Nefrologia 46 (2026) 501466

Sociedad Española de Nefrología

nefrología

Revista de la Sociedad Española de Nefrología

journal homepage: www.revistanefrologia.com

Case report

A very rare case report with *INF2* gene mutation related sporadic FSGS and response to treatment

Informe de un caso muy raro con GEFS esporádica relacionada con la mutación del gen INF2 y respuesta al tratamiento

Kübra Kaynar [a,*], İbrahim Erbay[b], Hakan Ertan[a], Beyhan Güvercin[a], Sevdegül Aydın Mungan[c], Neslihan Cinkara[d]

[a] *Department of Nephrology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey*
[b] *Department of Internal Medicine, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey*
[c] *Department of Pathology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey*
[d] *Department of Medical Genetics, Kanuni Training and Research Hospital, Health Sciences University, Trabzon, Turkey*

ARTICLE INFO

Keywords:
Glomerulosclerosis
Focal segmental
INF2 protein
Human
Mutation

ABSTRACT

Focal segmental glomerulosclerosis (FSGS) is classified into three forms: primary, secondary, and genetic FSGS. Genetic FSGS is defined as sporadic or familial types. The mutations in the gene inverted formin (INF)2 are mostly encountered in familial genetic FSGS cases. A 29-year-old female patient without any parental consanguinity and family history of kidney disease, who had nephrotic syndrome with inactive urine sedim and normal glomerular filtration rate was diagnosed as kidney biopsy-proven FSGS. She had partial remission under treatment of prednisone and cyclosporine. The patient was re-evaluated due to presence of relapse in proteinuria during her pregnancy. Genetic analysis revealed a heterozygous missense variant (NM_022489.4: c.653G > A; p.R218Q) in the *INF2* gene. This case report presents a young female patient with sporadic FSGS induced by *INF2* mutation.

Palabras clave:
Glomeruloesclerosis
Segmental focal
Proteína INF2
Humana
Mutación

RESUMEN

La glomeruloesclerosis focal y segmentaria (GEFS) se clasifica en tres formas: primaria, secundaria y genética. La GEFS genética se define como esporádica o familiar. Las mutaciones en el gen INF2 se encuentran principalmente en casos de GEFS genética familiar. Una paciente de 29 años, sin consanguinidad parental ni antecedentes familiares de enfermedad renal, con síndrome nefrótico con sedimentación urinaria inactiva y tasa de filtración glomerular normal, fue diagnosticada con GEFS confirmada mediante biopsia renal. Presentó remisión parcial bajo tratamiento con prednisona y ciclosporina. La paciente fue reevaluada debido a la presencia de una recaída de proteinuria durante el embarazo. El análisis genético reveló una variante heterocigótica sin sentido (NM_022489.4: c.653G > A; p.R218Q) en el gen INF2. Este informe de caso presenta el caso de una paciente joven con GEFS esporádica inducida por la mutación INF2.

Introduction

Focal segmental glomerulosclerosis (FSGS), defined as presence of characteristic light microscopic (LM) findings in kidney biopsy (segmental glomerular hyalinosis and/or sclerosis without specific immune deposits) is responsible for nearly 30% of the cases with nephrotic syndrome. The pathogenesis and treatment of FSGS differ between the patients based on the classification which includes primary, secondary, and genetic.[1]

The prevalence of genetic FSGS (sporadic or familial) can change from less than 5–30% of all FSGS cases.[2] Familial FSGS are nearly 1% of all FSGS cases.[3] At the initial time of diagnosis, absence of nephrotic syndrome, presence of immunosuppressive drug-resistant nephrotic

* Corresponding author.
E-mail address: kkaynar@yahoo.com (K. Kaynar).

https://doi.org/10.1016/j.nefroe.2026.501466
Received 3 August 2025; Accepted 23 November 2025
2013-2514/© 2025 Sociedad Española de Nefrología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

syndrome, family history for FSGS, and syndromic presentation in a patient whom diagnosed as FSGS on kidney biopsy require genetic screening.[2,4] The most common genetic defects responsible for FSGS development in adults change based on the type of genetic mutation. For sporadic cases, mutations in the genes for nephrin (NPHS1) were commonly encountered, however, for monogenic cases, mutations in the gene inverted formin (INF)2 were mostly detected.[2,5]

Here, we present the outcome and follow up of a patient whom diagnosed as genetic FSGS secondary to sporadic mutation in *INF2* gene four years ago.

