A Cardiac Variant of Fabry Disease Diagnosed with Chance Urinary Mulberry Cells

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Abstract:
Fabry disease is an X-linked lysosomal storage disorder caused by a deficiency of α-galactosidase A and is classified into two types: classical and variant. The classical type exhibits classic manifestations, but the variant type does not and is therefore difficult to identify sometimes. A 73-year-old woman with a first episode of heart failure was admitted to our hospital. Her left ventricular wall motion was mildly reduced without hypertrophy. Urine sediment revealed mulberry cells, leading to the diagnosis of Fabry disease. In cases without typical clinical findings, urinary mulberry cells may help diagnose Fabry disease.

Key words: fabry disease, mulberry body, mulberry cell, cardiac variant

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Introduction
Fabry disease is an X-linked lysosomal storage disorder caused by a deficiency of α-galactosidase A (α-GAL) that leads to globotriaosylceramide (GL-3) deposition in many tissues (1).

Fabry disease is classified into two types: classical and variant. Patients with classical type present with peripheral neuropathy, abdominal pain, nausea, and hypohidrosis during childhood; cardiac disease, renal disease, and cerebrovascular disease can develop during adulthood. Conversely, those with variant type lack such classic manifestations because the residual enzyme activity slows the disease progression. Therefore, patients with Fabry disease exhibit various phenotypes, including cardiac, renal, or cerebrovascular diseases.

We herein report a case of cardiac variant of Fabry disease diagnosed by the presence of urinary mulberry cells.

Case Report
A 73-year-old woman treated for rheumatoid arthritis was admitted to our hospital because of worsening dyspnea and bilateral lower extremity edema. She had no history of heart failure, chronic kidney disease, hypohidrosis, or peripheral pain. She had been prescribed methotrexate 4 mg weekly, and prednisolone 3 mg and etodolac 400 mg daily.

On examination, her blood pressure, heart rate, and percutaneous oxygen saturation were 124/66 mmHg, 74 beats/min (regular sinus rhythm), and 98%, respectively. A physical examination showed decreased bilateral pulmonary sounds and bilateral pitting edema in the legs. A neurological examination revealed no abnormalities such as peripheral nervous system disorders.

Table shows the laboratory data on admission: blood urea nitrogen level, 20.0 mg/dL; serum creatinine level, 1.13 mg/dL; N-terminal pro-brain natriuretic peptide level, 124/66 mmHg, 74 beats/min (regular sinus rhythm), and 98%, respectively. A physical examination showed decreased bilateral pulmonary sounds and bilateral pitting edema in the legs. A neurological examination revealed no abnormalities such as peripheral nervous system disorders.

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Table shows the laboratory data on admission: blood urea nitrogen level, 20.0 mg/dL; serum creatinine level, 1.13 mg/dL; N-terminal pro-brain natriuretic peptide level, 6,749 pg/mL; and D-dimer level, 4.6 μg/mL. A urinalysis showed no sugar, protein, or red blood cells. Chest radiography revealed small bilateral pleural effusions. A 12-lead electrocardiogram showed a normal sinus rhythm, left axis deviation, and poor R wave progression in the precordial leads. Echocardiography revealed global left ventricular hypokinesis with a left ventricular ejection fraction of 30%. The interventricular septum thickness was 7.2 mm, and the left ventricular posterior wall thickness was 8.1 mm with the presence of a thrombus inside of the left ventricle (Fig. 1).

Coronary computed tomography angiography showed no obvious stenoses in the coronary arteries.
The patient was diagnosed with heart failure and administered azosemide and enarapril. Her symptoms gradually improved, and she was prescribed carvedilol. During hospitalization, urinary sediment revealed the presence of mulberry cells and bodies (Fig. 2). Her leukocyte α-GAL activity was slightly decreased, 45.5 nmol/mg (range, 49.8-116.4 nmol/ mg). We performed a genetic test and identified a missense heterozygous mutation, c. 395 G/G>G/A, p. G132E in GLA. A myocardial biopsy was not performed because she refused invasive tests. The left ventricular apical thrombus disappeared after one month of anticoagulant treatment with warfarin. The patient’s symptoms improved, and she was discharged.

