A Case of Hereditary Xanthinuria Type 1 Accompanied by Bilateral Renal Calculi

Yutaka Fujiwara¹, Yoshikazu Kawakami², Yoshihiko Shinohara³ and Kimiyoshi Ichida³,⁴

Abstract

Hereditary xanthinuria is an extremely rare purine metabolism disorder caused by a genetic abnormality in xanthine dehydrogenase. A new case of hereditary xanthinuria type 1 accompanied by bilateral renal calculi was encountered. We performed an allopurinol loading test and diagnosed classical type 1 xanthinuria. Through genetic diagnosis, we identified a mutation site in the xanthine dehydrogenase gene. Genetic analysis revealed a homozygous deletion of cytosine 2,567 in the xanthine dehydrogenase gene, and as a result, a stop codon was formed at position 928. Renal failure caused by the deposition of xanthine crystals is a known complication because xanthine is poorly soluble in water. With high fluid intake and low purine diet, no significant increase in calculi has been observed in this patient for 2 years.

Key words: hereditary xanthinuria, renal calculi, xanthine dehydrogenase

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Introduction

Hereditary xanthinuria is an extremely rare purine metabolism disorder caused by a genetic abnormality in xanthine dehydrogenase, an enzyme that catalyzes the final two reactions to uric acid, which is the end product of purine metabolism. Xanthinuria is a familial disease with an autosomal recessive mode of inheritance. The disorder is characterized by a pronounced decrease in uric acid production and elevated levels of xanthine and hypoxanthine in serum and urine (1-3).

Classical xanthinuria has recently been classified into two subtypes (4, 5). Type 1 lacks only xanthine dehydrogenase activity and is characterized by hypouricemia accompanying xanthine dehydrogenase deficiency, while type 2 lacks both xanthine dehydrogenase and aldehyde oxidase activity. As there have been few reports, however, that clearly classify xanthinuria by subtype, the frequency of each subtype remains unknown.

Here, we report a new case of xanthinuria type 1 in whom bilateral renal calculi and hypouricemia were seen in a routine health examination, and we identified a mutation site in the xanthine dehydrogenase gene of this patient.

Case Report

The patient was a 67-year-old woman. Hypouricemia with a serum uric acid level of 0.5 mg/dL was discovered in a routine health examination, and the patient was referred to our facility for a more detailed examination. There were no overt symptoms of molybdenum cofactor deficiency, such as convulsive seizures, myopathy or polyarthritis. The patient also showed no myositis due to xanthine deposits in the tissue. We investigated the family history of the patient, whose parents were first cousins. The patient’s father had undergone lithotripsy for renal calculi. The patient’s mother and six siblings were all healthy with no findings of malignant tumors, cardiovascular disease or renal failure. A detailed intrafamilial investigation of uric acid metabolism abnormalities and renal calculi could not be conducted.

Findings on physical examination were normal. Both urinalysis and blood count were normal. Examination of kidney function was normal with a creatinine clearance of 113
hypouricemia, such as xanthinuria, and overexcretion-type hypouricemia, such as renal hypouricemia.

Xanthine dehydrogenase catalyzes the oxidation of hypoxanthine to xanthine, and xanthine to uric acid in the final stages of purine metabolism. Xanthinuria resulting from a deficiency in xanthine dehydrogenase is characterized by hypouricemia, decreased urinary uric acid excretion, and increased levels of xanthine and hypoxanthine in serum and urine, respectively.

Xanthinuria was first reported by Dent and Philpot in 1954 (1); it is such a rare metabolic disorder that only 60 patients had been reported through 1976. There have been more than 100 cases of hereditary xanthinuria reported worldwide.

Bradford et al. performed a detailed comparison of the metabolism of these substances in a xanthinuria patient and in healthy subjects (7). They found that in the xanthinuria patient, serum uric acid was 0.8 mg/dL, daily urinary uric acid excretion averaged 6.5 mg/24h, and daily urinary excretion of hypoxanthine and xanthine averaged 54.4 and 219 mg/24h, respectively. Thus, urinary uric acid excretion was markedly lower, and urinary excretion of both hypoxanthine and xanthine were substantially higher than in healthy subjects. The laboratory data for the present patient correspond with those reported previously.

Both type 1 and type 2 are nearly asymptomatic with regard to clinical signs, but urinary tract calculi mainly consisting of xanthine are sometimes identified in 30% to 40% of cases due to increased urinary oxypurine levels. Differentiation between type 1 and type 2 can therefore be performed by measuring oxypurinol in serum or urine after administration of allopurinol (6). Allopurinol is oxidized to oxypurinol by xanthine dehydrogenase and aldehyde oxidase. Therefore, if allopurinol is administered but is not metabolized to oxypurinol, the xanthinuria is type 2, which lacks both xanthine dehydrogenase and aldehyde dehydrogenase, while if it is metabolized to oxypurinol, type 1 is diagnosed. The present patient was diagnosed as type 1 because serum oxypurinol levels were elevated after allopurinol loading.

