IJKD KIDNEY DISEASES

# Tip Lesion Variant of Focal Segmental Glomerulosclerosis in Familial Relapsing Polychondritis

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Relapsing polychondritis (RP) is a rare autoimmune disorder with minimal reported renal involvement. We describe the first case of tip lesion variant of focal segmental glomerulosclerosis (FSGS) in a 60-year-old male with familial RP. The patient initially presented with nephrotic syndrome concomitant with RP, which was diagnosed 17 years ago; renal biopsy revealed minimal change disease at that time. Over the subsequent 17 years, he experienced four RP flares without nephrotic syndrome recurrence until his recent presentation with severe nephrotic syndrome. Repeated renal biopsy confirmed tip lesion variant of FSGS, demonstrating excellent response to corticosteroid therapy with prednisolone 1 mg/kg/day; proteinuria declined from 7g/24h to 0.98g/24h and serum albumin increased from 0.9g/dL to 2.2g/dL within three months. This case underscores the importance of considering FSGS in RP-associated nephrotic syndrome and suggests potential shared immune/genetic mechanisms. To our knowledge, this represents both the first report of tip lesion FSGS in RP and the first documented familial RP case with FSGS development.

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Case Report

## INTRODUCTION

Relapsing polychondritis (RP) is a rare, immune-mediated systemic disorder characterized by recurrent inflammation of cartilaginous structures, including the ears, nose, larynx, and trachea, often accompanied by ocular, audio-vestibular, and cardiovascular manifestations.[1,2] With an estimated incidence of 3.5 cases per million annually, RP predominantly affects adults aged 40–60 years, though familial cases suggesting a genetic predisposition are increasingly recognized.[3,4] While RP primarily targets proteoglycan-rich tissues, renal involvement is uncommon and poorly characterized. Reported renal pathologies include IgA nephropathy, [5-8] membranous nephropathy,[9,10] and rarely, focal and segmental glomerulosclerosis (FSGS), [11, 12] and notably, the Tip lesion variant of FSGS defined by segmental sclerosis at the tubular pole has never been associated with RP. Amyloidosis has also been described in some cases.[13]

Tip lesion variant of FSGS typically exhibits steroid responsiveness and a favorable prognosis compared to other FSGS subtypes.[14, 15] Recently, a genetic mutation linked to RP was identified through exome sequencing in a Chinese family.[16] The significance of our observation is to describe this first case of familial RP in which a member developed severe nephrotic syndrome with tip lesion variant of FSGS.

## CASE PRESENTATION

A 60-year-old man with a 17-year history of relapsing polychondritis (RP) was referred to our nephrology department in May 2024 for evaluation of progressive generalized edema, an 8-kg weight gain, and exertional dyspnea (New York Heart

Association class II) that had developed over the preceding two months.

The patient's RP was first diagnosed at age 43, which coincided with the initial onset of nephrotic syndrome. At that time, a renal biopsy revealed 12 glomeruli that appeared normal on light microscopy with negative immunofluorescence. There was no evidence of tubular atrophy, interstitial fibrosis, or segmental sclerosis. Based on these findings, a diagnosis of minimal change disease (MCD) was made.

His subsequent RP course was characterized by recurrent bilateral auricular chondritis, seronegative polyarthritis, and episcleritis, managed with intermittent corticosteroids. Between 2017 and 2024, he experienced four RP flares without recurrence of nephrotic syndrome until the current presentation.

Notably, the patient had a strong familial predisposition for RP, with his father and paternal aunt affected (II-6 and II-7, Figure 1), although no consanguinity was reported. His brother (III-10, Figure 1) was also followed in our Internal Medicine Department for RP, presenting with similar auricular lesions and swollen, sclerotic fingers (Figure 2). A comprehensive immunological workup excluded lupus and scleroderma in both siblings. The brother was maintained on 10 mg of corticosteroids every other day, with escalation to 1 mg/kg/day tapered over 6–12 months during relapses associated with elevated CRP and ESR.

