# Focal segmental glomerulosclerosis associated with anti-synthetase syndrome: coincidental coexistence or potential causal relationship?

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A 48-year-old female patient (body mass index of 22.3 kg/m²) presented to our hospital May 24, 2025 with bilateral symetric pitting edema of the lower extremities that had persisted for 20 days, accompanied by dizziness and foamy urine. She denied hematuria, dysuria, arthralgia, myalgia, rash, fever, and respiratory symptoms. Her past medical, family, and personal history was unremarkable, with no history of hypertension, obesity, or renal volume reduction.

On admission, her vital signs were as follows: temperature 36.7°C, heart rate 103 beats per min, blood pressure 121/88 mm Hg. Physical examination revealed mild bilateral symmetric pitting edema of the lower extremities, with no other abnormalities detected. Laboratory findings revealed: 24-hour urinary protein excretion of 2.657 g/day (reference range: 0–0.150), serum creatinine of 129 µmol/l (reference range: 41.0–81.0), total cholesterol of 6.74 mmol/l (reference range: 0–5.60), and triglycerides of 2.62 mmol/l (reference range: 0–2.30). Antinuclear antibody testing by indirect immunofluorescence (IIF) was positive at a titer of 1 : 160 with a speckled pattern; further autoimmune workup showed negative results for anti-dsDNA, anti-Sm, anti-SSA/SSB, anti-RNP, antineutrophil cytoplasmic antibodies (ANCA), and anti-PLA2R antibodies, with serum complement levels within normal limits. Chest computed tomography (CT) demonstrated bilateral lower lobe inflammatory infiltrates, chronic fibrotic changes in the right upper lobe, and multiple small pulmonary nodules. Renal ultrasound revealed diffuse renal parenchymal echogenicity abnormalities, multiple cysts, and small calculi in both kidneys (Figure 1 A). Fundus examination showed no hypertensive or diabetic retinopathy, and echocardiography showed no obvious abnormalities.

Renal biopsy revealed 18 glomeruli on light microscopy, with global sclerosis affecting 9 glomeruli and segmental sclerosis involving 2 glomeruli. The remaining glomeruli showed mild, diffuse mesangial hypercellularity and matrix hyperplasia. Tubular epithelial cells showed granular and vacuolar degeneration, with focal atrophy affecting approximately 30% of renal tubules. The renal interstitium exhibited focal edema, multifocal inflammatory cell infiltration, and interstitial fibrosis. Small arteries showed wall thickening and intimal fibrosis. Immunofluorescence staining was negative for IgG, C3, and C1q; albumin was absent; and only trace amounts of IgA and IgM deposition was detected. Electron microscopy demonstrated extensive podocyte foot process effacement

(51–75%), segmental thinning of the glomerular basement membrane, and absence of electron-dense deposits. The pathological diagnosis was focal segmental glomerulosclerosis (FSGS) with moderate chronic tubulointerstitial injury (Figures 1 B–F).

The patient was initially diagnosed with stage 3 chronic kidney disease and FSGS and commenced on telmisartan, finerenone, and atorvastatin. However, she subsequently developed recurrent fevers reaching 40.0°C, followed by progressive myalgia, muscle weakness, and arthralgia with joint swelling. Electromyography (EMG) examination performed after the onset of myogenic symptoms revealed electrophysiological changes consistent with myogenic damage, accompanied by markedly increased spontaneous activity. Repeat laboratory testing revealed a markedly elevated creatine kinase of 1398 U/l (reference range: 40–200), myoglobin level of 1142.0 ng/ml (reference range: 0–70.0), C-reactive protein level of 72.6 mg/l (reference range: 0–6.0), and erythrocyte sedimentation rate of 89 mm/h (reference range: 0–15). All microbiological investigations including

