease.[3,7,10,11] In our second patient, nephrotic-range proteinuria persisted even as serum creatinine improved, showing that biochemical recovery alone does not necessarily mean remission. Serial monitoring of proteinuria, not just conventional measures of renal function, matters during follow-up. Comorbid conditions added further complexity. Liver cirrhosis with gross ascites in the first patient complicated assessment of volume status, while diabetes mellitus and autoimmune disease in the third patient broadened the differential diagnosis of acute kidney injury. Overlapping conditions like these can delay recognition of underlying glomerular disease if renal biopsy is deferred. These cases show why a high index of suspicion for FSGS matters in adults with persistent proteinuria or otherwise unexplained renal dysfunction.[2,4,6]

The main strength of this case series is that it includes biopsy-proven cases representing distinct clinical phenotypes seen in routine practice. Rather than focusing on rare histological variants or novel therapeutic interventions, these cases show that a common pathological diagnosis can come with markedly different clinical manifestations, treatment responses, and short-term outcomes. Large observational cohorts have reported similar findings, supporting individualized management based on comprehensive clinicopathological assessment in adult FSGS.[6,7,10] This report has limitations. The small sample size limits generalizability, and long-term follow-up was not available for all patients. Electron microscopy and genetic testing could not be performed because of financial constraints and limited patient resources, restricting further subclassification of FSGS. Still, these biopsy-proven cases offer practical insight into the diverse clinical spectrum of adult FSGS and support early diagnosis, renal biopsy, and individualized management as ways to improve patient outcomes.[1,3,8]

CONCLUSION

Biopsy-proven adult focal segmental glomerulosclerosis shows considerable clinical heterogeneity despite a common histopathological diagnosis. The three patients in this series had distinct clinical manifestations, disease severity, and treatment responses, which shows the value of integrating clinical findings with renal biopsy to guide diagnosis and management. Early recognition, timely histopathological confirmation, and individualized treatment remain central to improving outcomes for adults with FSGS.

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