10.5152/turkjnephrol.2023.22467

Turkish Journal of Nephrology

Frustrating Case of Adult-Onset Steroid and Calcineurin Inhibitor-Resistant Focal Segmental Glomerulosclerosis: Podocalyxin Gene Mutation

Harshal Kamlesh Joshi[1], Sachin Ramanlal Gadiya[2], Deepali Vijay Lodha[2], Kshitij Sanjay Kumat[2]

[1]Department of Nephrology, SBKS Medical Institute and Research Center, Sumandeep Vidyapeeth deemed to be university, Vadodara, India
[2]Department of Medicine, SBKS Medical Institute and Research Center, Sumandeep Vidyapeeth deemed to be university, Vadodara, India

Corresponding author: Harshal Kamlesh Joshi ✉ harshal11joshi@gmail.com **Received:** December 21, 2022 **Accepted:** April 13, 2023

Cite this article as: Joshi HK, Gadiya SR, Lodha DV, Kumat KS. Frustrating case of adult-onset steroid and calcineurin inhibitor resistant focal segmental glomerulosclerosis: PODXL gene mutation. *Turk J Nephrol.* 2023;32(4):372-373.

Focal segmental glomerulosclerosis (FSGS) is a histopathological lesion, which is characterized by segmental sclerosis in at least 1 glomerulus (in light microscopy) and diffuse effacement of the podocyte foot processes (in electron microscopy).[1] Focal segmental glomerulosclerosis is a heterogeneous disease with varied etiologies.[2] There are no definitive clinical or histopathological findings to distinguish genetic FSGS from other types. Conversely, because the genetic disease often presents in early childhood, it is commonly overlooked in adult-onset FSGS patients.[3] Here, we present a case of adult-onset steroid and calcineurin inhibitor (CNI)-resistant FSGS who was found to have a genetic cause for FSGS.

A 23-year-old male patient presented to the nephrology outpatient department with generalised edema for 3 months. There was no history of drug intake or known comorbidity. Developmental and family history were unremarkable. On examination, the patient was afebrile with a pulse rate of 84 per minute and blood pressure of 130/80 mm Hg. Systemic examination was within normal limits other than anasarca. Patients' investigations included urine exam: Albumin: +3, Sugar: Nil, white blood cells: Nil, red blood cells: Nil, Cast: absent, 24-hour urine protein: 22 g/day, hemoglobin (Hb): 14.1 g/dL, serum creatinine: 1.3 mg/dl, estimated glomerular filtration rate: 72 ml/min/1.73m^2, albumin: 1.8, g/dL cholesterol: 560 mg/dL, triglycerides: 599 mg/dL and low-density lipoproteins: 390 mg/dL

Ultrasound revealed bilateral normal-sized kidneys and Kidney biopsy was done, which on light microscopy showed non-proliferative glomerulopathy, 2 out 24 glomeruli were globally sclerosed with rest normal appearing glomeruli. Immunofluorescence microscopy was negative. Electron microscopy was not done due to financial constraints. Considering the diagnosis of nephrotic syndrome due to podocytopathy patient was started on oral steroids—prednisolone (1 mg/kg/day) with other supportive treatment. On follow-up patient's proteinuria and pedal edema persisted. At 4 months, he continued to have persistent albuminuria (+3), urine protein creatinine ratio (UPCR): 4 g/g, Hb: 14 g/dL, serum creatinine: 0.9 mg/dL, and albumin: 2.0 mg/dL. Thus, the patient was labeled as steroid-resistant FSGS, the steroid was tapered, and the patient was started on tacrolimus 0.1 mg/kg/day. After 6 months of completion of tacrolimus therapy, the patient still had edema, urine protein was +3, UPCR: 5 g/g, serum creatinine: 0.8 mg/dL, and s albumin 1.6 mg/dL. Tacrolimus levels were in the therapeutic range (5-10 ng/dL). Considering steroid and calcineurin inhibitor -resistant FSGS, the patient was started on a third-line agent, mycophenolate mofetil according to Kidney Disease Improving Global Outcomes (KDIGO) 2012 Glomerulonephritis (GN) guidelines.[4] The patient was advised of genetic testing. The genetic testing was suggestive of podocalyxin (PODXL) gene mutation. Variant description: A homozygous 6 base pair insertion in exon 1 of the PODXL gene (chr7:131241044_131241045insGACGGT; Depth: 2x) that results in an in-frame