In xanthinuria, urolithiasis and myositis are sometimes observed because of increased urinary xanthine excretion or the xanthine deposition in tissues. This patient was also bilaterally affected by renal calculi. Cartier and Perigon reported lithiasis as a complication in 15 of 38 xanthinuria patients (39.5%). It has been reported that these calculi are uniquely xanthine calculi (8), and there have been no reports of hypoxanthine calculi. This finding has been explained as follows: in contrast to xanthine, a salvage mechanism acts on hypoxanthine to convert it to inosine-5’-monophosphate, and the increase in urinary hypoxanthine excretion is therefore not as conspicuous as the increase in urinary xanthine excretion. We inferred that the calculi in this patient were composed of xanthine via this salvage mechanism.

Xanthinuria has an autosomal recessive mode of inheritance, and it develops when the causative gene has been in-

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**Table 1. Laboratory Data**

<table>
<thead>
<tr>
<th>Urinalysis</th>
<th>Biochemistry and Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (-)</td>
<td>T.P 7.9 g/dL</td>
</tr>
<tr>
<td>Glucose (-)</td>
<td>T.Bil 0.5 mg/dL</td>
</tr>
<tr>
<td>Ketone Body (-)</td>
<td>GOT 21 IU/L</td>
</tr>
<tr>
<td>Occult Blood (-)</td>
<td>GPT 15 IU/L</td>
</tr>
<tr>
<td>ALP</td>
<td>261 IU/L</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>WBC 4,430 /μL</td>
<td></td>
</tr>
<tr>
<td>RBC 407×10⁴ /μL</td>
<td></td>
</tr>
<tr>
<td>Hb 11.6 g/dl</td>
<td></td>
</tr>
<tr>
<td>Ht 13.7 %</td>
<td></td>
</tr>
<tr>
<td>Plt 38.9×10⁴ /μL</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>&lt;113 mL/min</td>
</tr>
<tr>
<td>Urinary uric acid</td>
<td>&lt;0.3 mg/dL</td>
</tr>
</tbody>
</table>

mL/min, and similar to the serum uric acid levels, uric acid levels in urine were below the measurement sensitivity (Table 1). Abdominal echography revealed multiple bilateral renal calculi of approximately 1 cm in diameter (Fig. 1).

Serum and urinary levels of hypoxanthine and xanthine were measured by high pressure liquid chromatography (HPLC) according to the method of Ichida et al. (6), with some modifications. Serum hypoxanthine was within the normal range at 0.10 mg/dL, but serum xanthine levels were elevated (0.19 mg/dL), and urinary xanthine and hypoxanthine levels were also high (Fig. 2). No invasive biopsy of the liver or intestinal mucosa to measure xanthine dehydrogenase activity was performed. Allopurinol loading test was conducted according to the method by Ichida et al. (6). For allopurinol loading test, 300 (mg) of allopurinol was given orally, and serum allopurinol and serum oxypurinol levels were measured both before and at 3 hours after loading. Serum oxypurinol levels after allopurinol loading were elevated at 0.83 mg/dL, indicating that allopurinol had been metabolized to oxypurinol, leading to a diagnosis of xanthinuria type 1 (Fig. 3).

DNA from the patient’s white blood cells was prepared for genetic diagnosis and the sequences of the coding region of xanthine dehydrogenase gene (GenBank D114566.2) were examined, and a homozygous deletion of cytosine 2,567 in the xanthine dehydrogenase gene was confirmed (Fig. 4). This mutation, c.2567delC, led to a frameshift at amino acid 856, creating a stop codon at position 928 (Fig. 5).

**Discussion**

In contrast to hyperuricemia, an underlying disorder in gout, hypouricemia is not recognized to cause disease. It has been reported, however, that renal hypouricemia is associated with ureteral calculi and exercise-induced acute renal failure; thus, hypouricemia has recently been investigated because of its relationship with pathological conditions. Numerous reports have defined hypouricemia as serum uric acid levels of 2 mg/dL or less, and the reported frequency of hypouricemia in Japan ranges from 0.14% to 0.4%. Hypouricemia is categorized into 2 types; underproduction-type hypouricemia, such as xanthinuria, and overexcretion-type hypouricemia, such as renal hypouricemia.

In xanthinuria, urolithiasis and myositis are sometimes observed because of increased urinary xanthine excretion or the xanthine deposition in tissues. This patient was also bilaterally affected by renal calculi. Cartier and Perigon reported lithiasis as a complication in 15 of 38 xanthinuria patients (39.5%). It has been reported that these calculi are uniquely xanthine calculi (8), and there have been no reports of hypoxanthine calculi. This finding has been explained as follows: in contrast to xanthine, a salvage mechanism acts on hypoxanthine to convert it to inosine-5’-monophosphate, and the increase in urinary hypoxanthine excretion is therefore not as conspicuous as the increase in urinary xanthine excretion. We inferred that the calculi in this patient were composed of xanthine via this salvage mechanism.
might have a higher frequency because their urinary xanthine excretion increases, although the urolithiasis frequency of heterozygous carriers has not been reported. Wilson and Tapia reported that in heterozygous carriers, the urinary uric acid excretion is normal, and urinary xanthine excretion is substantially higher than in healthy subjects (9). However, Auscher et al. reported that in the same carriers, urinary excretion of xanthine was not higher than in healthy subjects (3). On the other hand, in some regions relatives tend to marry consanguineous persons or persons living in the same area. On this occasion, not only the father but also the mother might have been homozygote and affected by xanthinuria. Unfortunately, no further investigation of a clear-cut mode of inheritance in this family was conducted, but the familial aspect cannot be ruled out. A study of urolithiasis frequency and gene analysis in this family are necessary to estimate the frequency in heterozygous carriers.

