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Kidney Biopsy Teaching Case

A Case of Familial Glomerulopathy With Fibronectin Deposits Caused by the Y973C Mutation in Fibronectin

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Glomerulopathy with fibronectin deposits is a rare hereditary kidney disease characterized by the extensive deposition of fibronectin in glomeruli, particularly in mesangial regions and subendothelial zones. Prognostically, the disease is known as slowly progressive, leading to kidney failure in most cases. We recently diagnosed glomerulopathy with fibronectin deposits in a 24-year-old man in whom proteinuria was detected incidentally. Genetic analysis of the fibronectin 1 (*FN1*) gene showed heterozygosity for the Y973C mutation. The same mutation was found in his elder brother, who similarly experienced proteinuria. Both patients had normal kidney function but persistent proteinuria after 30 months and 11 years of follow-up, respectively.
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INDEX WORDS: Fibronectin; glomerulopathy; *FN1* gene; mutation; organized deposits.

INTRODUCTION

Glomerulopathy with fibronectin deposits (GFND) is a rare genetic disease that can lead to kidney failure. It is characterized by proteinuria, hematuria, hypertension, and organized glomerular deposits of fibronectin observed on kidney biopsy. In 1980, Bürgin et al[1] were the first to report diffuse glomerular lesions in 1 autopsy and 3 kidney biopsy specimens characterized by "subendothelial but frequently transmembranous and mesangial deposits."(p313) They used the description "familial glomerulopathy with giant fibrillar deposits"(p313) to define this entity. In 1995, Assman et al[2] and Strøm et al[3] showed extensive deposits in the mesangial and subendothelial areas with immunoreactivity of glomerular deposits to fibronectin in a few patients. They named the disease "familial glomerulonephritis with fibronectin deposits."(p313) Thereafter, a few case reports appeared in the literature describing familial and sporadic patients with GFND. In 2008, an association was identified between GFND and mutations in the gene encoding fibronectin (*FN1*).[4]

GFND shows an autosomal dominant pattern of inheritance with age-related penetrance and usually presents with proteinuria and varying degrees of hematuria during the third or fourth decade of life. Decreased glomerular filtration rate (GFR) and hypertension are accompanying clinical features in some patients.[2,5] Kidney biopsy with demonstration of extensive fibronectin deposition in glomeruli is essential for diagnosis. The disease often progresses to end-stage kidney disease within 15-20 years from clinical onset.[5]

In this article, we add to the reported cases of GFND with a description of 2 brothers who were both affected by proteinuria; the disease was confirmed in one of them by kidney biopsy. Screening of the *FN1* gene uncovered a previously described heterozygous mutation causing a substitution of the tyrosine at amino acid 973 by cysteine (Y973C) in both patients.

CASE REPORT

Clinical History and Initial Laboratory Data

A 24-year-old man (proband) was referred to our nephrology clinic due to proteinuria detected incidentally during his routine checkup. His medical history was insignificant except for asthma. He had a younger sister and an elder brother, who was known to have had heavy proteinuria since age 17 years. The brother had previously undergone kidney biopsy at another center; however, the pathologist was unable to make a precise diagnosis. His 22-year-old sister and his mother were healthy. His father had died several years ago due to unknown reasons.

Findings of physical examination in the proband included blood pressure of 110/75 mm Hg and no peripheral edema. The rest of his examination showed normal findings. He had normal kidney function with serum creatinine level of 0.82 mg/dL (corresponding to estimated GFR of 123 mL/min/1.73 m^2 as calculated by the 4-variable Modification of Diet in Renal Disease [MDRD] Study equation) and serum urea nitrogen level of 9 mg/dL. There was proteinuria with protein excretion of 1 g/d (albumin excretion, 400 mg/L) with bland sediment and no hematuria on urinalysis. Serum albumin and total protein levels were 4.04 g/dL and 7.22 g/dL, respectively. He had normal lipid and cholesterol profile results. Antinuclear antibody and anti–double stranded DNA were undetectable, complement levels were within the reference ranges (C3, 112

