IJKD KIDNEY DISEASES

A Classical Phenotype of Fabry Disease with Novel Mutation Found by Kidney Biopsy, A Case Report

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Fabry disease (FD) is a multi-organ disorder caused by a deficiency of alpha-galactosidase (α-GLA) or reduced activity of the enzyme due to mutations in the GLA gene on the X chromosome, making it an X-linked hereditary disease. A 37-year-old man previously diagnosed with sudden deafness and cardiac hypertrophy was referred to our department after an abnormal urine finding during a public health checkup. A renal biopsy revealed characteristic findings, and he was diagnosed with FD with a novel GLA abnormality (c.714dupT (p.I239Yfs*11)). We are currently administering enzyme replacement therapy (ERT) with agalsidase α. This case shows that a novel genetic abnormality in FD can be overlooked for 37 years, even in the presence of typical symptoms. The significance of a renal biopsy in diagnosing FD is emphasized, highlighting the crucial role of nephrologists.

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Case Report

INTRODUCTION

Fabry disease (FD) is a hereditary disorder caused by a deficiency in α-GLA located on the X chromosome, which leads to the buildup of various metabolites, such as lysosomal globotriaosylceramide (Lyso-Gb3), in multiple organs, resulting in various symptoms.[1]

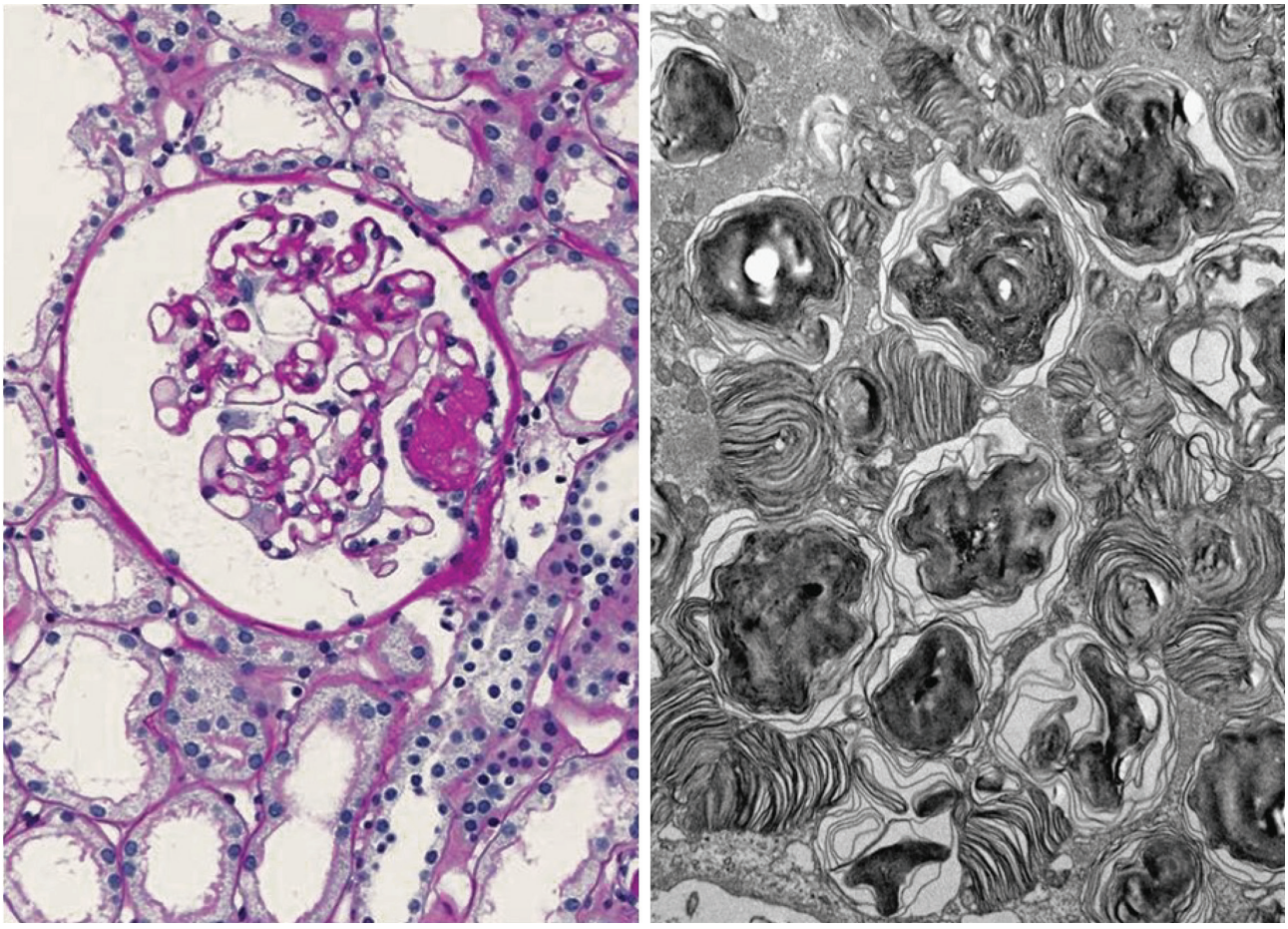
We herein report a case of classical FD with a novel hereditary mutation discovered on a kidney biopsy. Our findings underscore the importance of a renal biopsy in the diagnosis of FD.