Case presentation

A 29-year-old female patient without any parental consanguinity and family history of kidney disease, who had previously been diagnosed as hypothyrodism and nephrotic syndrome (proteinuria of 4.7 g/d) with inactive urine sedim and estimated glomerular filtration rate (eGFR) of 137 mL/min/1.73 m^2 (by CKD-EPI based formula) secondary to kidney biopsy-proven FSGS during her first pregnancy when she delivered a preterm (36 week) and low birth weight (2000 g) infant four years ago, and prescribed levothyroxine (50 mcg/d), prednisone (0.5 mg/kg/d), calcium + vitamin D, and cyclosporine (2.5 mg/kg/d) was re-evaluated due to presence of relapse in proteinuria (Fig. 1). Kidney biopsy which had been performed four years ago, had revealed global glomerular sclerosis in 5 out of 26 glomeruli, segmental glomerular sclerosis in 1 out of 26 glomeruli, mild–moderate cortical interstitial fibrosis (25%), subintimal arterial hyalinosis, by light microscopy (LM) (Fig. 2). However, fibrinoid necrosis, crescents, and diffuse basal membrane thickenings were not detected. There was no immune deposition (C3, C1q, C4d, Ig G, Ig A, Ig M, amyloid A) by immunofluorescence microscopy (IFM). Autoantibodies (such as antinuclear, anti-dsDNA, anti-Ro-52, anti-Ro/SSA, anti-centromere, anti-La/SSB, anti-Scl 70, anti-Smith, anti-glomerular basement membrane, anti-cardiolipin and anti-neutrophil cytoplasmic antibodies), and hypocomplementemia (C3 and C4 levels) were not detected.

After clinical evaluation of the patient and absence of complete remission despite the optimum treatment Schedule, we performed Common Inherited Disorders Panel, which includes 3324 genes [nephrin (NPHS1), *podocin* (NPHS2), *alpha-actinin-4* (ACTN4), transient receptor potential cation channel subfamily C member 6 (TRPC6), *phospholipase C epsilon 1* (PLCE1), etc.]. Genetic analysis revealed a heterozygous missense variant (NM_022489.4:c.653G > A; p.R218Q) in the *INF2* gene. This alteration is located in exon 4 of the *INF2* gene and results in the substitution of an arginine (R) at position 218 with a glutamine (Q). According to the guidelines of the American College of Medical Genetics and Genomics (ACMG), this variant is classified as pathogenic.[6]

The patient had been treated with previous drugs and followed with proteinuria of 0.7–1.49 g/day, serum creatinine of 0.75–0.8 mg/dL, and eGFR of 103–114 mL/min/1.73 m^2. Unexpectedly, she had become pregnant again. Although the treatment regimen continued, during second pregnancy, proteinuria increased from 0.73 g/d to 4.76 g/d, serum albumin levels decreased from 4.18 g/dL to 3.0 g/dL, eGFR mildly increased to 116–120 mL/min/1.73 m^2. During breast-feeding, she did not take cyclosporine, hence, proteinuria increased to 7.5 g/d and serum creatinine levels increased from 0.69 mg/dL to 0.94 mg/dL. After reusage of cyclosporine, proteinuria decreased to 1.41 g/d but serum creatinine levels increased to 1.1 mg/dL (Fig. 1).

Discussion

Human formin proteins (inverted formin 1 and 2) were first reported in 2008 as the major regulatory proteins for structural and functional integrity of actin filament and other cytoskeletal proteins which also maintain podocyte plasticity.[7] The first research identifying the association of *INF2* gene (located on chromosome 14) defects with familial autosomal dominant (AD) FSGS [with or without Charcot-Marie-Tooth disease (CMT), identified by demyelinating peripheral neuropathy] appearance was published in 2010.[8] Since then, genetic screening of FSGS patients resulted that these mutations have been among the most common mutations of the genetic FSGS.[3] Brown et al. reported the presence of heterozygous *INF2* gene mutations in 12% of families with FSGS.[8] Similarly, Gbadegesin et al. found that mutations in *INF2* gene were responsible for the 16.3% of the AD FSGS cases.[3] However, no *INF2* gene mutations were reported to be detected in individuals with idiopathic (sporadic) disease or those with autosomal recessive (AR) FSGS in their study.[3] The most