The patient was ex-smoker (10 pack-years) with no recent infections and no history of COVID-19 vaccination. On admission, he was afebrile (37.4°C) with blood pressure of 110/80 mmHg. Examination revealed active RP manifestations, including auricular deformity (Figure 3), left-sided sensorineural hearing loss, rhinolalia, and episcleritis. Signs of nephrotic syndrome were evident, with 3+ pitting edema of both lower limbs and generalized anasarca. His weight was 70 kg, height 178 cm, and body mass index (BMI) 21.6 kg/m².

Pedigree of the Algerian family with relapsing polychondritis (RP) and tip lesion variant of focal segmental glomerulosclerosis (FSGS).

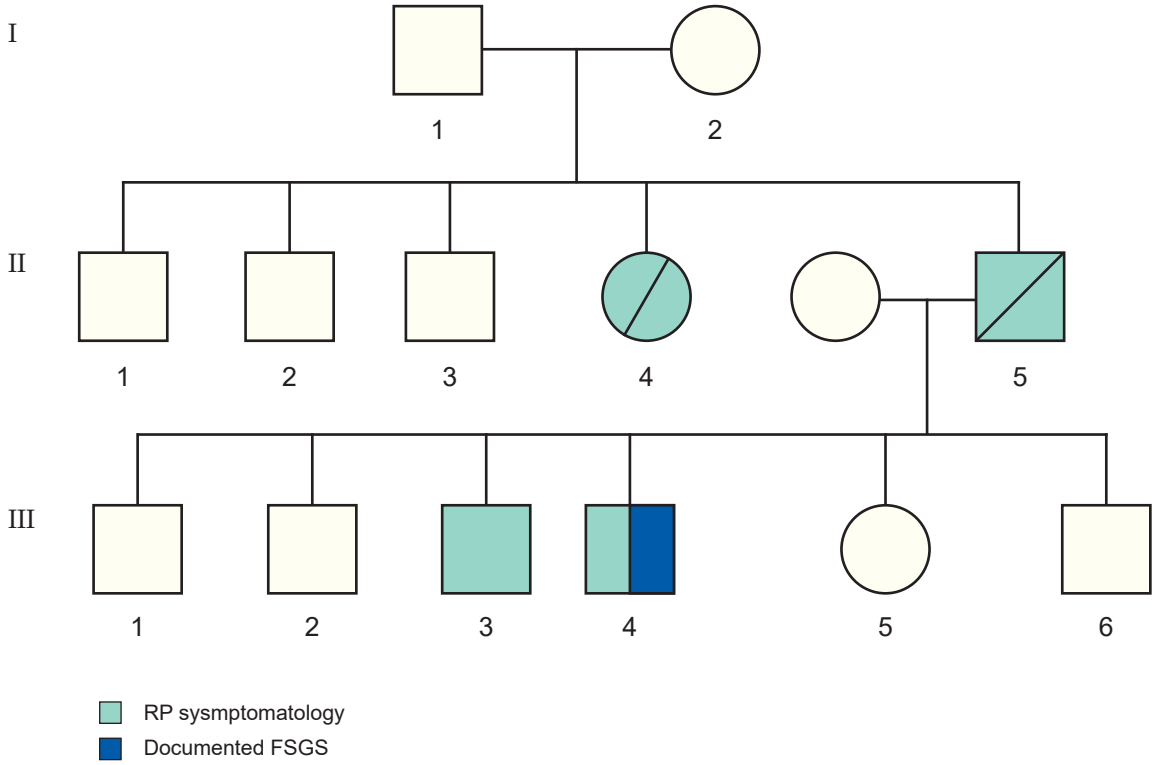



**Figure 1.** The pedigree spans three generations. Circles represent females, squares represent males. Filled symbols indicate affected individuals. Individual III-11 (proband) is marked by an arrow and carries both RP and tip lesion FSGS. Affected family members include II-6, II-7 (father and paternal aunt of the proband), and III-10 (brother of the proband), all of whom have RP without documented FSGS. No consanguinity was reported. The proband is the only family member diagnosed with Tip lesion FSGS.