CASE REPORT

A 37-year-old Japanese man was referred to our hospital because of proteinuria detected after a routine health checkup three years ago. The patient had previously experienced sudden deafness. Two years ago, electrocardiography had revealed high-voltage in precordial leads and apical hypertrophic cardiomyopathy was found in echocardiography. None of the patient's family members had had kidney diseases or received dialysis.

The patient's vital signs and physical examination results were within normal limits. A urinalysis showed 2+ proteinuria, no occult urinary blood, and a few granular casts with a urinary protein-to-creatinine ratio of 1570 mg/g. Blood biochemical tests showed normal kidney function (Cr = 0.82 mg/dL, eGFR = 86 mL/min/ 1.73m^2), liver function, and immunologic test results. Chest radiography, CT, and abdominal ultrasound revealed normal findings, while an electrocardiogram and echocardiography indicated left ventricular hypertrophy.

We suspected chronic glomerulopathy and performed a kidney biopsy, which showed 11 glomeruli, three of which presenting had global sclerosis while most of the majority of the other glomeruli showed enlarged podocytes containing small, clear vacuoles, seen as glycosphingolipid material on periodic acid-Schiff staining (Figure).



A B

The needle-biopsy specimen of the kidney showed 11 glomeruli, three of them were globally sclerosed. Panel A shows a glomerulus with numerous enlarged podocytes, characterized by the presence of small, clear vacuoles on the Periodic acid-Schiff staining. In electron microscopic examination (panel B), enlarged podocytes contain significant numbers of inclusion bodies that reputed myelin figures and zebra bodies.

Immunofluorescence microscopy revealed the absence of immune and other complement component deposits. Although some renal tubular cells had similar inclusion bodies, there were no similar findings in the mesangial cells. Electron microscopy showed that the enlarged podocytes had many inclusion bodies resembling myelin figures and zebra bodies.

We went over his medical history again and discovered that he had experienced numbness in his extremities while in bed or taking a bath, as well as hypo-hidrosis. Despite these symptoms, the patient had not sought medical care since he was unconcerned about them. Further hematological tests revealed undetectable levels of α-GLA activity, Lyso-GB3 levels of 109 nmol/L, and H-CTH levels of 10.0 nml/L.[3,4]

We initiated enzyme replacement therapy (ERT) with agalsidase alfa, 0.2 mg/kg every other week,[2] and conducted a genetic test on α-GLA, which revealed a previously unreported novel mutation in c.714dupT (p.I239Yfs*11). Lyso-GB3 and H-CTH levels fell modestly over half a year of follow up, reaching 62.6 and 8.1 nmol/mL, respectively.

DISCUSSION

In this particular case, two important points were determined. First, the genetic abnormality (c.714dupT (p.I239Yfs*11)) is a new GLA mutation. Second, even when classic symptoms are present, as in the present case, the diagnosis of FD remains challenging. However, a kidney biopsy can provide characteristic findings and facilitate the diagnosis.[5]

A previous study suggested that α-galactosidase activity could differentiate between classical and non-classical forms with a cutoff of 45.[6]

Diagnosing FD is challenging, as research indicates an average time span of over 13 years from the early stage to the definitive diagnosis.[7] The patient in the current study exhibited characteristic symptoms, including sudden hearing loss and cardiomegaly. Arends *et al.* proposed that the activity of α-GLA should be assessed in individuals below the age of 50 who have unexplained chronic kidney disease.[6]

Nephrologists are mostly involved in the diagnosis of FD.[8] This is most likely related to the usefulness of a kidney biopsy in this diagnosis. While standard light microscopy is typically considered to lack specific findings, in this particular case, significant features were detected, such as the presence of inclusion bodies of podocytes. Performing special pathological staining facilitates a more straightforward diagnosis. Electron microscopy can reveal even more characteristic findings, such as zebra bodies and myelin figures.

CONCLUSION

We reported a case of Fabry disease resulting from a newly identified gene mutation, which exhibited the typical features of the disorder. Diagnosing patients can still be challenging, even when they exhibit typical symptoms. The diagnosis of Fabry disease, even in the absence of severe or life-threatening organ damage, depends on a kidney biopsy, specifically utilizing standard light microscopy to verify the existence of the inclusion bodies in podocytes, which is a distinctive characteristic, highlighting the essential contribution of nephrologists in clinical practice.

INFORMED CONSENT

We received personal informed consent to perform this treatment and publish this case report.

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