Fibronectin Glomerulopathy: A Case Report of Membranoproliferative Glomerulonephritis

Case reports

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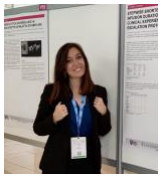
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ABSTRACT

Background. Fibronectin glomerulopathy (FNG) is a rare autosomal dominant glomerulopathy characterized by proteinuria, hematuria, hypertension, and gradual progression to end-stage renal disease (ESRD) over 15–20 years. The disease is caused by mutations in the FN1 gene. Currently, there is no specific treatment for FNG.

Case Report. A 22-year-old female presented with sub-nephrotic proteinuria and microscopic hematuria. Renal biopsy revealed mesangial expansion and electron-dense deposits consistent with FNG. Genetic testing confirmed a mutation in the FN1 gene (c.5773T>A, W1925R). No kidney disease was observed in patient's parents; later genetic diagnosis was confirmed also in the patient's brother. She was treated with conservative therapy. Three years later, her kidney function remained stable, with a serum creatinine of 0.5 mg/dL and proteinuria reduced to 0.7 g/24h.

Discussion. FNG is caused by mutations in the FN1 gene, leading to abnormal fibronectin deposition in the kidneys. No specific treatment exists, but conservative therapy with ACE inhibitors may help slow disease progression. Steroid therapy is controversial, with limited success in preventing ESRD.

Conclusion. Early diagnosis and conservative treatment are crucial for managing FNG. Further research is needed to explore effective therapies and better understand the disease's progression.

KEYWORDS: fibronectin glomerulopathy, FN1 mutation, proteinuria, renal biopsy, conservative therapy, ESRD

Background

Fibronectin glomerulopathy (FNG) is a rare autosomal dominant glomerulopathy that manifests at various ages in both sexes [1]. Common clinical features are mild proteinuria and varying degrees of hematuria, hypertension and slow progression to end-stage renal disease over 15–20 years [1]. Decline of kidney function over time is variable. Serum fibronectin levels are usually normal, and systemic manifestations have not been reported. Recurrence in the transplant may occur [2].

Currently, there is no specific treatment for fibronectin glomerulopathy.

Case report

A 22-year-old Italian female presented to our department for evaluation of sub-nephrotic proteinuria without edema. She didn't take any medications and her medical history was indifferent. Her blood pressure was 120/80 mmHg, heart rate 85bpm. Blood chemistry tests showed BUN 17 mg/dL, serum creatinine 0,6 mg/dL. Her estimated glomerular filtration rate (eGFR) was 120 mL/min/1.73m^2, as calculated using the CKD-EPI equation; urinalysis revealed proteinuria and microscopic hematuria in dipstick; the 24-hour urine collection showed urine total protein of 1700 mg/day (Table 1).

Blood test	
White Blood Cell	9400 /µL
Hemoglobin	12.3 g/dL
Platelet	303×10^3/µL
Total protein	6.3 g/dL
Albumin	3.6 g/dL
Urea nitrogen	17 mg/dL
Creatinine	0.6 mg/dL
eGFR	120 mL/min/1.73m^2
Cholesterol	194 mg/dL
HDL/LDL	58/120 mg/dL
Triglycerides	154 mg/dL
C-reactive protein	0.05 mg/dL

Immunoserology	
IgG	996 mg/dL
IgA	346 mg/dL
IgM	230 mg/dL
Complement 3	136 mg/dL
Complement 4	23 mg/dL
ANA	neg
Anti-GBM antibody	neg
MPO-ANCA	neg
PR3-ANCA	neg
PLA2R	neg
HBs-Ag	–
HCV-Ab	–

Urinalysis	
specific gravity	1.020
pH	6.2
Red Blood Cell	5-10/high power
Protein	1700mg/24h

Table 1. Laboratory data from initial admission.

Renal ultrasound showed kidneys with normal size and increased parenchymal echogenicity.