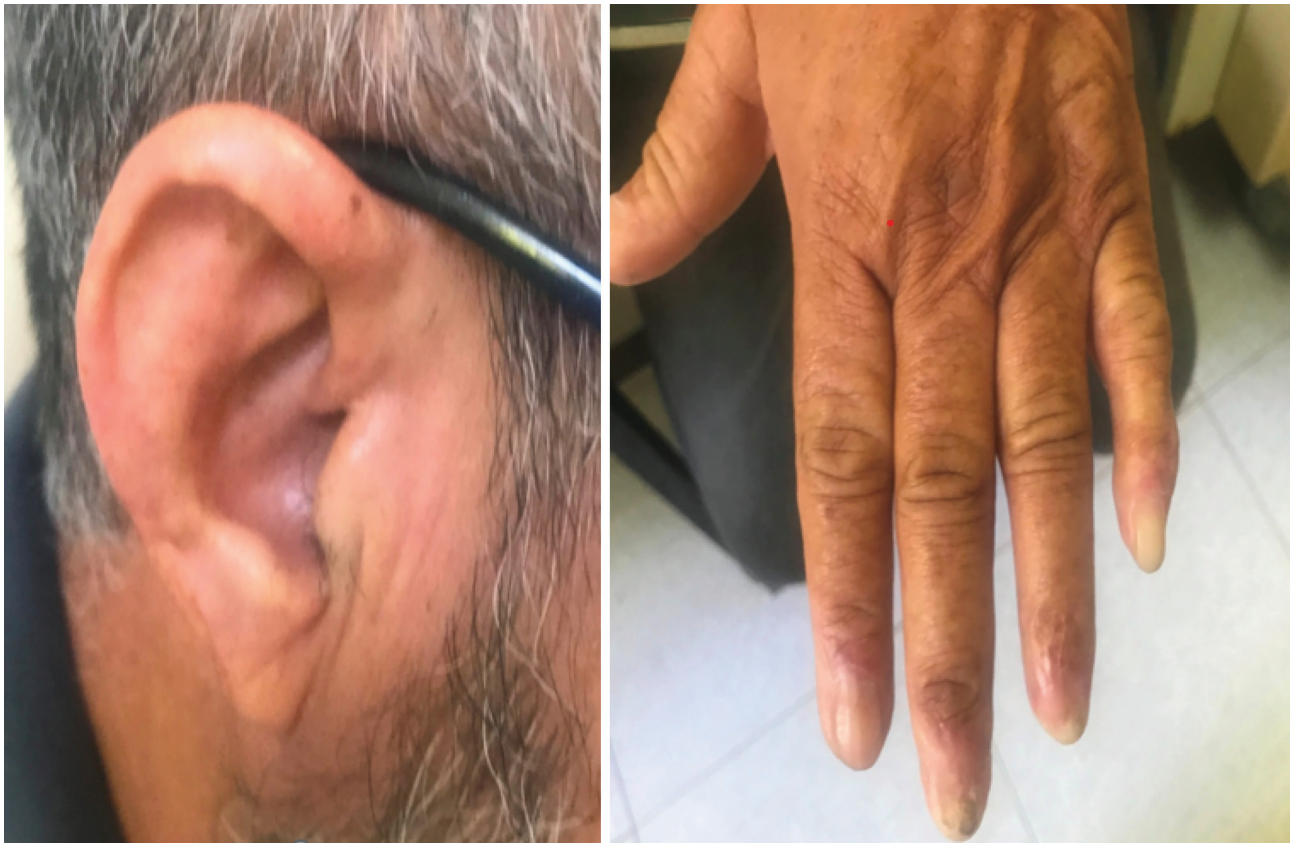


**Figure 2.** Auricular chondritis and distal necrosis of patient III 10.

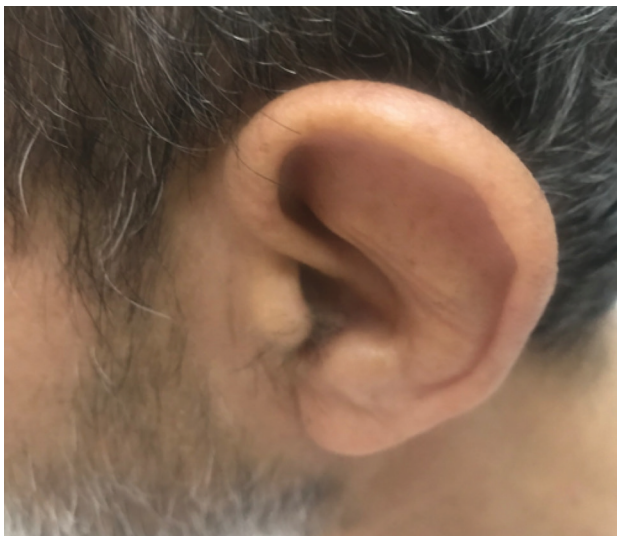
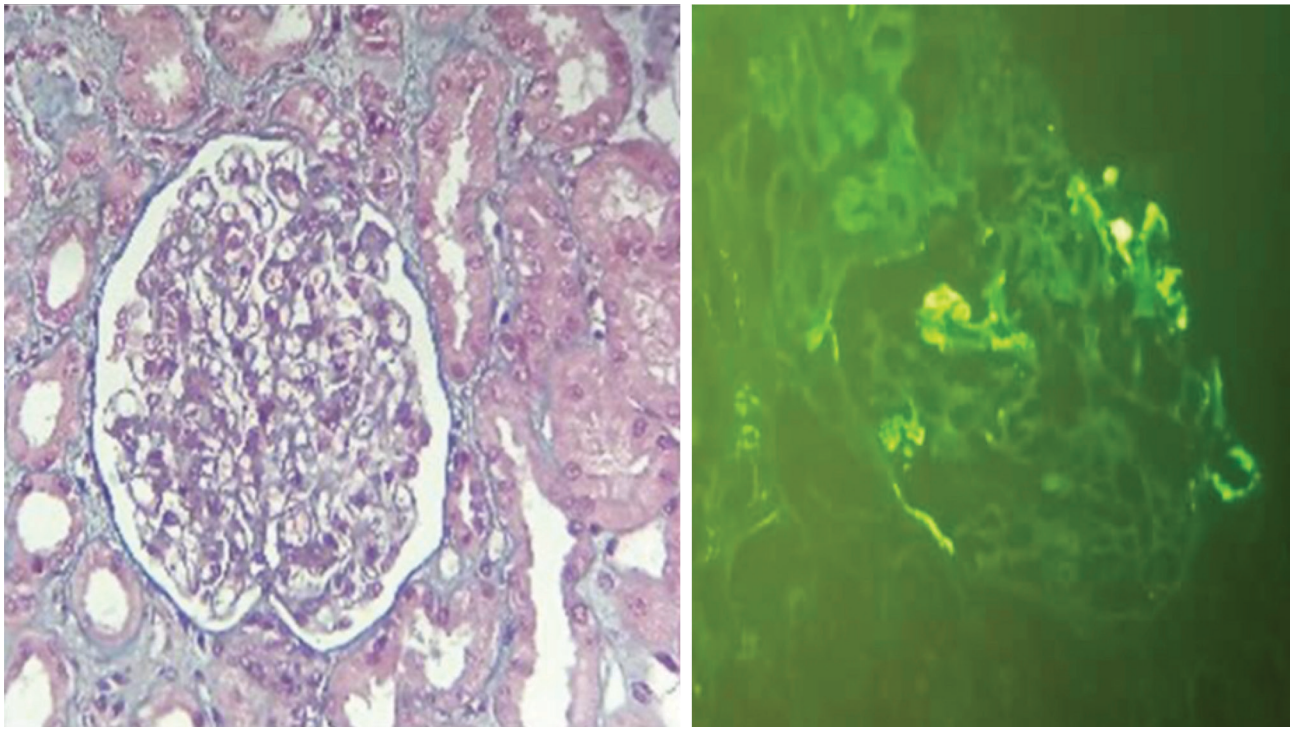


**Figure 3.** Auricular chondritis of the patient III 11 (index).

Laboratory findings confirmed nephrotic syndrome with 7 g/24 h proteinuria and hypoalbuminemia (serum albumin of 2.2 g/dL). Serum creatinine was 0.7 mg/dL, with an estimated glomerular filtration rate (eGFR) of 95 mL/min/1.73 m², indicating preserved kidney function. Serological and immunological testing including anti-nuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA), , anti-neutrophil cytoplasmic antibody (ANCA), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and cryoglobulins were negative.

