INTERNAL MEDICINE

□ CASE REPORT □

A Renal Variant of Fabry Disease Diagnosed by the Presence of Urinary Mulberry Cells

Homare Shimohata, Yujiro Ogawa, Hiroshi Maruyama,
Kouichi Hirayama and Masaki Kobayashi

Abstract

Fabry disease is a lysosomal storage disorder caused by a deficiency of α-galactosidase A. This disease is classified into two types, namely a classical and variant type. We herein present the case of a 36-year-old man who showed a renal variant of Fabry disease and was diagnosed at an early stage by the presence of mulberry cells. He had no history of general symptoms except for proteinuria. The presence of mulberry cells caused us to suspect Fabry disease and he was thereafter diagnosed to have a renal variant of Fabry disease based on the findings of a renal biopsy, a mutation analysis and a low level of α-galactosidase A activity.

Key words: Fabry disease, mulberry bodies, mulberry cells, renal variant

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Introduction

Fabry disease is a lysosomal storage disorder caused by a deficiency of alpha-galactosidase A and the progressive accumulation of glycosphingolipids, especially globotriaosylceramide, which results in multiple organ insufficiency. Since Fabry disease is an X-linked inherited disease, hemizygous male patients show severe general symptoms, such as neuropathic pain, angiokeratoma, hypohidrosis, corneal opacities at a young age, and dysfunction of the heart, brain and kidney in adulthood. On the other hand, heterozygous female patients can show milder symptoms after lyonization of the abnormal X chromosome.

In addition to the abovementioned classical types that show general symptoms, Desnick et al. described in 2002 the existence of an atypical male variant of Fabry disease which lacked the classic manifestations, such as neuropathic pain, angiokeratoma, and hypohidrosis, and only manifested renal symptoms. They named this disease entity a "renal variant" (1). One year later, Nakao et al. reported on six patients with the renal variant phenotype of Fabry disease among male patients undergoing hemodialysis therapy; thereafter, the existence of the renal variant became widely recognized (2). After their report, not only dialysis patients found by screening, but also choric kidney disease patients whose renal function was preserved were reported. However, it is difficult to identify the renal variant of Fabry disease at an early stage because such patients show no general symptoms, except for proteinuria and renal failure.

In general, Maltese cross in urine sediment is a famous renal feature of Fabry disease, but it is not specific for Fabry disease. On the other hand, urinary mulberry cells are the characteristic feature of Fabry disease and their diagnostic value is high, but their usefulness for the early diagnosis of Fabry disease is not generally recognized because their detection depends on the skill and knowledge of urine test technicians (3).

We herein present the case of a pure renal variant of Fabry disease that was diagnosed at an early stage by the presence of mulberry cells. We show the usefulness of this symptom for the early detection of renal variant Fabry disease.

Case Report

A 36-year-old Japanese man was admitted to our hospital to investigate the cause of proteinuria that had persisted for one year. He had no history of neuropathic limb pain or hypohidrosis. On examination, his blood pressure was 154/82

Department of Nephrology, Tokyo Medical University Ibaraki Medical Center, Japan
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Correspondence to Dr. Homare Shimohata, h-shimo@tokyo-med.ac.jp

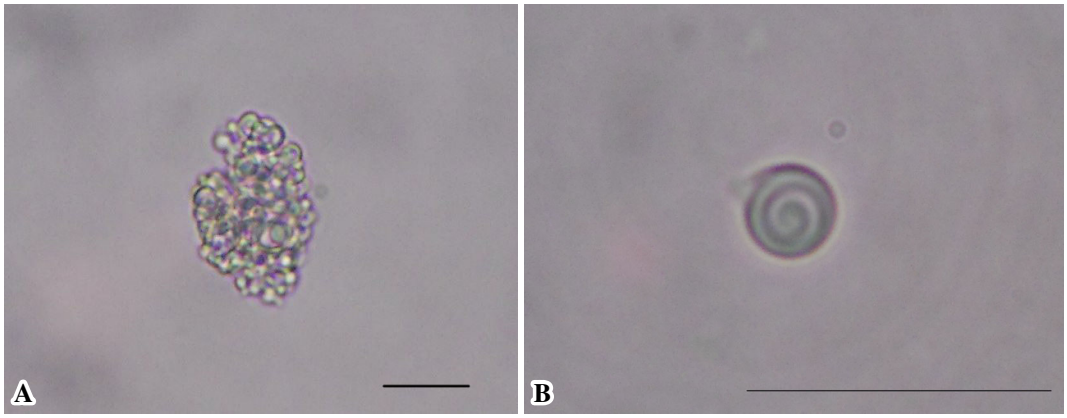

Figure 1. **(A) Mulberry cells in the urine sediment. The appearance resembles a mulberry. Magnification is ×400 and scale bar represents 10 μm. (B) A mulberry body in the urine sediment. A lamellar appearance is the characteristic picture of mulberry bodies. Magnification is ×1,000 and scale bar represents 10 μm.**