A renal biopsy was performed: immunofluorescent staining revealed mild glomerular deposition of IgA, C3 and Lambda while the results for IgG, IgM, C4, Kappa and Fibrinogen were negative. Light microscopy examination detected thirteen glomeruli one of which was sclerotic. The other glomeruli had normal size, exhibited significant mesangial expansion and lobular accentuation, normal glomerular basement membranes, thickening of Bowman's capsule without extracapillar proliferation. The renal tubular epithelial cells were vacuolated, and there were no pathological changes in the renal interstitium, it appeared edematous with diffuse inflammatory infiltrates. (Figure 1, 2, 3 e 4)

Congo-red staining was negative for amyloid; electron microscopy showed mesangial and subendothelial electron-dense deposits (EDD) with high density, mostly granular with focal fibrillary substructure (Figura 5).

Immunohistochemistry for CD3 showed strong positive staining in the interstitial inflammatory infiltrate while immunohistochemistry for CD20 and CD138 were negative. Also immunohistochemistry for DNAJB9 was negative.

Genetic testing of whole-blood samples (using the Sanger method) revealed an FN1 gene mutation with a thymine changed to adenine at nucleotide 5773 of the complementary DNA (c.5773T>A) causing a substitution in which the tryptophan at amino acid 1925 is replaced by arginine (W1925R).

The conclusive diagnosis was Fibronectin glomerulopathy (FNG).

Family history was investigated. The patient's brother had never undergone nephrological evaluation before. Following sister's diagnosis of the disease, he underwent urinalysis, which revealed proteinuria and microscopic hematuria too – in normal renal function; consequently, genetic testing was performed, confirming the same pathogenic mutation identified in his sister (W1925R).

None of the patient's parents showed renal disease or proteinuria; her father died young without apparent cause.

The patient started conservative therapy with ACE-I and low salt diet. Three years after kidney biopsy, serum creatinine was 0.5 mg/dL (eGFR 125 mL/min/1.73m^2) and proteinuria reduced to 0.7g/24h, chemistry panel was unchanged.

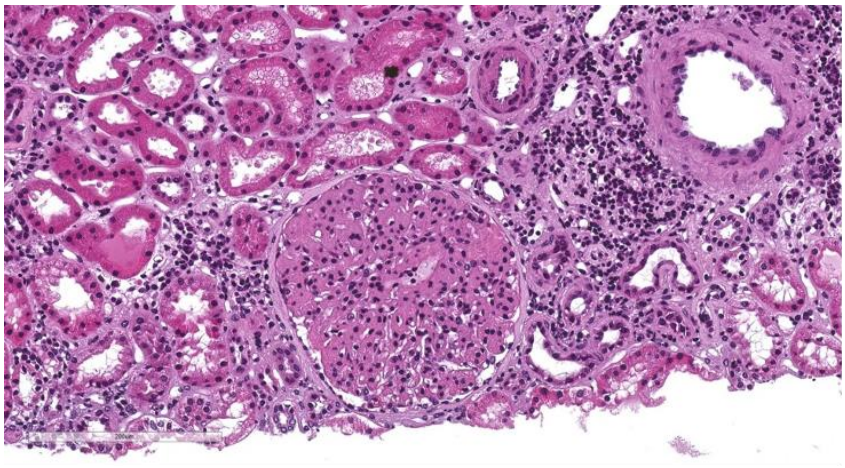

Figure 1. Hematoxylin and eosin staining: increased mesangial matrix, renal interstitium appeares edematous with inflammatory infiltrate.

