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CASE REPORT

Fibronectin Glomerulopathy Caused by the Y973C Mutation in Fibronectin: A Case Report and Literature Review

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Abstract Fibronectin glomerulopathy is a rare autosomal dominant inherited glomerular disease associated with massive deposition of fibronectin. We recently diagnosed fibronectin glomerulopathy in a 29-year-old woman presenting nephrotic syndrome. Genetic analysis of fibronectin 1 gene showed heterozygosity for the Y973C mutation. However, this mutation was not found in her parents. She had stable renal function but persistent nephrotic proteinuria after one-year follow-up.

FIBRONECTIN glomerulopathy is a rare, autosomal dominant, non-amyloid glomerular disease. It was firstly reported by Burgin and his colleagues in 1980.[1] Thereafter, a few case reports were published describing familial and sporadic patients with fibronectin glomerulopathy.[2-5] It usually onsets in adolescence with proteinuria, microhematuria, hypertension, and slowly progressive renal failure. In pathology, it is characterized by nonimmune lobular glomerulopathy with massive mesangial and subendothelial deposits composed of fibronectin. In 2008, Castelletti *et al*[6] identified three mutations in the gene encoding fibronectin 1 (*FN*1) in the different pedigrees of fibronectin glomerulopathy.

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In this article, we reported a Chinese patient of fibronectin glomerulopathy, which was confirmed by kidney biopsy. Genetic sequencing of *FN1* detected a previously described heterozygous mutation causing a substitution of the tyrosine at amino acid 973 by cysteine (Y973C) in the affected patient.

CASE DESCRIPTION

A 29-year-old woman was hospitalized due to systemic edema and hypertension. She had cerebral infarction three years ago in past medical history. In family history, her father had diabetes and hypertension. Findings of physical examination included obesity, elevated blood pressure of 150/90 mm Hg and peripheral edema. Urinalysis revealed massive proteinuria and microscopic hematuria with bland sediment, and 24-hour urine protein was 15.43 g. Serum albumin and creatinine levels were 28 g/L and 79.6 μmol/L [corresponding to estimated glomerular filtration rate (eGFR) of 86 ml/min·1.73 m^2 calculated by Chronic Kidney

Disease Epidemiology Collaboration (CKD-EPI) equation], with hypercholesterolemia. Antinuclear antibody and anti-double stranded DNA were negative, as well as hepatitis serologic test. No hypocomplementemia or cryoglobulinemia was detected. Serum protein electrophoresis did not show monoclonal protein. Enlarged kidneys (left was 13.4 cm, and right was 13.2 cm in long diameter) were found in ultrasonography.

Light microscopy revealed enlarged and hyperlobular glomeruli with a homogeneous material in the mesangium and subendothelium (Fig. 1A). There was mild mesangial hyperplasia, without endocapillary or extracapillary proliferation, necrosis, or inflammatory infiltration. The deposited material was period acid-Schiff positive (Fig. 1B) and methenamine silver negative (Fig. 1C). Negative result of Congo red staining excluded amyloidosis.

Immunofluorescence microscopy was negative for immunoglobulin, light chain, or complement components. Electron microscopy showed massive electron-dense deposits in the mesangial and subendothelial space, with some admixture of irregularly arranged fibrils (15 nm in width) (Fig. 1D and 1E). Indirect immunofluorescence staining for fibronectin was performed, and glomerular deposits stained brightly with monoclonal anti-fibronectin antibody (Fig. 1F).

The diagnosis of fibronectin glomerulopathy was established on the basis of renal pathology. As an additional investigation, we performed genetic sequencing of *FN1* in the patient and her parents. Genomic DNA was extracted from peripheral blood. The whole exons of *FN1* were screened by Sanger sequencing (Sangon Biotech Co., Ltd, Shanghai, China). DNA sequencing showed a previously described heterozygous mutation in exon 19 in which an adenine is substituted by a guanine at nucleotide 2918 of the complementary DNA (c. 2918 A>G) (Fig. 2), leading to replacement of a tyrosine at amino acid 973 by a cysteine (Y973C). No *FN1* mutation was detected in her parents.

Anti-hypertensive therapy including angiotensin II receptor antagonist, calcium channel blocker, α and β receptor blocker was given as well as statin for hyperlipidemia. At her last evaluation 12 month after diagnosis, serum creatinine level was 86.6 μmol/L (eGFR 81 ml/min·1.73 m^2) while serum albumin level was 30 g/L. 24-hour urine protein was unchanged.

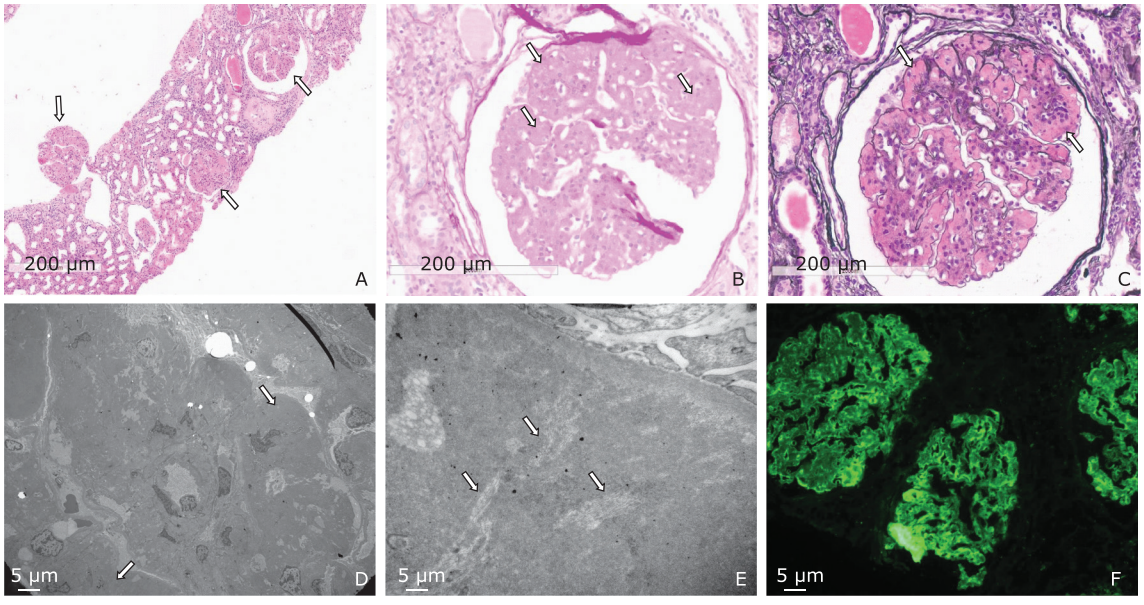

Figure 1. Pathological changes of kidney with fibronectin glomerulopathy. A. Glomeruli were diffusely enlarged with lobular accentuation and minimal hypercellularity (arrows). (HE staining) B. Period acid-Schiff-positive material expanding the mesangium and subendothelium of an enlarged glomerulus (arrows). C. The deposits in the subendothelium and mesangium (arrows) failed to stain with silver. (Jones methenamine silver stain) D. Electron microscopy showed mesangial and subendothelial deposits (arrows). E. The electron dense deposits as well as 15 nm fibrils (arrows) arranged randomly were observed. F. Intense immunofluorescence staining showed glomerular deposits with antisera against fibronectin [primary antibody: mouse monoclonal anti-human fibronectin antibody, clone IST-4 (Sigma-Aldrich); secondary antibody: fluorescin isothiocynanate-conjugated goat anti-mouse]. (×200)