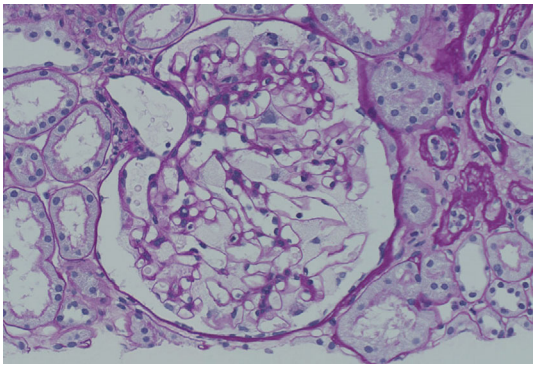

Figure 2. **Light microscopic image of a kidney biopsy sample. Enlarged and vacuolated podocytes are shown. Vacuolated change was also observed in some of the tubular epithelium cells (periodic acid-Schiff stain ×400).**

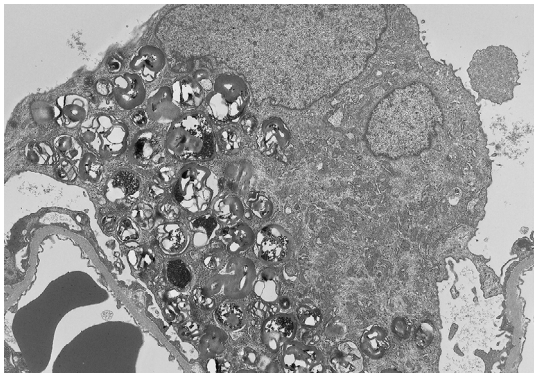

Figure 3. **Electron microscopic image of a kidney biopsy sample. Myelin-like bodies are present in the podocytes (×2,500).**

mmHg, the pulse rate was 72 beats/min (regular sinus rhythm) and his body temperature was 37.1℃. Angiokeratomas and corneal opacities, which are the characteristic findings of Fabry disease, were not observed. Laboratory data on admission showed the serum creatinine and blood urea nitrogen levels to be 0.77 and 13 mg/dL, respectively. Hemoglobin and serum albumin were 14.4 g/dL and 4.5 g/dL. White blood cells, platelets, C-reactive protein, alkaline phosphatase, lactate dehydrogenase, blood glucose, and electrolytes were all normal. Low-density lipoprotein cholesterol and triglyceride levels were within the normal limits. Regular urinalysis tests showed proteinuria (548 mg/gCre), and mulberry cells and bodies in the urinary sediment (Fig. 1). From these results, we assumed the presence of Fabry disease and conducted a percutaneous renal biopsy to reveal the reasons for the proteinuria.

Three needle core biopsy samples including twenty-eight glomeruli were submitted for analysis. Three glomeruli showed global sclerosis. The other twenty-five glomeruli contained strikingly enlarged and vacuolated podocytes (Fig. 2). Vacuolated change was also observed in some of the tubular epithelium cells. No membranous change or local lesions were observed. Immunofluorescence studies showed no deposits in the glomeruli. Enlarged lysosomes packed with lamellated membrane structures (myelin-like bodies) were detected in podocytes by electron microscopy (Fig. 3), and the rate of foot process fusion was 50 %. After performing the renal biopsy, we investigated the alpha-galactosidase A activity in the leucocytes and confirmed that it was very low (1.3 nmol/mg protein/hour) (normal range: 49.8-116.4 nmol/mg protein/hour). Next, we measured the level of Lyso-Gb3 in plasma and revealed that it was high (25 nmol/L) (normal range: <2 nmol/L), and urinary Gb3 was also detected. Furthermore, mutation analysis was performed by polymerase chain reaction amplifying seven α-gal A exons. In this mutation analysis, G360S in exon 7 was identified. Although echocardiography, electrocardiography and brain magnetic resonance imaging were conducted during hospitalization, we could not find any abnormal findings. From these biochemical and genetic results, clinical manifestations, and image findings, we diagnosed this patient to have the pure renal variant of Fabry disease. After diagnosis, enzyme replacement therapy with recombinant

alpha-galactosidase A (agalsidase α 0.2 mg/kg biweekly) was started. At present, his renal function is normal, his urinary protein level is low, and no further clinical symptoms have been observed.