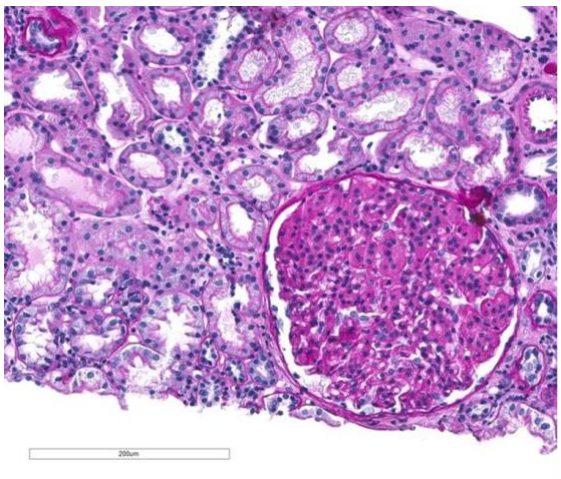

Figure 2. Periodic acid–Schiff staining shows PAS–positive material expanding the mesangium with lobular formation and limited increase in mesangial cellularity, also present along the glomerular basement membranes; vacuolated renal tubular epithelial cells with no pathological interstitium.

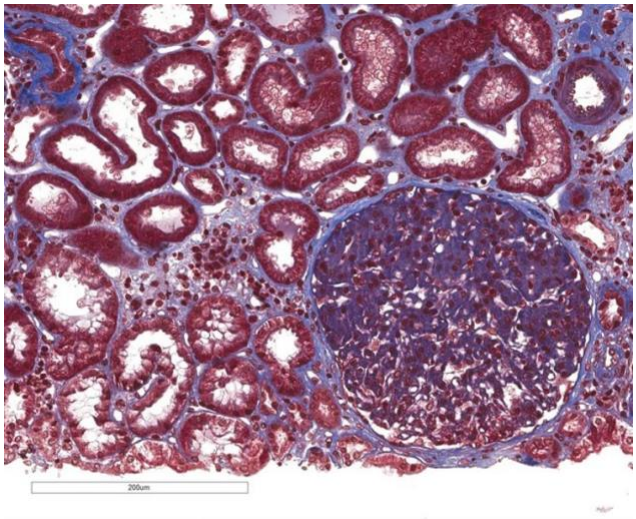

Figure 3. On Masson's trichrome staining, fibronectin glomerulopathy shows reddish-violet amorphous mesangial and subendothelial deposits that do not stain blue like collagen, highlighting the non-collagenous nature of the accumulated material.

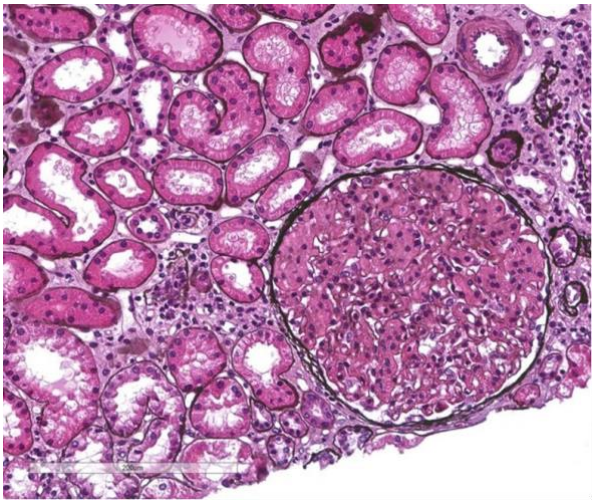

Figure 4. Periodic acid silver methenamine staining reveals thickening of the basement membrane with silver methenamine stain-negative and PAS-positive areas in the mesangium space (×200).

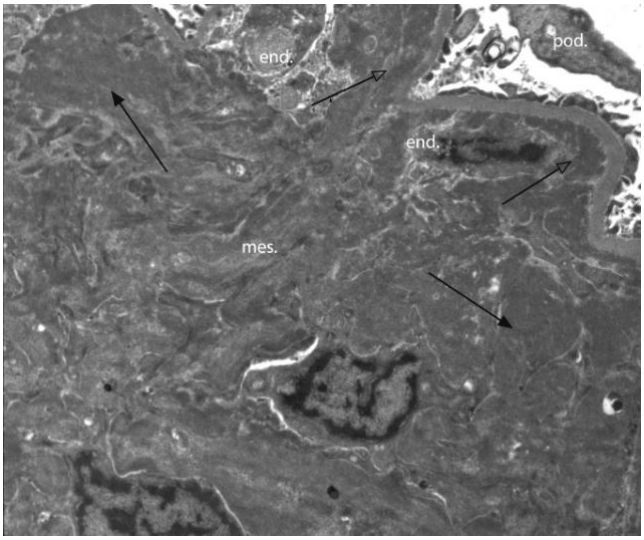

Figure 5. Electron microscopy: mesangial and subendothelial deposits (mostly granular) with focal fibrillary substructure.

