

[CASE REPORT]

Improvement in Decline Rate of Estimated Glomerular Filtration Rate after Febuxostat Treatment in a Fabry Disease Patient with Enzyme Replacement Therapy-resistant Proteinuria

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Abstract:

Fabry disease is an inherited lysosomal disorder caused by mutations in the alpha-galactosidase A gene. We herein report a Fabry disease patient with enzyme replacement therapy (ERT)-resistant proteinuria who showed improvement in the estimated glomerular filtration rate (eGFR) decline rate after uric acid (UA)-lowering therapy. The patient was diagnosed with Fabry disease at 36 years old. After that, even under ERT, proteinuria and eGFR decline persisted. During the clinical course, serum UA levels were elevated with increases in renal tubular damage markers. Febuxostat administration immediately improved tubular damage and prevented further eGFR decline. UA-mediated tubulopathy may become an additional therapeutic target for eGFR decline in Fabry disease.

Key words: Fabry disease, hyperuricemia, tubular cell damage, xanthine oxidase inhibitor, urate crystal

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Introduction

Fabry disease is an inherited lysosomal disorder caused by mutations in the X chromosome-linked alpha-galactosidase A (*GLA*) gene, leading to cataracts, cardiac diseases, painful peripheral neuropathy, skin lesions and renal damage via the accumulation of globotriaosylceramide in the lysosomes of affected tissues (1-4). Regarding renal involvement, podocytopathy-mediated proteinuria, rather than tubular dysfunction, is considered the main pathology related to the renal prognosis (5-7). The only effective treatment for Fabry disease is enzyme replacement therapy (ERT) with recombinant human *GLA* (8-10). No treatment has been established for patients with ERT-resistant proteinuria to date. Thus, the development of a novel treatment

strategy is urgently needed.

We herein report a patient with ERT-resistant proteinuria whose renal tubular damage markers and estimated glomerular filtration rate (eGFR) decline rate were significantly improved by uric acid (UA)-lowering therapy with febuxostat, a xanthine oxidase inhibitor. Therefore, we propose UA-mediated tubulopathy as an additional therapeutic target for this disease.

Case Report

The patient was diagnosed with proteinuria at 25 years old but had not been further examined for approximately a decade. At 36 years old, she visited the nephrology department in our hospital for a detailed examination. On a physical examination at the first visit, she was alert, and her

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Table. Laboratory Data at Initial Visit.

CBC		γ -GTP	21 mg/dL	Urinalysis	
RBC	$32.2 \times 10^4/\mu\text{L}$	BUN	16.4 mg/dL	pH	6.5
HT	10.1 %	Cr	0.86 mg/dL	Osm	1.010
Hb	4.17 g/dL	eGFR	60.5 mL/min/1.73m ²	Protein	2+
WBC	$6,100/\mu\text{L}$	UA	4.8 mg/dL	Blood	2+
PLT	$250 \times 10^4/\mu\text{L}$	Na	137 mEq/L	Glucose	-
		K	3.8 mEq/L	Ketone	-
Blood chemistry		CL	101 mEq/L	TP	2.25 g/gCr
TP	6.4 g/dL	Ca	8.3 mg/dL	Urinary sediment	
ALB	3.7 g/dL	P	4.2 mg/dL	RBC	0-1 /HPF
AST	20 IU/L	β 2-MG	2.0 mg/L	WBC	0-1 /HPF
ALT	17 IU/L	T-Cho	210 mg/dL	Epithelial cells	10-20 /HPF
LDH	269 IU/L	TG	126 mg/dL		
ALP	165 IU/L	HDL	73 mg/dL		
T-Bil	0.57 mg/dL	CRP	0.07 mg/dL		

