Coexistence of Fabry Disease and Membranous Nephropathy

Ying Liu, Hua Xie, Hongli Lin, Shuni Chen, Weidong Wang, Guangben Zhao, Xu Zhang

Department of Nephrology, the First Hospital of Dalian Medical University, Dalian, China

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A 21-year-old man with no family history or characteristic symptoms of Fabry disease presented with proteinuria. Histological and immunofluorescent analysis of kidney tissue collected revealed stage 1 membranous nephropathy. Electron microscopy of the same tissue revealed a large number of myeloid bodies (zebra bodies) in the glomerular epithelial cytoplasm and a mild irregular thickening of basement membrane. A diagnosis of Fabry disease was supported by the low α-galactosidase A activity detected in the patient's plasma, and confirmed by the detection of a pathogenic homozygous mutation in the α-galactosidase A gene. Therefore, the final diagnosis was of coexistent Fabry disease and stage 1 membranous nephropathy. This is the first case study reporting the coexistence of Fabry disease and membranous nephropathy. Our results emphasize the importance of electron microscopy in Fabry disease diagnosis.

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Case Report

INTRODUCTION

Fabry disease is an X-linked inherited disorder caused by mutations of the α-galactosidase A encoded by the α-galactosidase A (*GLA*) gene. Deficient α-galactosidase A activity results in progressive globotriaosylceramide accumulation in the lysosomes of a variety of organs including the kidney. Fabry nephropathy manifests as proteinuria and kidney dysfunction, and half of the patients develop end-stage renal disease.[1,2] A diagnosis of Fabry disease could be confirmed by the analysis of α-galactosidase A activity in the affected males. Females may have normal activity of the enzyme, and therefore, they should be identified through pathologic examination and genetic analysis.[3]

Fabry disease may coexist with various glomerular diseases, including immunoglobulin A nephropathy, crescentic glomerulonephritis, thin basement membranous nephropathy, lupus nephritis, and rheumatoid arthritis-associated renal diseases.[4-10] However, concurrent Fabry disease and membranous nephropathy has not been previously reported. Here, we report a patient with combined hemizygous Fabry disease and stage 1 membranous nephropathy.

CASE REPORT

A 21-year-old man was referred with proteinuria in 2014. He denied any family history of genetic disorders or any special medication history. The initial physical examinations found no signs or symptoms of edema, neuralgia, rash, or gastrointestinal discomfort, and his blood pressure was 150/90 mm Hg. Fundus examination was normal. The patient's laboratory findings were as follows: proteinuria, 4787 mg/24 h; serum creatinine, 76 µmol/L (reference range, 53 µmol/L to 97 µmol/L); serum uric acid, 550 µmol/L (reference range, 208 µmol/L to 428 µmol/L); serum albumin, 33 g/L (reference range, 40.0 g/L to 55.0 g/L); and estimated glomerular filtration rate, 128.62 mL/min/1.73 m^2. Other measurements including liver function tests, glycated hemoglobin, lupus-related indicators, immunoglobulins and complements, and markers associated with hepatitis C, hepatitis B, human immunodeficiency virus, and syphilis were

normal or negative. Renal ultrasonography showed normal renal size and structure. Echocardiography revealed no abnormality.

The patient underwent renal biopsy. Immunofluorescent analysis showed granular immunoglobulin G (++), immunoglobulin G4 (+), and complement C3 (+) deposition along the capillary loops (Figure 1, Left). Four of the 18 glomeruli examined by light microscopy exhibited global sclerosis and thickened glomerular basement membranes. The glomerular basement membrane contained visible vacuoles and granules (Figure 1, Middle and Right). That led us to a diagnosis of membranous nephropathy. However, electron microscopy examination revealed a large number of myeloid bodies (zebra bodies) in the cytoplasm of glomerular epithelial cells, which was typical of Fabry disease, and a slightly but irregularly thickened basement membrane. Additionally, epithelial cells exhibited diffuse effacement of the foot processes, with few electron dense deposits visible under the epithelium (Figure 2). This led to suspicion of coexisting Fabry nephropathy.

To confirm Fabry nephropathy, the plasma α-galactosidase A activity of the patient was measured, which was 0.7 nmol/h/mg protein (reference range, 29.0 nmol/h/mg protein to 64.4 nmol/h/mg protein). Furthermore, genetic analysis indicated the existence of a pathogenic homozygous mutation in the *GLA* gene (*GLA* c.335G > A p. Arg112His), which has been reported to be a causative mutation of Fabry disease.[11] Moreover, the same mutation was detected in heterozygous form in the patient's mother. The patient was prescribed with conventional treatment including telmisartan, α-keto acid, and a high-quality low-protein diet.