This work is licensed under a Creative Commons Attribution 4.0 International License.

insertion of amino acids proline and serine at codons 30 and 31, respectively (p.Pro30_Ser31dup; ENST00000294053.3). Thus, the patient was diagnosed to have genetic FSGS and was advised and counseled for kidney transplantation. The patient's immunosuppressant was stopped. The patient did not undergo kidney transplantation and developed protein-energy malnutrition and succumbed to death due to sepsis after 6 months.

The genetic FSGS may manifest as sporadic or familial disease, with autosomal dominant, autosomal recessive, X-linked, or mitochondrial inheritance patterns. Usually it presents in early childhood, but with the identification of additional mutations associated with FSGS, adult-onset genetic FSGS cases are increasingly reported. There is an inverse relationship between the likelihood of identifying the monogenic cause of FSGS and the age of disease onset. Pathogenic mutations are identified in 60-100% during the infantile period, 40-60% in young children, 25-40% in older children, and 10-25% in adolescents.[5] Currently, more than 50 genes are known to be involved in FSGS, such as the podocyte-related genes NPHS1, NPHS2, TRPC6, and INF2 and the GBM-related genes such as COL4A3/A4/A5.[6] In the index case, PODXL gene mutation was found in next-generation sequencing testing which was further confirmed by Sanger sequencing. According to the American college of medical genetics and genomics (ACMG) classification, the variant fits into class 3: Variant of uncertain significance. To the best of our knowledge, this is the first case of PODXL gene mutation presenting as FSGS from India. Though the mutation at present is of unknown significance, reporting such mutation is of utmost importance to help generate the database. Podocalyxin is a negatively charged, heavily glycosylated integral membrane protein, which is proposed to be required for the proper functioning of podocytes as glomerular filters. Podocalyxin is thought to act as an anti-adhesin that maintains the patency of the filtration slits between adjacent podocytes through charge repulsion. Podocalyxin expression is reduced in numerous proteinuric glomerulopathies in humans.[7]

In conclusion, the probability of a monogenic disease and the potential impact of identifying genetic FSGS on the management should be considered in the diagnostic work-up of steroid-resistant adult-onset FSGS.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.J.; Design – H.J., S.G., D.L.; Supervision – H.J.; Resources – H.J., S.G., D.L., K.K.; Materials – H.J., S.G.; Data Collection and/or Processing – S.G., D.L., K.K.; Analysis and/or Interpretation – H.J.; Literature Search – H.J., S.G.; Writing Manuscript – H.J., S.G.; Critical Review – H.J.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. D'Agati V. Pathologic classification of focal segmental glomerulosclerosis. *Nephrol*. 2003;23(2):117-134. [CrossRef]
2. Fogo AB. Causes and pathogenesis of focal segmental glomerulosclerosis. *Nat Rev Nephrol*. 2015;11(2):76-87. [CrossRef]
3. McCarthy HJ, Bierzynska A, Wherlock M, et al. Simultaneous sequencing of 24 genes associated with steroid-resistant nephrotic syndrome. *Clin J Am Soc Nephrol*. 2013;8(4):637-648. [CrossRef]
4. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Inter, Suppl*. 2012;2:139-274.
5. Lipska BS, Iatropoulos P, Maranta R, et al. Genetic screening in adolescents with steroid-resistant nephrotic syndrome. *Kidney Int*. 2013;84(1):206-213. [CrossRef]
6. Ranganathan S. Pathology of podocytopathies causing nephrotic syndrome in children. *Front Pediatr*. 2016;4:32. [CrossRef]
7. Miao J, Pinto E Vairo F, Hogan MC, et al. Identification of genetic causes of focal segmental glomerulosclerosis increases with proper patient selection. *Mayo Clin Proc*. 2021;96(9):2342-2353. [CrossRef]