The patient had a son and daughter; neither of them had displayed any symptoms and had no particular medical histories. After their mother’s diagnosis, they underwent genetic screenings, and the same mutation was found in the daughter only. Echocardiography of the daughter revealed mild left ventricular hypertrophy, while the findings of the son were normal.

### Table. Laboratory and Urine Tests on Admission.

| Test                  | Result       |
|-----------------------|--------------|
| Complete blood count  |              |
| WBC                   | 93.3 x10^9/μL|
| RBC                   | 489 x10^9/μL |
| HGB                   | 14 g/dL      |
| PLT                   | 29 x10^9/μL  |
| Chemistry             |              |
| AST                   | 39 U/L       |
| ALT                   | 32 U/L       |
| TP                    | 7.9 g/dL     |
| Alb                   | 4.2 g/dL     |
| T-Bil                 | 1.4 mg/dL    |
| BUN                   | 20 mg/dL     |
| Cre                   | 1.13 mg/dL   |
| eGFR                  | 36.6 mL/min/1.73m² |
| UA                    | 4.7 mg/dL    |
| Na                    | 147 mmol/L   |
| K                     | 3.6 mmol/L   |
| Cl                    | 101 mmol/L   |
| TG                    | 118 mg/dL    |
| Glucose               | 116 mg/dL    |
| HbA1c (NGSP)          | 6.9 %        |
| NT-proBNP             | 6,749 pg/mL  |
| Coagulation           |              |
| PT (INR)              | 1.16         |
| APTT                  | 26.3 s       |
| D dimer               | 4.6 μg/mL    |
| Urine Test            |              |
| Protein               | (-)          |
| Glucose               | (-)          |
| Urine blood           | (-)          |

**Figure 1.** Transthoracic echocardiogram. Apical four-chamber view in end diastole (left side) and systole (right side) showing the thrombus in the apex of the left ventricle (arrow). Echocardiography revealed global left ventricular hypokinesis and no left ventricular hypertrophy.
ments. Nevertheless, we believe that urine microscopy may be a useful tool for the diagnosis of variant-type Fabry disease.

To our knowledge, this is the first report on the cardiac variant of Fabry disease without typical hypertrophy diagnosed by the presence of urinary mulberry cells. Our case has two implications. First, even without typical clinical findings, urinary mulberry cells may indicate Fabry disease as the cause of otherwise unexplained heart failure. In our case, we did not suspect Fabry disease until observing the urinalysis results because echocardiography did not show cardiac hypertrophy, which is one of the common cardiac features of the disease. However, Niemann et al. showed that myocardial hypertrophy is less common in women with Fabry disease than in men (8); thus, a urinalysis may be helpful for diagnosing women with unknown heart failure with or without cardiac hypertrophy. Second, even if the urinary protein test is negative, detecting the presence of urinary mulberry cells is useful for diagnosing Fabry disease. Fabry disease has been detected in patients with renal failure. Shimohata et al. showed the usefulness of mulberry cells in a patient without proteinuria (9). Our results support the notion that testing for mulberry cells is an important screening tool for diagnosing Fabry disease in patients without proteinuria.

Enzyme replacement therapy (ERT) controls the progression of cardiomyopathy in patients with Fabry disease (10) and is recommended when patients have a definite diagnosis of Fabry disease (11). In our patient, ERT was suggested; however, she declined the treatment. Her daughter was diagnosed with Fabry disease, and she underwent ERT. The mutation has not been published in any paper yet. The detection of mulberry bodies enabled us to not only diagnose our patient but also her children; therefore, we were able to initiate appropriate treatment.

Conclusion

We describe the rare case of a woman with cardiac variant of Fabry disease diagnosed based on the presence of urinary mulberry bodies. Our experience suggests that patients with heart failure without typical symptoms of Fabry disease should undergo screening for urinary mulberry bodies, as it may lead to a diagnosis and help them undergo ERT at an early stage.

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

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