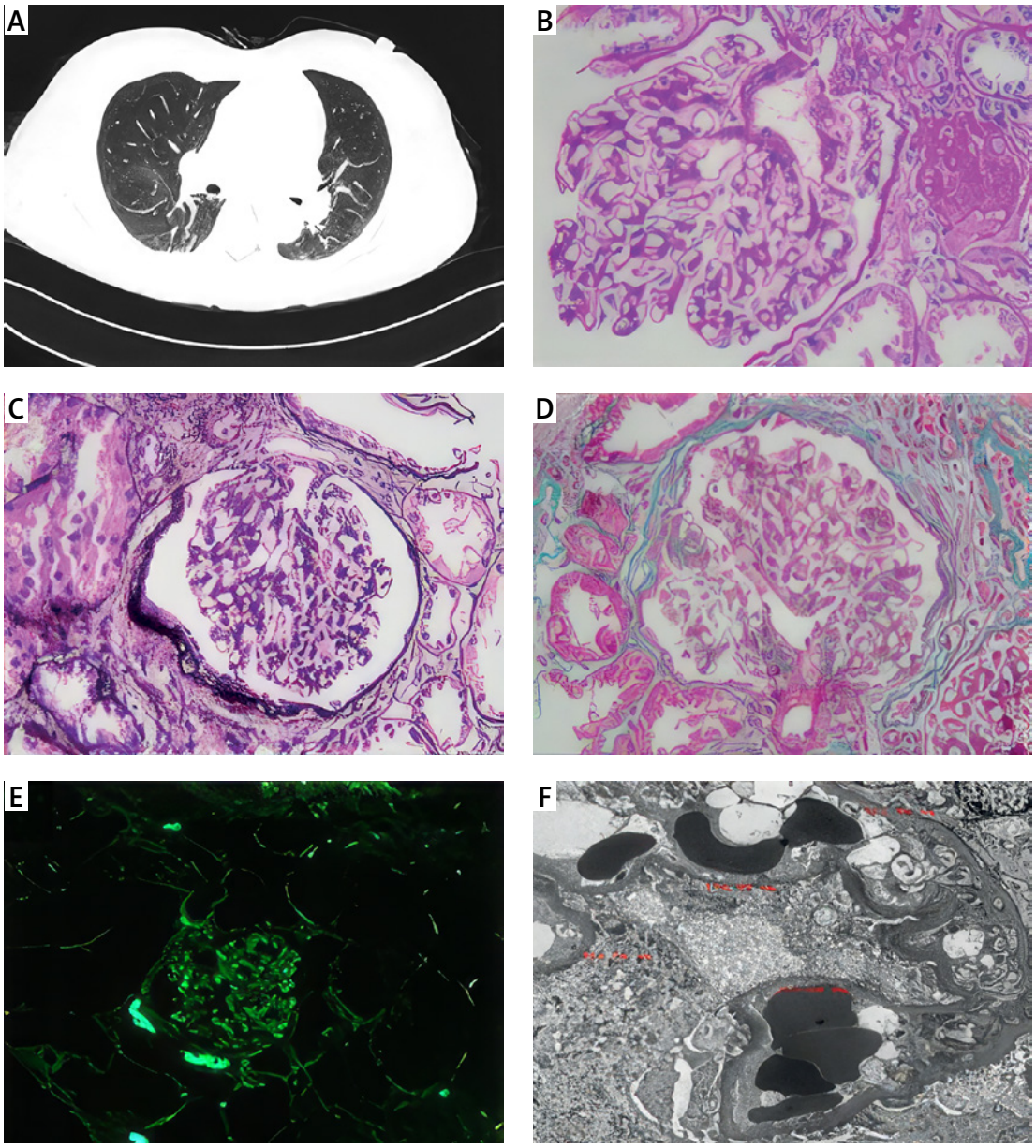


**Figure 1. A** – Lung CT showed inflammatory lesions in both lower lungs, chronic inflammation with fibrosis in the right upper lung, and multiple small pulmonary nodules. **B–F** – Renal biopsy findings. **B** – Globally sclerosed glomerulus (periodic acid-Schiff stain, original magnification ×400). **C** – Segmental sclerosis (Masson stain, original magnification ×400). **D** – Tubular atrophy and interstitial fibrosis (Masson stain, original magnification ×200). **E** – IgM deposition (Immunofluorescence ×400). **F** – Electron microscopy showing extensive foot process fusion (51–75%) and segmental glomerular basement membrane thinning

blood cultures and serum cell-free DNA next-generation sequencing were negative. Follow-up chest CT demonstrated progressive bilateral lower lobe lung lesions, new interstitial abnormalities, and bilateral pleural effusions.