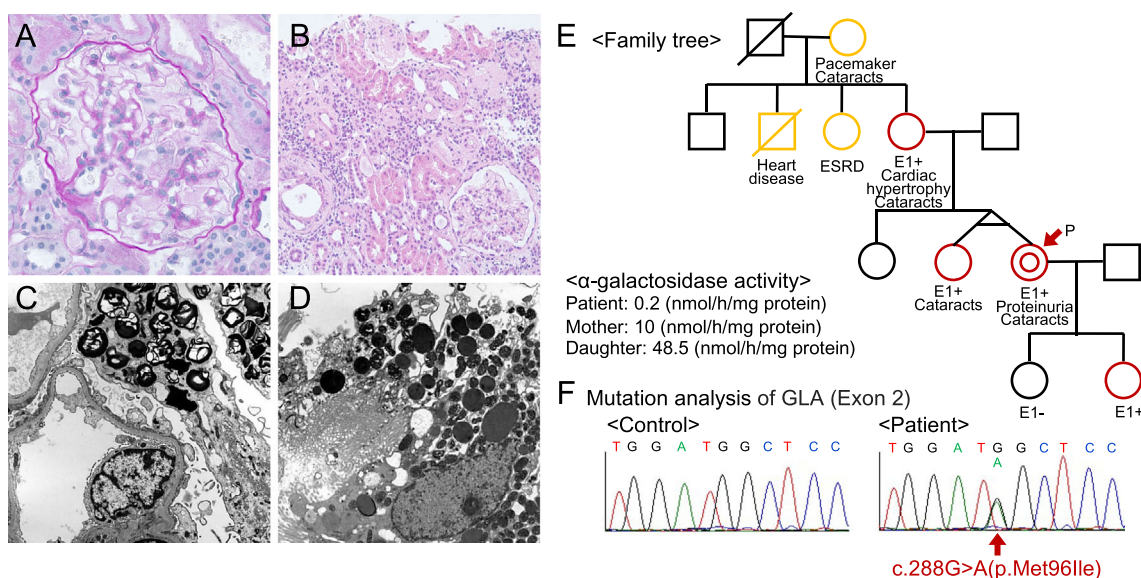


Figure 1. The diagnosis of Fabry disease. (A-D) Renal pathological findings. Glomerular lesion by PAS stain (A), tubulointerstitial lesion by Hematoxylin and Eosin staining (B), an electron microscopic analysis in glomeruli (C) and proximal tubular cells (D). (E) Family tree of the patient in this report (double circle). Red indicates those diagnosed with Fabry disease by a genetic examination (E1+). E1- indicates a negative result of a genetic examination. Yellow indicates those with organ dysfunction related to Fabry disease. P indicates the proband. (F) A mutation analysis of α -galactosidase (*GLA*) in the patient.

blood pressure, pulse rate and temperature were 138/74 mmHg, 64 beats per minute (regular) and 36.4°C, respectively. Auscultations of the lung and heart were normal. No peripheral edema or skin lesions were observed. The abdomen was soft and flat with no tenderness. Her neurological examination revealed no abnormalities. Furthermore, except for a low eGFR of 60.5 mL/min/1.73 m² and proteinuria of 2.25 g/gCr without excretion of deformed red blood cells in the urine (Table), no obvious abnormalities were noted in blood, electrocardiogram or echocardiography tests.

A renal biopsy was performed for the diagnosis of proteinuria. A microscopic examination showed enlarged podocytes (Fig. 1A) with a tubulointerstitial lesion (Fig. 1B), and electron microscopy revealed zebra bodies in both podocytes and tubular cells (Fig. 1C, D), suggesting Fabry disease (4).

Furthermore, a urine sediment examination showed increased epithelial cells, including mulberry cells (Table). Her family history revealed that several maternal relatives, including her twin sister, had symptoms related to Fabry disease, such as kidney failure, cardiac diseases and early-onset cataracts, suggesting hereditary Fabry disease (Fig. 1E). A genetic diagnosis in the patient and her mother revealed a mutation in exon 2 of the *GLA* gene (c.288G>A(p.Met96Ile)) (Fig. 1E, F), and the *GLA* activity in leukocytes was