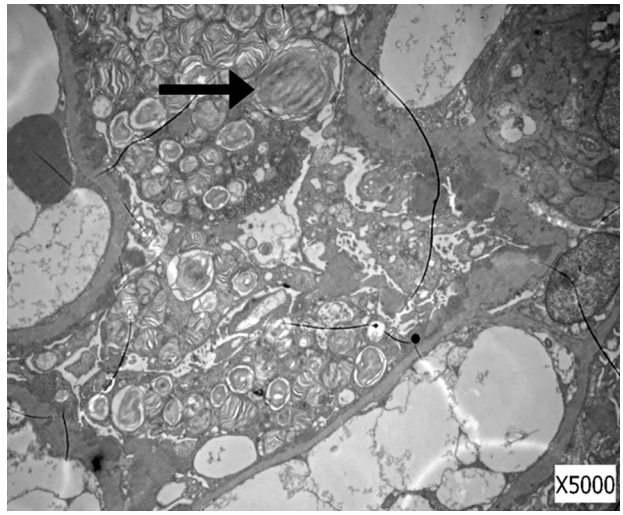

Figure 2. A large number of myeloid bodies (zebra bodies, black arrow) were visible via electron microscopy in the glomerular epithelial cytoplasm. The basement membrane appeared slightly but irregularly thickened. Epithelial cells showed diffuse effacement of the foot processes, with few electron-dense deposits visible under the epithelium (× 5000; scale bar, 2 μm).

However, enzyme replacement treatment was not administrated because of financial issue of the patient. Prednisone was considered for future treatment for membranous nephropathy.

DISCUSSION

Podocytopathy is a term referring to a variety of kidney diseases that are characterized by structural and functional podocyte abnormalities.[12] Membranous nephropathy is a typical podocytopathy.[13] Because globotriaosylceramide accumulation causes progressive podocyte injury and vacuolar degeneration, Fabry disease has come to be regarded as a type of podocytopathies known as inherited focal segmental glomerulosclerosis.[14-16]

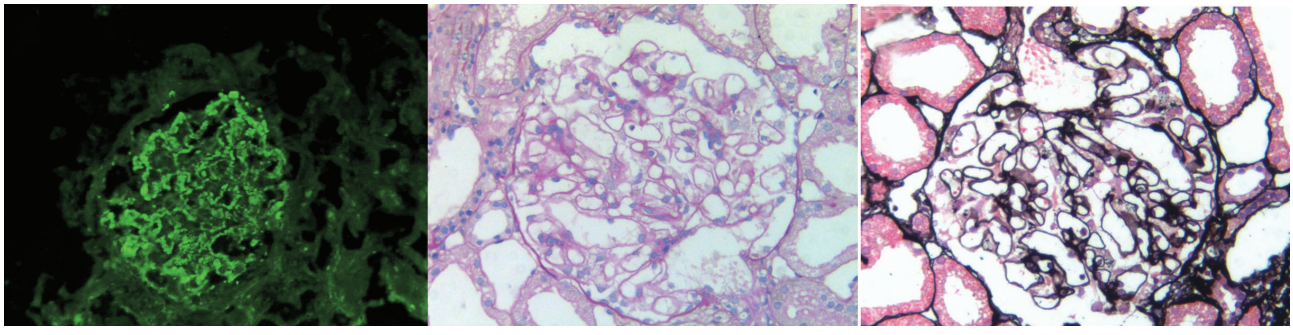

Figure 1. Renal biopsy morphology. **Left,** Immunofluorescent evaluation of renal tissues (× 400) showed granular IgG4 and C3 deposition along capillary loops. **Middle,** Histological analysis of biopsy tissues via light microscopy showed mild segmental glomerular mesangial cell proliferation, eosinophilic deposits under the epithelium, and a thickening of the basement membrane with vacuoles, and granules visualized by periodic acid-Schiff staining (× 400). **Right,** Periodic acid methenamine silver staining visualization also highlighted vacuoles and granules (× 400).

It has been demonstrated that globotriaosylceramide may play a role in Fabry disease by promoting the release of glomerular injury mediators.[17,18] We speculate that globotriaosylceramide deposition in podocytes may induce the formation of membrane attack complexes, resulting in glomerular basement membrane damage and the resultant membranous nephropathy. Further studies are needed to prove it.

In summary, we report a rare case of hemizygous Fabry disease with stage 1 membranous nephropathy. The patient exhibited none of the characteristic symptoms of Fabry disease and had no obvious family history, except for proteinuria. In such case, electron microscopy plays an important role in the diagnosis of Fabry disease.

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CONFLICTS OF INTEREST

None declared.

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Correspondence to:
Hua Xie and Hongli Lin
Department of Nephrology, the First Hospital of Dalian Medical University
No 222 Zhongshan Rd, Dalian 116011, China
Tel: +86 411 8363 596, ext 3140
Fax: +86 411 8363 5956
E-mail: wlciq007@163.com, hllin@dlmedu.edu.cn

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