Renal biopsy (ultrasound-guided, left kidney) demonstrated 13 glomeruli, of which one was globally sclerotic. Four glomeruli showed segmental sclerosis at the urinary pole with epithelial cell hypertrophy and adhesion to Bowman's capsule, consistent with tip-lesion FSGS according to the Columbia classification (Figure 4A). Interstitial fibrosis and tubular atrophy involved ~20% of the cortical area. Immunofluorescence revealed granular IgM (1-2+) and C3 (1+) limited to the sclerotic segments, while IgG, IgA, and C1q were negative (Figure 4B). Electron microscopy was not performed, as it is not routinely available in our practice.

Secondary causes of FSGS were systematically excluded. The patient had a normal BMI, no history



A B

**Figure 4.** Renal biopsy of patient III 4. (A) Trichrome stain (400×) showing Tip lesion (arrow). (B) IgM granular deposits along sclerotic segments IF (400×).

of chronic hypertension (confirmed by 24-hour ambulatory blood pressure monitoring), normal fundoscopic examination, no prior vesicoureteral reflux (excluded by retrograde cystoureterography), and no history of nephrotoxic drug exposure (NSAIDs were only used intermittently, and there was no use of heroin, cocaine, bisphosphonates, or interferon). He reported no symptoms suggestive of obstructive sleep apnea, and no recent viral infections (HBV, HCV, HIV, CMV, EBV) were detected. Renal ultrasonography showed normal-sized kidneys with good corticomedullary differentiation and normal echogenicity. After exclusion of secondary etiologies, RP was considered the systemic disease underlying the FSGS.

Treatment consisted of oral prednisolone 1 mg/kg/day combined with losartan 50 mg/day. Proteinuria decreased to 2 g/24 h after one month (partial remission). At three months, while the corticosteroid regimen had been reduced to 1 mg/kg every other day, proteinuria further declined to 0.98 g/24 h, consistent with complete remission. At six months, he was on 0.25 mg/kg of prednisolone every other day, proteinuria decreased to 0.3 g/24 h with serum albumin rising to 3.3 g/dL. At 12 months, the patient remained in remission with no relapse, maintained on prednisolone 10 mg every other day (Figure 5).

## DISCUSSION

This report describes the first documented case of tip lesion variant of focal segmental glomerulosclerosis (FSGS) in a patient with familial relapsing polychondritis (RP) in the Nephrology Department of Bab El Oued University Hospital Center (Hôspital Mohamed Lamine Debaghine), Algiers, Algeria, adding to the limited literature on renal involvement in this rare autoimmune disorder. The patient's progression from minimal change disease (MCD) to FSGS over 17 years suggests a potential shared pathophysiology between RP and glomerular injury, warranting further exploration.

### RP and Renal Disease: A Rare Association

Renal manifestations in RP are uncommon, with prior reports having described IgA nephropathy,[5-8] membranous nephropathy,[9,10] and only two cases of FSGS.[11,12] However, the tip lesion variant of FSGS characterized by segmental sclerosis at the tubular pole has not been previously linked to RP. The