Discussion

In this report, we present a case of FNG with a pathological diagnosis of Membranoproliferative Glomerulonephritis (MPGN). The diagnosis was confirmed by Electron Microscopy (EM) and genetic analysis – patient's parents did not have a history of kidney disease – with later genetic diagnosis confirmed also in the patient's brother as well.

FNG is caused by mutations in the fibronectin 1 gene (FN1) on chromosome 2 [3] and is featured by massive deposition of mutant fibronectin in the mesangium and along capillary walls [2, 4, 5].

Molecular Background

Fibronectin (FN) is a high-molecular-weight glycoprotein component of the extracellular matrix. It is normally produced by the liver and renal mesangial cells [2]. FN is present in plasma as a soluble form (pFN) or deposited in extracellular matrix as insoluble organized fibrils (cellular FN) [6]. The Hep-II and -III domains play a main role in regulating FN assembly into organized fibrils in extracellular matrix, through complex FN–FN and FN–cell surface proteoglycan interactions [7–10].

The pathogenic mechanism of fibronectin accumulation is not completely understood but may involve the production of a fibronectin variant that cannot be cleared, or the formation of a variant fibronectin formed by attachment of a circulating factor. The deposits consist predominantly of the soluble plasma-derived form of fibronectin, rather than the insoluble cellular form. Another proposed mechanism is a defect in the catabolism of fibronectin [2].

Fibronectin 1 (FN1) gene mutation is usually detected in about 40% of patients in Castelletti study group [3] and is believed to be responsible for the occurrence of the disease. However, no specific treatment is currently available. [3, 11, 12]. The W1925R variant identified in the present case was reported in literature to cause glomerulopathy with fibronectin deposits [3]: in this study W1925R variant was identified in all affected by FG and was not found in any of 100 healthy subjects [3].

They sequenced the *FN1* in 15 unrelated pedigrees and found three heterozygous missense mutations, the W1925R, L1974R, and Y973C, that cosegregated with this glomerulopathy [3].

Mutations in the FN1 gene have been implicated in a variety of collagen-related diseases due to fibronectin's essential role in the extracellular matrix and its interactions with collagen. Studies have

shown that alterations in FN1 have been linked to early-onset osteoarthritis, where impaired interactions between fibronectin and collagen type II affect cartilage integrity [13]. Furthermore, skeletal dysplasias have been associated with FN1 mutations, as fibronectin is critical for the correct formation of collagen fibers in bones [14]. In the context of Ehlers-Danlos syndrome, a connective tissue disorder primarily caused by defects in collagen, FN1 mutations may exacerbate collagen dysfunction, further destabilizing the extracellular matrix and contributing to the clinical manifestations of the disease [15].

Our W1925R mutation introduces a basic amino acid in the Hep-II hydrophobic core; this mutation could theoretically increase the Hep-II affinity for heparin, by providing additional cationic charge to the domain; however, it could also alter the folding of the domain and impair its function. So they suggest that GFND-associated mutations in FN1 impair the control of the assembly of FN into fibrils and the balance between soluble and insoluble FN, which could explain the abnormal incorporation of nonfibrillary pFN in the glomerular matrix that has been documented in renal biopsy [3].