We cloned xanthine dehydrogenase cDNA and identified both genes responsible for type 1 and type 2 xanthinuria, respectively (6, 10, 11). The present patient in this study had

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
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<tbody>
<tr>
<td>Serum xanthine</td>
<td>0.19 mg/dL</td>
<td>(0.05-0.05)</td>
</tr>
<tr>
<td>Serum hypoxanthine</td>
<td>0.10 mg/dL</td>
<td>(0.31)</td>
</tr>
<tr>
<td>Urinary xanthine</td>
<td>9.93 mg/dL</td>
<td>(0.06-0.65)</td>
</tr>
<tr>
<td>Urinary hypoxanthine</td>
<td>2.89 mg/dL</td>
<td>(0.55-0.77)</td>
</tr>
</tbody>
</table>

**Figure 1.** Abdominal echography. Abdominal echography revealed multiple bilateral renal calculi of approximately 1 cm in diameter.

**Figure 2.** Purine metabolism-related laboratory data of the patient. Serum and urinary levels of hypoxanthine and xanthine were measured by high pressure liquid chromatography (HPLC) according to the method of Ichida et al. (6), with some modification. First, 200 μL of 0.3 M perchloric acid was added to deproteinize 50-μL samples of urine and serum (n=3). Samples were centrifuged, the supernatant was filtered through a membrane filter (0.45 μm), and 20 μL of the filtrate (2 μL for urine) was subjected to HPLC. The peak area for each purine body was calculated, and the amount of each purine was determined using a calibration curve prepared using a series of reference standards. Numbers in parenthesis represent the normal range.
the same mutation as a previously reported patient, and this is the fourth such family lineage that has been discovered (6).

For a definitive diagnosis of hereditary xanthinuria, a decrease in xanthine dehydrogenase activity in the tissues of the liver or intestinal mucosa must clearly be shown, but that investigation was not conducted in this patient. We did not check for abnormalities in the quantity of xanthine dehydrogenase, but on genetic diagnosis of DNA prepared from white blood cells, cytosine residue 2,567 in the xanthine dehydrogenase gene was deleted, causing a frame-shift mutation, and no enzymatic activity could be detected. This was inferred to be the cause of type 1 xanthinuria in this patient. Through this mutation, only the first two-thirds of the enzyme protein would have the normal amino acid sequence, and substituted amino acids and amino acid deficits would be involved in three-fifths of the molybdopterin cofactor binding domain (Fig. 5) (12-15). Thus, we judged this mutation to be the cause of the disease in this patient.

Because xanthine is poorly soluble in water, renal failure is sometimes caused by the deposition of xanthine crystals. There have been reports suggesting that allopurinol is effective in preventing renal failure, but we have concluded that the evidence is not sufficient, and we have not prescribed it. Moreover, because xanthine is poorly soluble in both acidic and alkaline urine, urinary alkalization in this type of calculi is ineffective in preventing a calculous recurrence. At present, the only treatment for this patient is to dilute the urine by drinking large amounts of fluids and eating a low purine diet. With this treatment, no significant increases in calculi have been observed in this patient for 2 years.

It has been reported that, in many diseases, xanthine dehydrogenase is converted to xanthine oxidase, which generates active oxygen and causes tissue damage (16). Xanthinuria is a fascinating disease, as this enzyme is absent, and it is believed that the benefits and drawbacks of xanthine dehydrogenase itself can be better understood by future investigations into the life prognosis of xanthinuria patients, as well as assessing the complication rates and severity of various diseases in such patients.

Hyperuricemia has been identified as a possible independent risk factor in cardiovascular disease. This suggests that uric acid itself has arteriosclerosis promoting activity and/or active oxygen generated during the process of uric acid production accelerates arteriosclerosis, as mentioned above. Conversely, it has been pointed out that uric acid is an active oxygen scavenger, acting to protect organs against oxidative stress (18). Accordingly, uric acid has contradictory characteristics in the body. Uric acid acts as a scavenger in vitro, but the extent of this action in vivo is unknown, and
no conclusions have been reached on the contradictory action of uric acid in vascular disease. Xanthinuria may provide insight into unraveling the effects of uric acid on the body. It has been reported that xanthinuria is accompanied by urinary tract calculi, but there have been no reports suggesting an association with cardiovascular disease, arteriosclerosis, malignant tumors, or degenerative diseases. No such diseases were observed in this patient’s family.

There is no established theory for the mechanisms by which humans acquire reabsorption-dominant uric acid kinetics in the kidneys, but excess or insufficient serum uric acid levels are detrimental, and serum uric acid levels must be precisely controlled (19).

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

Acknowledgement

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References

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