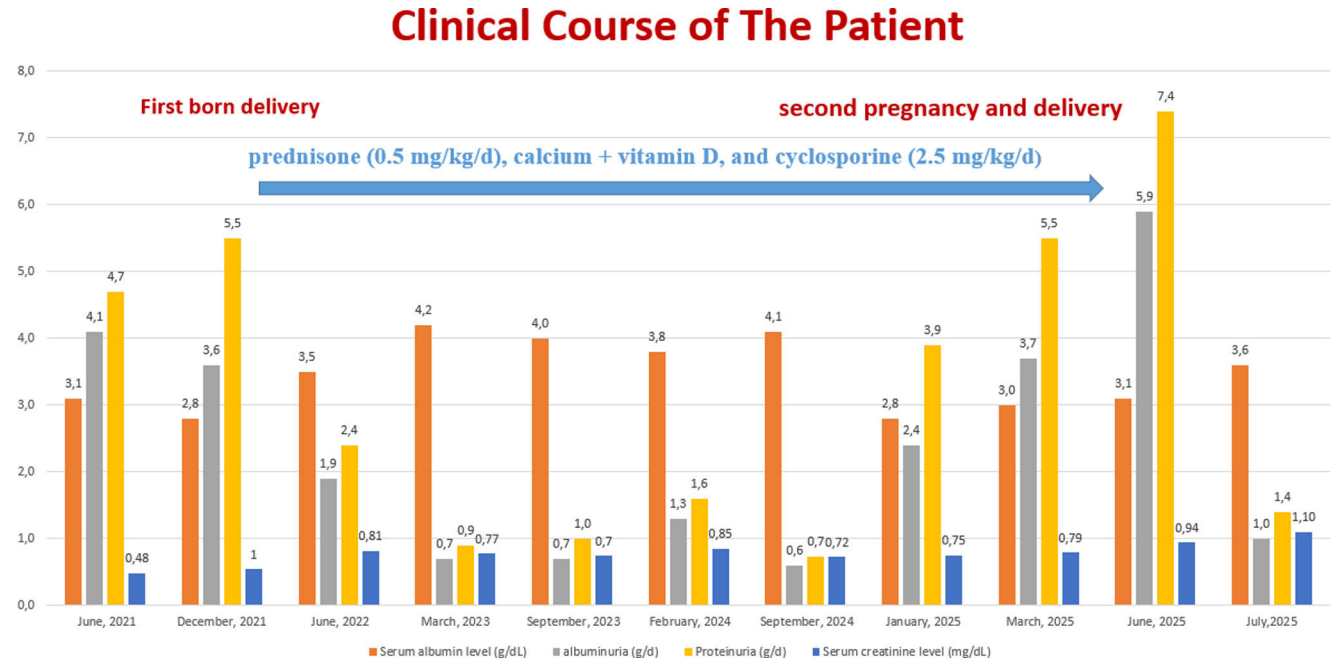

Fig. 1. Clinical course of the patient.