Pathophysiology

Usually, the biopsy shows by light microscopy lobular accentuation with mesangial expansion with minimal hypercellularity and variable expansion of glomerular basement membranes by strongly periodic acid-Schiff-positive and silver-negative material. Congo red stain is negative. There are nonspecific tubulointerstitial and vascular changes with increased fibrosis with progression of disease. Immunofluorescence/immunohistochemistry microscopy is usually negative, but may show nonspecific staining for immunoglobulins and C3 [2]. Electron microscopically, fibronectin deposition is shown as finely granular or fibrillary substructures with randomly arranged 12–16-nm fibrils [2, 4, 5] and we could testify it with the help of electron microscope.

Clinical Management

Ti Zhang et al. Reported a case series of 19 patients with FNG diagnosis that were treated with renin-angiotensin system blockade, including 11 patients who were treated with Tripterygium Wilfordii Hook (TWHF), and 4 patients with corticosteroid therapy in combination with immunosuppressive therapies, including 2 with mycophenolate mofetil (MMF) and 2 with tacrolimus. The mean follow-up duration was 78 months (range 14–147 months, median 87). At last follow-up, 7 patients progressed to ESRD despite supportive therapy and required initiation of dialysis, 2 of whom received renal transplantation [16]. In most of cases reported in literature, corticosteroid therapy doesn't help to reduce or prevent kidney disease progression [17, 18]. Steroid therapy has been tested, but its effectiveness is controversial. Prednisolone treatment decreased proteinuria in some patients with nephrotic-level proteinuria [19] but did not yield a clear treatment response in other patients [17, 18] and is commonly attempted in cases with a histological diagnosis of MPGN [20].

Currently angiotensin-converting enzyme inhibitors and ARBs are generally used for renal protection. The initiation of steroid therapy for FNG should be carefully considered on an individual basis [17].

Conclusion

We encountered a case of FNG in a 22-year-old female patient presenting with sub-nephrotic range proteinuria, supported by both histological features of membranoproliferative glomerulonephritis on kidney biopsy and subsequently confirmed by genetic testing. Following the patient's diagnosis, genetic screening was also extended to first-degree relatives (brother), with a positive result for the disease.

We therefore decided to use a conservative therapy, because of the steroids side effects and the absence of nephrotic syndrome in our patient, with a normal kidney function.

After three years kidney function remained stable and proteinuria reduced to 0.7 g/die.