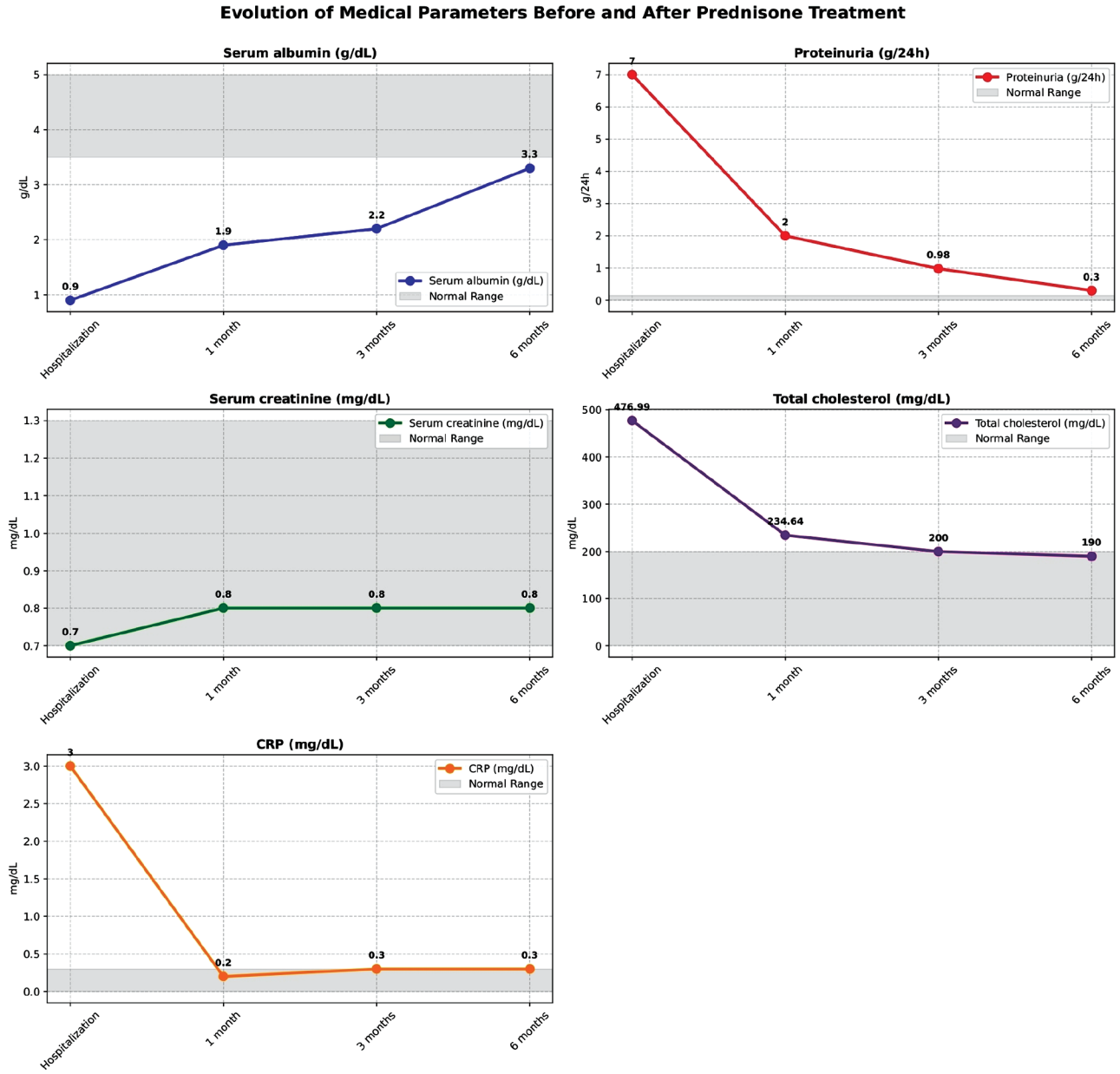



**Figure 5.** Evolution of Medical parameters before and after oral prednisone treatment.

initial presentation of nephrotic syndrome with MCD, coinciding with the first RP flare, strongly suggested a common immunological trigger at disease onset. The recurrence of nephrotic syndrome 17 years later with a diagnosis of tip lesion FSGS poses a significant diagnostic challenge. The initial MCD diagnosis could represent a sampling error, where the tip lesion, which may have been present in non-sampled juxtamedullary glomeruli (where FSGS typically begins), was missed on the first biopsy. Alternatively, this could represent a true transformation or progression from a podocytopathy (MCD) to a sclerosing lesion (FSGS) over nearly two decades of relapsing autoimmune inflammation.