Discussion

Although cases of Fabry disease with only renal manifestation had been described in the 1990s (4, 5), the concept of a renal variant of Fabry disease that shows only renal symptoms without classical Fabry symptoms only became widely accepted after the report of Nakao et al. (2) in 2003. They found these patients from among their hemodialysis patients. After their report, patients at dialysis clinics worldwide began to undergo Fabry disease screening, and many new Fabry patients were thus identified (6-9). Some of these patients were categorized as having the renal variant of Fabry disease.

On the other hand, only a few cases of the renal variant of Fabry disease diagnosed before the induction of renal replacement therapy because almost all such cases show no general symptoms except for proteinuria and thus are often overlooked. In this report, we present a patient demonstrating the renal variant of Fabry disease who was diagnosed at a quite an early stage.

In previous reports, Rosenthal et al. showed a 65-year-old man who was diagnosed with the renal variant of Fabry disease by renal biopsy (10). At the time of renal biopsy, his creatinine clearance was 69 mL/min/1.73 m^2. He was treated conservatively in the 5 years after diagnosis, during which time his renal function progressively worsened. Consequently, he underwent a preemptive renal transplantation. Another case of the renal variant of Fabry disease was presented by H Mukdsi et al. (11). They showed the effect of enzyme replacement therapy for the renal variant Fabry disease. Their patient's pre-treatment creatinine level was 1.72 mg/dL, and during the three years of enzyme replacement therapy with agalsidase beta, the creatinine level had remained stable (1.99 mg/dL). Furthermore, they showed a moderate reduction of podocyte lamellar inclusions on electron microscopy. Lee et al. published an interesting report about the renal-protective effect of enzyme replacement therapy for renal-variant Fabry disease (12). They described three brothers with the renal variant of Fabry disease. Among them, the eldest brother was treated by agalsidase beta and at that time, his serum creatinine was 3.0 mg/dL. Unfortunately, after two years of treatment with agalsidase beta, his renal function worsened and chronic ambulatory peritoneal dialysis was started. On the other hand, although his two younger brothers were also diagnosed and treated identically, their renal function remained stable during the two-year treatment period. The dissimilarity between the eldest brother and two younger brothers lay in the creatinine levels at the time of the start of enzyme replacement therapy. In the two younger brothers, treatment was started before the renal function had dramatically worsened (Their creatinine levels were 1.1 and 1.0 mg/dL, respectively). These reports emphasize the importance of early detection and treatment with enzyme replacement therapy in patients with the renal-variant of Fabry disease.

Urinary mulberry cells are the characteristic feature of Fabry disease, and their identification is a quick, inexpensive and noninvasive tool for the early detection of Fabry disease. They are regarded as distal tubular epithelial cells in which Gb-3 has accumulated, and they can occasionally be detected before the presence of renal injury. They are similar to oval fat bodies, but can be distinguished by the difference in refractivity, size and inner lamellar appearance. A part of mulberry cells is the mulberry body. A lamellar appearance is the characteristic picture of mulberry body (Fig. 1B). Mulberry cells are specific to Fabry disease, but similar cells are also observed in metachromatic leukodystrophy. Although there is a precedent for Fabry cases diagnosed by mulberry cells in Japan (13-15), worldwide the degree of recognition of mulberry cells is very low. In the present study, we could show that mulberry cells were useful markers for the quick detection of renal-variant Fabry disease. In a future study, it is important to elucidate the positive rate of mulberry cells in Fabry patients in order elucidate the usefulness of this marker as an evaluation tool of therapeutic efficacy.

Another intriguing point associated with our case was the result of a mutation analysis. We identified the G360S mutation in exon 7. In general, the enzyme activity and stability are influenced by various gene mutation patterns. Since the same mutation that occurred in a non-conserved region has been found in classic Fabry disease (16), the mutation in our case is not specific for the renal variant of Fabry disease. Until now, the precise mechanism by which organ-specific symptoms occur has not been elucidated. Further accumulation of the mutation analysis findings of the renal variant type and detailed correlations of the genotypes and phenotypes may help to elucidate the pathogenesis of renal-specific symptoms in Fabry disease.

In conclusion, the detection of mulberry cells enabled us to discover the presence of renal-variant Fabry disease in a patient before the onset of renal impairment. Nephrologists and technicians of urine examinations should therefore be trained to look for mulberry cells and mulberry bodies in urine sediment tests to diagnose Fabry disease at an early stage.

The authors state that they have no Conflict of Interest (COI).

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