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BIBLIOGRAPHY

1. Gemperle O, Neuweiler J, Reutter FW, Hildebrandt F, Krapf R. Familial glomerulopathy with giant fibrillar (fibronectin-positive) deposits: 15-year follow-up in a large kindred. Am J Kidney Dis. 1996;28(5):668–75. https://doi.org/10.1016/s0272-6386(96)90247-4
2. Lusco MA, Chen YP, Cheng H, et al. AJKD atlas of renal pathology: fibronectin glomerulopathy. Am J Kidney Dis. (2017) 70:e21–2. https://doi.org/10.1053/j.ajkd.2017.09.001
3. Castelletti F, Donadelli R, Banterla F, et al. Mutations in FN1 cause glomerulopathy with fibronectin deposits. Proc Natl Acad Sci USA. (2008) 105:2538–43. https://doi.org/10.1073/pnas.0707730105
4. Strøm EH, Banfi G, Krapf R, Abt AB, et al. Glomerulopathy associated with predominant fibronectin deposits: a newly recognized hereditary disease. Kidney Int. (1995) 48:163–70. https://doi.org/10.1038/ki.1995.280
5. Ohashi T, Erickson HP. Fibronectin aggregation and assembly: the unfolding of the second fibronectin type III domain. J Biol Chem. (2011) 286:39188–99. https://doi.org/10.1074/jbc.M111.262337
6. Yamada KM, Kennedy DW (1979) Fibroblast cellular and plasma fibronectins are similar but not identical. J Cell Biol 80:492–498. https://doi.org/10.1083/jcb.80.2.492
7. Santas AJ, Peterson JA, Halbleib JL, et al. Alternative splicing of the IIICS domain in fibronectin governs the role of the heparin II domain in fibrillogenesis and cell spreading. J Biol Chem (2002) 277:13650–13658. https://doi.org/10.1074/jbc.m111361200
8. Bultmann H, Santas AJ, Peters DM. Fibronectin fibrillogenesis involves the heparin II binding domain of fibronectin. J Biol Chem. 1998. 273:2601–2609. https://doi.org/10.1074/jbc.273.5.2601
9. Maqueda A, Moyano JV, Hernandez Del Cerro M, et al. The heparin III-binding domain of fibronectin (III4-5 repeats) binds to fibronectin and inhibits fibronectin matrix assembly (2007) Matrix Biol 126:642–651. https://doi.org/10.1016/j.matbio.2007.06.001
10. Mao Y, Schwarzbauer B. Fibronectin fibrillogenesis, a cell-mediated matrix assembly process. (2005) Matrix Biol 25:389–399. https://doi.org/10.1016/j.matbio.2005.06.008
11. Ohtsubo H, Okada T, Nozu K, et al. Identification of mutations in FN1 leading to glomerulopathy with fibronectin deposits. Pediatr Nephrol. (2016) 31:1459–67. https://doi.org/10.1007/s00467-016-3368-7
12. Aslam N, Singh A, Cortese C, Riegert-Johnson DL. A novel variant in FN1 in a family with fibronectin glomerulopathy. Hum Genome Var. (2019) 6:11. https://doi.org/10.1038/s41439-019-0042-1
13. van Hoolwerff M, Rodríguez Ruiz A. et al. High-impact FN1 mutation decreases chondrogenic potential and affects cartilage deposition via decreased binding to collagen type II. Nature Genetics, 2021 Nov 5;7(45):eabg8583. https://doi.org/10.1126/sciadv.abg8583
14. Neha E.H. Dinesh, Philippe M. Campeau, Dieter P. Reinhardt. The integral role of fibronectin in skeletal morphogenesis and pathogenesis. Matrix Biology 134 (2024) 23–29. https://doi.org/10.1016/j.matbio.2024.08.010
15. Nicoletta Zoppi, Marco Ritelli, Marina Colombi. Type III and V collagens modulate the expression and assembly of EDA(+) fibronectin in the extracellular matrix of defective Ehlers-Danlos syndrome fibroblasts. Biochim Biophys Acta (2012) 1820(10):1576-87. https://doi.org/10.1016/j.bbagen.2012.06.004
16. Ti Zhang, Wei Zhang, Ke Zuo and Zhen Cheng. Clinicopathologic Features and Outcomes in Fibronectin Glomerulopathy: A Case Series of 19 Patients, Brief research report article Front. Med., 14 August 2020, Volume 7 – 20. https://doi.org/10.3389/fmed.2020.00439
17. Hata M, Mori T, Hirose Y, et al. A case of unexpected diagnosis of fibronectin glomerulopathy with histological features of membranoproliferative glomerulonephritis. BMC Nephrol. 2024;25(1):25. https://doi.org/10.1186/s12882-024-03456-7
18. Yoshino M, Miura N, Ohnishi T, et al. Clinicopathological analysis of glomerulopathy with fibronectin deposits (GFND): a case of sporadic, elderly-onset GFND with codeposition of IgA, C1q, and fibrinogen. Intern Med. 2013;52(15):1715–20. https://doi.org/10.2169/internalmedicine.52.0046
19. Goldman BI, Panner BJ, Welle SL, Gross MD, Gray DA. Prednisone-induced sustained remission in a patient with familial fibronectin glomerulopathy (GFND). CEN Case Rep. 2021;10(4):510–4. https://doi.org/10.1007/s13730-021-00595-w
20. Noris M, Remuzzi G. Translational mini-review series on complement factor H: therapies of renal diseases associated with complement factor H abnormalities: atypical haemolytic uraemic syndrome and membranoproliferative glomerulonephritis. Clin Exp Immunol. 2008;151(2):199–209. https://doi.org/10.1111/j.1365-2249.2007.03558.x