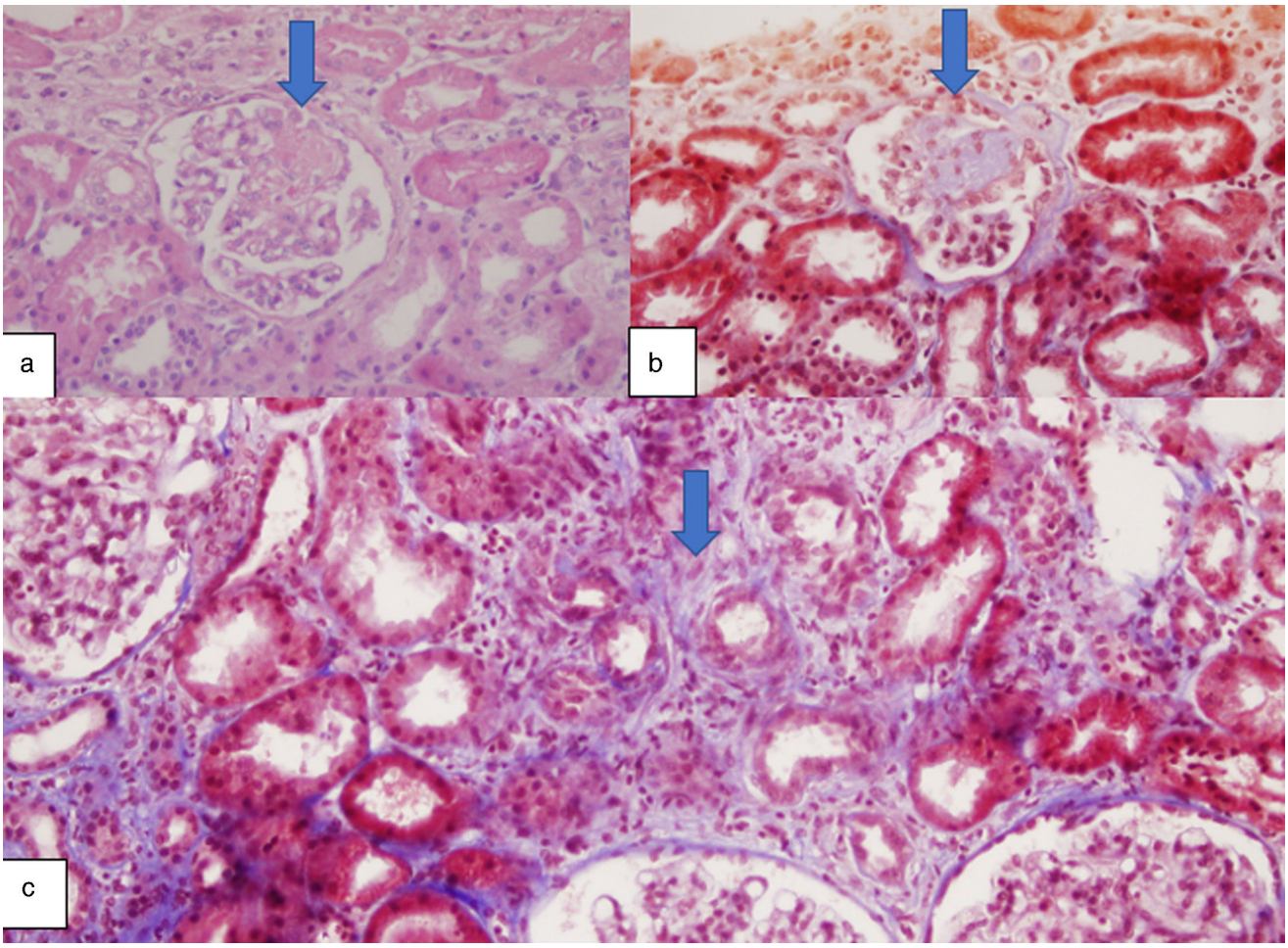

Fig. 2. Kidney biopsy showing (a) glomerular segmental sclerosis, H&E 400×; (b) glomerular segmental sclerosis, Trichrome stain 400×; (c) interstitial fibrosis, Trichrome stain 200× by light microscopy.

commonly mutated gene which has been reported to be found in sporadic FSGS patients is NPHS1.[5]

The genetic location of the FSGS caused by *INF2* mutations has been found on 14q32.33 (https://omim.org/entry/610982).[8] The locus of exon 4 of this gene has been reported to contain nearly most of the FSGS-causing variants.[3] The variant in the *INF2* gene of the present case has been previously reported and is not novel. Although there is a link between FSGS induced by *INF2* gene mutations and CMT, peripheral neuropathy which is the main manifestation of CMT, was not found in our patient. The *INF2* mutations are more commonly encountered in patients with both FSGS and CMT (75%) than FSGS solo (12–17%).[9] In addition, *INF2* gene mutations have been very rarely reported in sporadic FSGS patients.[10] Barua et al. searched the presence of *INF2* mutations among 281 individuals with sporadic FSGS and they have found only 2 cases. Based on this research, they reported that *INF2* mutations were rarely found in sporadic cases of FSGS.

INF2-mutated familial FSGS patients have variable clinical penetrance with the first presentation and onset of kidney failure approximately at the ages of 20–40 and 30–40.[10] Sporadic cases with *INF2* mutations are very rare, as far as we know, less than 5 cases are reported in the literature. Therefore, the clinical perspective of these cases is not clear, childhood onset has been documented in these rare cases.[10,11] Finally the accurate treatment for these sporadic cases is not present.