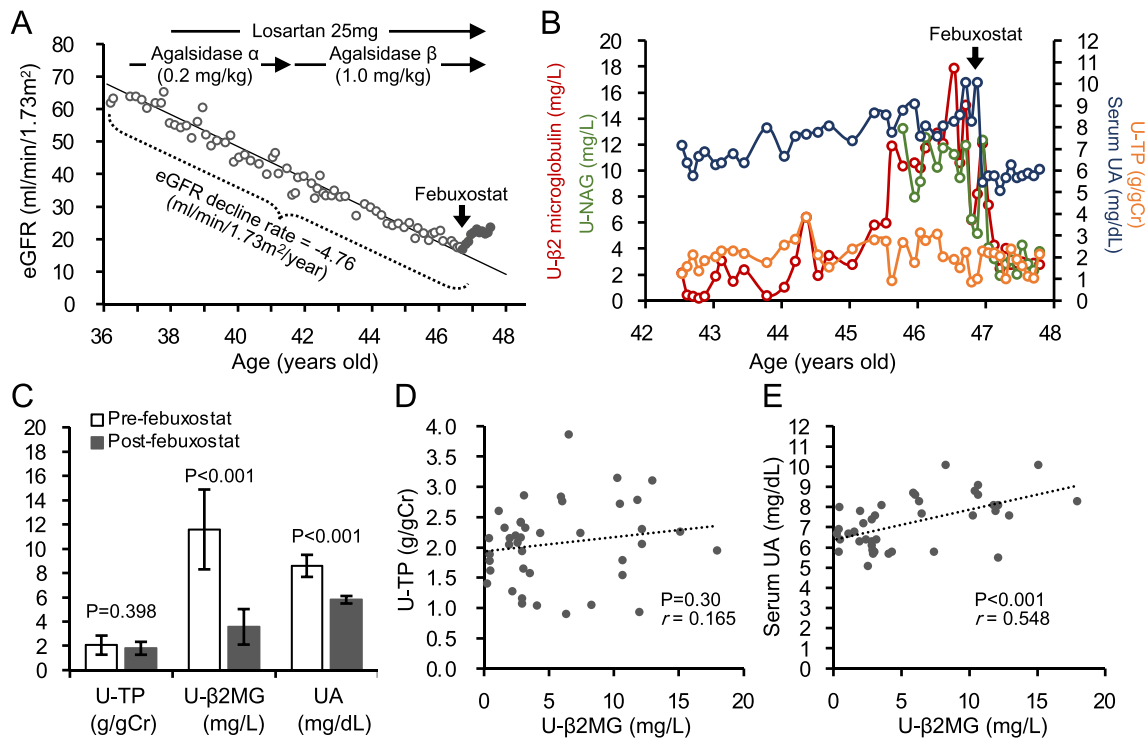


Figure 2. Clinical course after the diagnosis of Fabry disease. (A) eGFR plot to show the rate of eGFR decline and the treatment details over the entire time the patient was cared for in our hospital. (B) Urinary β 2-microglobulin (U- β 2MG), urinary N-acetyl- β -D-glucosaminidase (U-NAG), urinary protein (U-TP) and serum uric acid (UA) levels from 42 to 48 years old. (C) The mean value of each index measured 10 times before and after februxostat administration. Data are shown as the mean \pm SD. $p<0.05$ indicates statistically significant differences (Student's *t*-test). (D, E) The correlation between U- β 2MG levels and U-TP levels (D) and between U- β 2MG levels and serum UA levels (E) in Fig. 2B. *r*: Pearson's correlation coefficient. $p<0.05$ indicates statistically significant correlation.

almost absent and decreased in the patient and her mother, respectively (Fig. 1E). In addition, the same genetic mutation was identified in the younger daughter of the patient, although her GLA activity was maintained (Fig. 1E, F).

In addition to these examination findings, the medical history interview revealed that the patient had been previously diagnosed with cataracts (in junior high school), but no history of cerebrovascular or cardiovascular diseases or lower extremity pain was noted. Based on these findings, we diagnosed this patient with a renal variant of Fabry disease.

After the diagnosis, ERT with agalsidase β (0.2 mg/kg) was started and administered every 2 weeks (Fig. 2A). Subsequently, with no apparent improvement in proteinuria and gradual progression of cardiac hypertrophy, the treatment was switched to agalsidase α (1.0 mg/kg). However, her proteinuria remained refractory, and her systolic blood pressure was mildly elevated, ranging from 130 to 140 mmHg. Therefore, antihypertensive treatment with losartan (25 mg/day) was added starting at 38 years old. Her systolic blood pressure improved to approximately 110 mmHg, but her proteinuria levels did not improve. The eGFR continuously declined at a rate of approximately 5.0 mL/min/1.73 m² per year, and her renal function declined to end-stage kidney disease over the next 1-2 years (Fig. 2A). As the eGFR con-

tinued to decline, hyperuricemia was observed, and februxostat was initiated as a UA-lowering therapy (Fig. 2A). Immediately after februxostat administration, the eGFR recovered slightly, and the eGFR slope almost stabilized (Fig. 2A).