Systematic exclusion of all classic secondary causes of FSGS in our patient reinforces the likelihood that this lesion is directly associated with the underlying familial RP, suggesting a possible common genetic susceptibility to podocyte injury. The exclusion of secondary FSGS was rigorous (normal BMI, no chronic hypertension, no vesicoureteral reflux, no nephrotoxic drugs, no sleep apnea, no viral infections). Therefore, medication-induced, obesity-related, or hyperfiltration-mediated FSGS

are highly unlikely, leaving RP as the most plausible underlying etiology. Regarding pathogenesis, while molecular mimicry between cartilage and glomerular basement membrane components (e.g., heparan sulfate proteoglycans) could theoretically trigger podocyte injury,[17,18] the presence of IgM and C3 deposits in the sclerotic segments is a common finding in primary FSGS. This is not considered evidence of an immune complex-mediated process, but rather a non-specific trapping of immunoglobulins in areas of sclerosis (an "innocent bystander" effect) or a result of podocyte injury exposing novel antigens. Therefore, these deposits do not support an immune complex pathogenesis but are consistent with the diagnosis of FSGS.

### mTOR Pathway Dysregulation

Both RP and FSGS have been linked to mTOR signaling hyperactivation.[19] Chronic inflammation in RP may upregulate mTOR, promoting podocyte dysfunction and sclerosis. This aligns with the efficacy of corticosteroids (which indirectly modulate mTOR) in our patient, though targeted therapies like sirolimus could be explored in refractory cases.[20]

### Genetic Predisposition

Familial clustering of RP (as seen in our patient's pedigree) hints at a genetic component, such as mutations in COL2A1 or other cartilage-related genes.[16] Whether these variants also predispose to FSGS remains unknown but warrants genetic profiling in future studies.

### Clinical Implications

Diagnostic Vigilance: RP patients with proteinuria should undergo early renal biopsy to identify FSGS variants, as tip lesions have a favorable steroid response.[20,21] Our patient achieved complete remission with corticosteroids, underscoring this variant's treatability. Monitoring: Given RP's relapsing nature, long-term nephrological follow-up is essential to detect late-onset glomerular disease.

Therapeutic Considerations: While corticosteroids are first-line, Janus kinase (JAK) inhibitors (e.g., tofacitinib) may hold promise for steroid-resistant cases, as reported in other tip lesion FSGS cases.[20]

## LIMITATIONS

This single-case study cannot establish causality between RP and FSGS. Genetic testing (e.g., whole-exome sequencing) was not performed, and the absence of electron microscopy limits ultrastructural insights.

## CONCLUSION

Our case highlights Tip lesion FSGS as a novel renal complication associated with RP, likely mediated by shared immune or genetic mechanisms. Clinicians should consider FSGS in RP patients with nephrotic syndrome, as early intervention can mitigate progression. Future research should explore autoantibody profiles in RP-associated FSGS, the role of mTOR (e.g., sirolimus) for refractory RP-associated glomerulopathies and explore genetic links (e.g., COL2A1 mutations) via whole-exome sequencing in familial RP-FSGS cases.

## AUTHOR CONTRIBUTIONS

G.K: Clinical diagnosis, patient management, identification of relapsing polychondritis I performed the patient follow-up, family investigation, and wrote the manuscript., R.HS: Formal analysis, histopathological reading of the renal biopsy. S.C: Writing review & editing, language revision, correction of errors in the manuscript. LD: Investigation, renal biopsy procedure., N.D: Supervision, oversight of the pathology department, validation of histopathological interpretation., A.B: Supervision, head of the nephrology department, overall project administration.

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## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

This article does not contain any studies involving human participants or animals conducted by any of the authors.

## INFORMED CONSENT

Informed consent includes publication of images

was obtained from the patient whose case is reported in this paper.

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