A comprehensive myositis-specific antibody panel was performed, including anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-SRP, anti-MDA5, anti-TIF1γ, anti-NXP2, and anti-Mi-2. All of these antibodies were negative, with only anti-Jo-1 antibody being strongly positive. Based on the clinical and serological constellation, including FSGS, myositis, interstitial lung disease (ILD), arthritis, recurrent fever, and strong positivity for anti-Jo-1 antibody, the diagnosis was revised to anti-Jo-1 positive antisynthetase syndrome (ASS), with FSGS as a possible renal manifestation of ASS.

Treatment was initiated with oral methylprednisolone 32 mg once daily and tacrolimus 1 mg twice daily. The patient's fever resolved promptly, and myalgia, muscle weakness, and peripheral edema improved progressively. At the 3-month follow-up, serum creatinine had decreased to 90.0 µmol/l, and 24-hour urinary protein excretion was 0.993 g. At the 6-month follow-up, the patient remained asymptomatic with normalized muscle enzymes, stable renal function, and 24-hour urinary protein excretion of < 0.5 g. Chest CT demonstrated marked resolution of interstitial lung disease.

Antisynthetase syndrome is a distinct clinical subset of idiopathic inflammatory myopathies (IIM) characterized by the presence of autoantibodies targeting aminoacyl-tRNA synthetase (ARS). Classic clinical manifestations include polymyositis, dermatomyositis, interstitial lung disease, inflammatory arthritis, systemic fever, mechanic's hands, and Raynaud's phenomenon. Anti-Jo-1 antibody, targeting histidyl-tRNA synthetase, is the most prevalent anti-aminoacyl-tRNA synthetase antibody, accounting for 60–80% of all cases [1].

Traditionally, organ involvement in ASS has been observed predominantly in skeletal muscles, lungs, and joints. Renal involvement is exceedingly rare and under-recognized in clinical practice, and frequently overlooked, especially when it manifests as the initial presenting feature. Most reported renal complications in IIM result from rhabdomyolysis-associated acute kidney injury, whereas glomerular diseases attributable to autoimmune mechanisms are exceedingly rare [2]. We report a rare case of anti-Jo-1 positive ASS that presented initially with FSGS, followed by the emergence of classic extrarenal manifestations.

ASS is a systemic autoimmune disorder characterized by marked clinical heterogeneity. Although renal involvement has been reported in 20–23% of patients with idiopathic inflammatory myopathies, it is most commonly attributable to rhabdomyolysis-associated acute tubular necrosis [2]. Glomerular diseases associated with ASS are extremely rare, with only isolated case reports of mesangial proliferative glomerulonephritis, membranous nephropathy, and crescentic glomerulonephritis [3–5]. To our knowledge, this is the first reported case of ASS presenting initially with FSGS.