Based on the assessment of proteinuria and urinary β 2-microglobulin as markers of glomerular and tubular damage, respectively, the urinary levels of β 2-microglobulin appeared to respond to the change in proteinuria levels until 45 years old. However, subsequently, the serum UA level began to increase. Once it exceeded 8.0 mg/dL, as the serum UA level increased, so did the urinary β 2-microglobulin, even though the proteinuria levels were unchanged (Fig. 2B, C). After the serum UA levels decreased with februxostat treatment, the urinary β 2-microglobulin levels also immediately decreased, and the eGFR decline stopped (Fig. 2B, C). Furthermore, the urinary β 2-microglobulin levels were positively correlated with the serum UA levels but not proteinuria levels after 45 years old (Fig. 2D, E). In addition, the urinary levels of N-acetyl- β -d-glucosaminidase decreased (Fig. 2B), and urinary epithelial cell excretion was completely abolished after treatment. These results suggested that higher UA levels caused tubular cell damage, which resulted in progressive eGFR decline.

Discussion

We experienced a woman with Fabry disease and progressive eGFR decline that was refractory to ERT but responsive to UA-lowering treatment. In a previous report, 124 Fabry disease patients were followed for 7.4 ± 3.7 years to examine plasma UA levels and prognoses (11). The results showed that high UA levels were associated with a decreased renal function and increased mortality (11). However, it was not an interventional study, and it did not conclude that UA-lowering therapy led to an improved prognosis (11). Furthermore, no other article has demonstrated an association between Fabry disease and UA. Although our study is a case report, it is the first, to our knowledge, to show that UA-lowering therapy affects the renal prognosis in Fabry disease.

It is not clear whether the tubular damage caused by UA was a coincidence in this case alone (as in gouty nephritis), or whether it is a condition that occurs in all cases of Fabry disease. Fabry disease is a condition that causes cytotoxicity due to lysosomal dysfunction, and it is presumed that the combination of other factors that cause lysosomal damage may contribute to the worsening of the condition. Recently, UA crystals were reported to exacerbate tubular damage in a mouse model with abnormal autophagy and lysosome dysfunction in proximal tubular cells (12). These results suggest that the addition of hyperuricemia in patients with an inadequate lysosomal function may show exacerbated cytotoxicity. Therefore, hyperuricemia may pose a significant risk for worsening tubular damage in Fabry disease cases with abnormal lysosomes, and UA-lowering therapy may be an additional renoprotective strategy for these patients.

Another question is whether the treatment outcomes in this case were due to the lowering of the UA level or the administration of a xanthine oxidase inhibitor. Because serum UA levels are positively associated with urinary β 2-microglobulin during febuxostat treatment, the change in serum UA levels (UA crystals in the kidney) is most likely responsible for the change in the eGFR decline rate, as suggested by the animal study mentioned above (12). However, in the present case, the eGFR decline rate did not accelerate, even when the UA level increased before the start of febuxostat treatment. This result may alternatively suggest that the administration of a xanthine oxidase inhibitor itself might have contributed to the improved renal prognosis in this case, regardless of serum UA levels. Additional evaluations with comparisons between febuxostat and uricosuric drugs will be required to clarify this point.

Several limitations associated with the present study warrant mention. First, whether or not UA-lowering therapy is effective for other organ damage, including cardiac events, is unclear. Second, because the urinary excretion of UA was not tested before febuxostat treatment, whether or not increased urinary UA levels are associated with tubular damage remains to be elucidated. Third, because globotriaosyl-

ceramide levels were not frequently measured, the effect of UA-lowering therapy on the progression of Fabry disease itself is unknown. Finally, this case may simply have involved comorbid Fabry disease and gouty nephritis, so whether or not this strategy is effective for all Fabry patients requires further verification.

In conclusion, UA crystals exacerbate renal tubular damage in Fabry disease, and UA-lowering therapy is effective for preventing eGFR decline, suggesting that UA-mediated tubulopathy provides an additional therapeutic target for preventing renal function decline in ERT-resistant Fabry disease. In patients with Fabry's disease, UA levels and tubular damage markers need to be followed with more attention than in other renal diseases, and management goals of serum UA levels to improve the renal prognosis may need to be considered.

Informed consent was obtained from the participant described in this report.

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

Shinji Kume and Mako Yasuda-Yamahara contributed equally to this study.

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