In conclusion, unplanned pregnancies of patients with proteinuria lead to exacerbation of nephrotic syndrome and preclampsia as maternal outcome, preterm births (defined as <37 weeks) and low birth weight (defined as 2500 g) as fetal outcome.[12] Exacerbation of maternal proteinuria and preterm delivery also occurred in our case. Our case is important because it presents the presence, clinical presentation, renal outcome during 4-year of follow up, and achievement of partial remission with prednisone and cyclosporine in a young female patient with sporadic FSGS induced by *INF2* mutation.

ORCID ID

İbrahim Erbay: 0000-0003-0004-2449
Hakan Ertan: 0009-0003-8624-2376
Beyhan Güvercin: 0000-0003-4157-4513
Sevdegül Aydın Mungan: 0000-0002-4882-352X
Neslihan Cinkara: 0000-0003-4869-0891

CRediT authorship contribution statement

Kubra Kaynar: Conception, design, analysis and interpretation of data, drafting the article and revising it. İbrahim Erbay: Documentation of the patient data, literature research. Hakan Ertan: Literature research and interpretation of data. Beyhan Güvercin: Literature research. Sevdegül Aydın Mungan: Interpretation of pathological findings. Neslihan Cinkara: Interpretation of genetic analysis.

Compliance with ethical standards

Written informed consent regarding this article was obtained from the patient.

Informed consent

Written informed consent was obtained from the patient regarding the publishment of this manuscript.

Declaration of generative AI and AI-assisted technologies in the writing process

No AI was used for this manuscript.

Funding

No fund was taken.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Fervenza FC, Sethi S. Focal segmental glomerulosclerosis: clinical features and diagnosis. UpToDate.com;2025, Available from: https://www.uptodate.com/contents/focal-segmental-glomerulosclerosis-clinical-features-and-diagnosis? [Accessed 26 June 2025]
2. Fervenza FC, Sethi S, Gbadegesin RA. Focal segmental glomerulosclerosis: genetic causes. UpToDate.com;2025, Available from: https://www.uptodate.com/contents/focal-segmental-glomerulosclerosis-genetic-causes? [Accessed 27 June 2025]
3. Gbadegesin RA, Lavin PJ, Hall G, Bartkowiak B, Homstad A, Jiang R, et al. Inverted formin 2 mutations with variable expression in patients with sporadic and hereditary focal and segmental glomerulosclerosis. Kidney Int. 2012;81:94–9.
4. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. Kidney Int. 2021;100:S1–276.
5. Zhuo L, Huang L, Yang Z, Li G, Wang L. A comprehensive analysis of NPHS1 gene mutations in patients with sporadic focal segmental glomerulosclerosis. BMC Med Genet. 2019;20:111.
6. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24.
7. Young KG, Thurston SF, Copeland S, Smallwood C, Copeland JW. INF1 is a novel microtubule-associated formin. Mol Biol Cell. 2008;19:5168–80.
8. Brown EJ, Schlöndorff JS, Becker DJ, Tsukaguchi H, Tonna SJ, Uscinski AL, et al. Mutations in the formin gene INF2 cause focal segmental glomerulosclerosis. Nat Genet. 2010;42:72–6.
9. Zhao W, Ma X, Zhang X, Luo D, Zhang J, Li M, et al. INF2 p.Arg214Cys mutation in a Chinese family with rapidly progressive renal failure and follow-up of renal transplantation: case report and literature review. BMC Nephrol. 2021;22:51.
10. Barua M, Brown EJ, Charoonratana VT, Genovese G, Sun H, Pollak MR. Mutations in the INF2 gene account for a significant proportion of familial but not sporadic focal and segmental glomerulosclerosis. Kidney Int. 2013;83:316–22.
11. Boyer O, Benoit G, Gribouval O, Nevo F, Tête MJ, Dantal J, et al. Mutations in INF2 are a major cause of autosomal dominant focal segmental glomerulosclerosis. J Am Soc Nephrol. 2011;22:239–45.
12. De Castro I, Easterling TR, Bansal N, Jefferson JA. Nephrotic syndrome in pregnancy poses risks with both maternal and fetal complications. Kidney Int. 2017;91:1464–72.