To clarify the etiology of FSGS, we systematically excluded common alternative causes. Hypertension-related FSGS was ruled out because the patient had no prior history of chronic hypertension, with normal blood pressure on admission and no sustained hypertension documented during hospitalization. No evidence of hypertensive end-organ damage was identified, including hypertensive retinopathy or structural and functional abnormalities of the left ventricle; renal biopsy also showed no typical features of hypertensive arteriolosclerosis. Obesity-related FSGS was ruled out because the patient had a normal body mass index and no history of long-term overweight or obesity. This subtype of secondary FSGS is mediated by chronic glomerular hyperfiltration, typically follows an indolent progressive course, and responds poorly to immunosuppressive therapy. In contrast, the patient achieved rapid and significant remission of proteinuria after initiation of glucocorticoid plus calcineurin inhibitor therapy. Adaptive FSGS was considered unlikely because the patient had no medical history of conditions leading to reduced nephron mass, such as unilateral nephrectomy or congenital renal hypoplasia. The pathogenesis of adaptive FSGS is primarily driven by hemodynamic mechanisms, and it exhibits no response to immunosuppressive treatment, whereas our patient showed marked improvement in both renal function and proteinuria following immunomodulatory therapy. Genetic FSGS was deemed highly improbable, though definitive exclusion is not possible without targeted genetic sequencing. Adult disease onset, absent family history of chronic kidney disease, and rapid sustained remission of proteinuria after combination immunosuppressive therapy are all inconsistent with the classic clinical features of hereditary FSGS. Furthermore, other autoimmune etiologies, including lupus nephritis, Sjögren syndrome-associated renal involvement, and ANCA-associated vasculitis, were ruled out based on negative comprehensive autoantibody panel results and normal serum complement levels. Collectively, anti-synthetase syndrome (ASS) represents the most likely etiology of FSGS in this patient, although coincidental coexistence of these two rare disorders cannot be fully excluded in a single case report [6].

The pathogenesis of FSGS-associated ASS remains incompletely understood. Based on existing evidence, we propose three biologically plausible hypotheses: (1) Direct podocyte injury mediated by anti-Jo-1 antibodies: histidyl-tRNA synthetase, the autoantigen targeted by anti-Jo-1 antibodies, is constitutively expressed in glomerular podocytes. Anti-Jo-1 antibodies may cross-react with podocyte antigens through molecular mimicry, potentially contributing to cytoskeletal disorganization and foot process effacement [7]. (2) Indirect injury mediated by inflammatory cytokines: elevated circulating levels of pro-inflammatory cytokines including IL-6, IL-1β, and TNF-α observed during active ASS may impair glomerular endothelial cells, mesangial cells, and podocytes, thereby promoting extracellular matrix deposition and progressive glomerulosclerosis [8, 9]. (3) Renal vascular injury: ASS may involve small renal arteries, resulting in intimal hyperplasia and luminal stenosis, leading to chronic renal ischemia and secondary FSGS [10]. We acknowledge that these hypotheses require further validation through functional studies and larger cohort studies, as the current evidence is limited to this single case.

This case highlights several important clinical considerations. First, clinicians should maintain a high index of suspicion for ASS in atypical presentations. Some patients do not present with classic myositis or ILD at the early stage; instead, isolated organ damage such as renal lesions may appear first, followed by typical extrarenal manifestations. Second, in patients with unexplained FSGS, especially those exhibiting antinuclear antibody positivity, recurrent non-infectious fever, elevated skeletal muscle enzymes, or interstitial lung abnormalities, screening for myositis-specific antibody should be performed to exclude ASS. Third, early initiation of glucocorticoids combined with calcineurin inhibitors may effectively suppress disease activity and help preserve renal function in ASS-associated glomerular disease.

We report a rare case of anti-Jo-1-positive ASS that presented initially with FSGS. This case expands the recognized clinical spectrum of renal involvement in ASS and emphasizes the importance of evaluating for autoimmune etiologies in patients with unexplained FSGS. Timely diagnosis and initiation of appropriate immunosuppressive therapy are crucial for optimizing patient outcomes.

This study has several limitations. First, as a single case report, definitive causality between ASS and FSGS cannot be established, and coincidental coexistence of the two rare conditions cannot be fully ruled out. Second, muscle MRI and biopsy were not performed, as the patient declined these additional examinations after rapid clinical improvement, though existing clinical, serological, and EMG findings were sufficient for ASS diagnosis. Third, we have not completed targeted genetic testing for hereditary FSGS; nor have we fully clarified the nature of the glomerular IgM deposits, which require further follow-up investigations. Fourth, the proposed pathogenic mechanisms remain hypothetical, requiring further experimental validation.

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## Ethical approval

Not applicable.

## Conflict of interest

The authors declare no conflict of interest.

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