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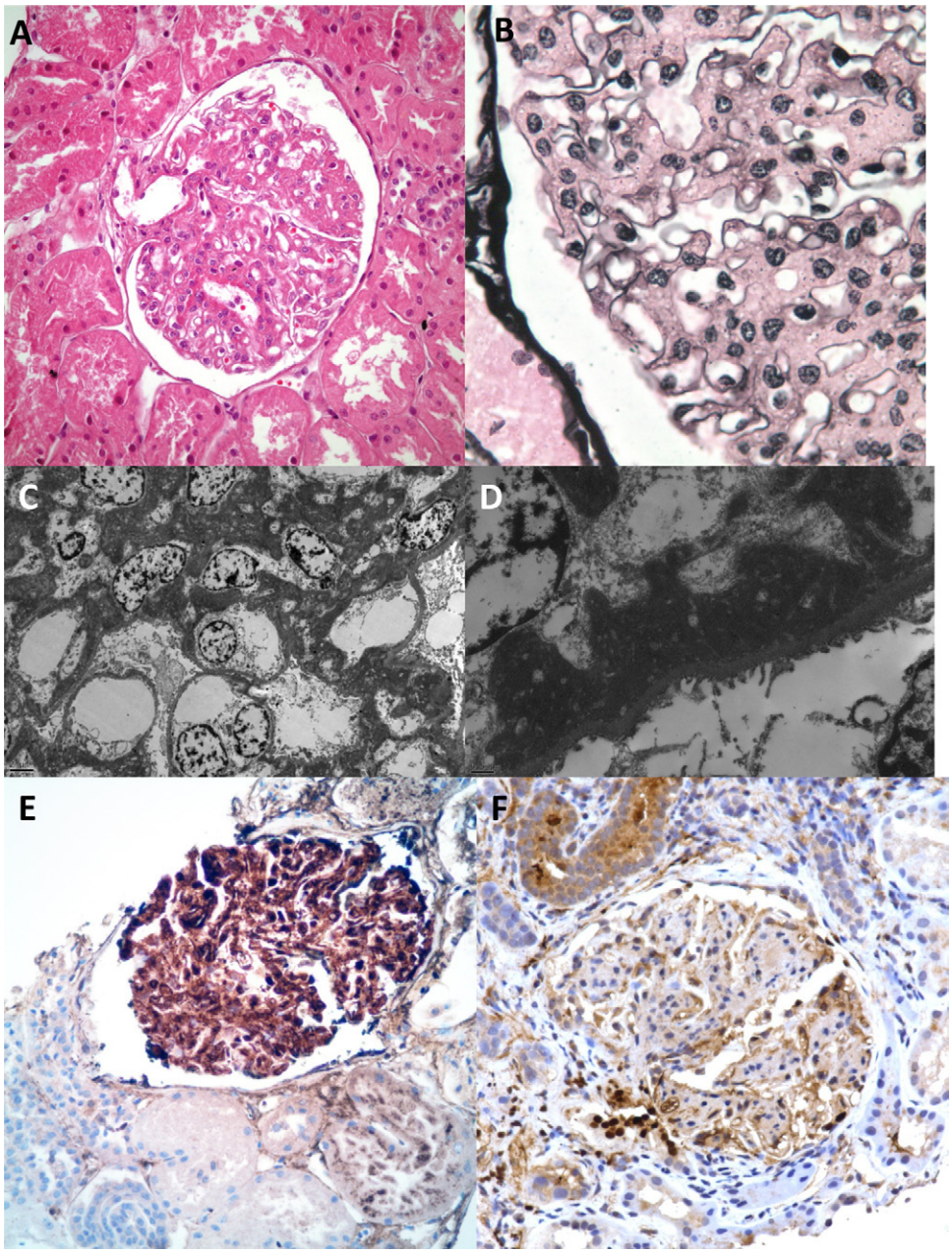

Figure 1. Fibronectin glomerulopathy. (A) Variable expansion of mesangial regions due to accumulation of eosinophilic material (hematoxylin and eosin stain; original magnification, ×400). (B) The accumulations involve subendothelial regions and mesangium and stain negative for silver (Jones methenamine silver stain; original magnification, ×1,000). Electron microscopy shows (C) deposits in both the mesangium and subendothelial locations (lead citrate and uranyl acetate staining; original magnification, ×5,000), which are (D) electron dense and finely granular; foot processes generally are preserved (lead citrate and uranyl acetate staining; original magnification, ×20,000). (E) Immunohistochemistry for fibronectin shows global and strong staining of the glomerulus (antifibronectin antibody; original magnification, ×400). (F) Specimen from a case of diabetic nodular glomerulosclerosis as the negative control for fibronectin immunostaining. Diabetic glomerulopathy is an entity that may enter into differential diagnosis due to the occurrence of mesangial expansions and nodules (antifibronectin antibody; original magnification, ×400).

mg/dL; and C4, 21.3 mg/dL), and hepatitis serologic test results were negative. Kidney ultrasound showed normal-sized kidneys. A needle biopsy of the kidney was performed to evaluate proteinuria in the patient.

Kidney Biopsy

Biopsy revealed significantly enlarged glomeruli due to deposition of eosinophilic proteinaceous material diffusely in all mesangial regions (Fig 1A). The deposits gave a lobular appearance to many glomerular tufts. Some subendothelial spaces also contained similar deposits. There was mild to moderate mesangial hyperplasia, but no endocapillary or extracapillary proliferation, necrosis, or inflammatory infiltrate. The deposited material was period acid–Schiff positive and methenamine silver negative (Fig 1B). Lack of staining with Congo red excluded amyloidosis.