**Case Report**

**A Case of Exercise-Induced Acute Renal Failure in a Patient with Idiopathic Renal Hypouricemia Developed during Antihypertensive Therapy with Losartan and Trichlormethiazide**

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Exercise-induced acute renal failure (ARF) developed in a 45-year-old man during antihypertensive therapy with losartan and trichlormethiazide. The antihypertensive therapy was stopped and marked hypouricemia became apparent during improvement of his renal function. The daily urinary excretion of uric acid was normal and an increased fractional excretion of uric acid was observed. Renal biopsy revealed that the kidney was recovering from acute tubular necrosis with interstitial fibrosis. Based on the results of pyrazinamide and benz bromarone tests, we classified this case as one of presecretory reabsorption defect of uric acid.

Antihypertensive therapy with benidipine and candesartan was initiated, and the patient has not had any ARF episodes since. Because idiopathic renal hypouricemia can be associated with exercise-induced ARF and chronic renal dysfunction, careful antihypertensive therapy and follow-up evaluation of renal function might be necessary for hypertensive patients with idiopathic renal hypouricemia. (*Hypertens Res* 2003; 26: 509–513)

**Key Words:** exercise-induced acute renal failure, idiopathic renal hypouricemia, urate transport, hypertension, losartan

**Introduction**

Hyperuricemia is one of the common complications in essential hypertension. It has been recognized that hyperuricemia is an independent risk factor for cardiovascular morbidity and mortality in hypertensive patients (1). The control of hyperuricemia might be important for antihypertensive therapy (2). In this regard, losartan, an angiotensin II (AII) receptor antagonist, is considered to be useful for the treatment of hypertensive patients with hyperuricemia because of its uricosuric property (3–5).

Idiopathic renal hypouricemia is a rare disorder with an incidence of 0.15% in Japan (6). The patients exhibit an increase in uric acid excretion due to an isolated defect in renal tubular transport of uric acid (7). Enomoto et al. recently provided evidence that patients with idiopathic renal hypouricemia have defects in a gene (*SLC22A12*) encoding for the urate transporter (URAT1) (8). This disorder usually has no clinical manifestation other than formation of uric acid stones of the urinary tract (6). However, an important complication of this disorder is exercise-induced acute renal failure (ARF), which was first reported by Erley et al. in 1989 (9). More than 50 cases of exercise-induced ARF in patients with idiopathic renal hypouricemia have been reported, and most of these have been young adults or children from Japan (9–19). We here report a case of exercise-induced ARF in a middle-aged man with idiopathic renal hypouricemia. He had been treated with losartan and trichlormethiazide as an antihypertensive therapy.

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A 45-year-old man was referred to Yamagata City Hospital for the evaluation of ARF on August 27, 2001. Hypertension had been diagnosed 2 years prior and an antihypertensive therapy with losartan (25 mg/day) and trichlormethiazide (1 mg/day) had been initiated 4 months prior. On August 20, he complained of nausea, malaise and slight fever after a Karate training session. He had done such training twice a week since his high school days, but this was his first episode of ARF. On August 25, he visited a doctor and laboratory evaluation revealed a serum creatinine (S-Cr) level of 6.0 mg/dl and blood urea nitrogen (BUN) level of 38.1 mg/dl. On admission, his blood pressure was 156/113 mmHg and his pulse was 77 beats/min. The results of a physical examination were entirely unremarkable. Urine volume was 1,500 ml/day. Urinalysis revealed a specific gravity of 1.009 and pH 5.5. Urinary protein and occult blood were negative. Urinary sediment showed hyaline granular casts and no uric acid crystals. Neither glycosuria nor aminoaciduria was seen. Laboratory data were as follows (Table 1): hemoglobin 14.6 g/dl, hematocrit 41.7%, white blood cell count 6,540/µl with normal differentiation, platelet count 32.4 × 10^4/µl, S-Cr 3.4 mg/dl, BUN 26.9 mg/dl, uric acid 2.0 mg/dl, sodium 140 mEq/l, potassium 4.5 mEq/l, chloride 102 mEq/l, calcium 9.2 mg/l, phosphate 3.1 mg/l, asparate aminotransferase 28 IU/l, lactate dehydrogenase 251 IU/l, creatinine phosphokinase 124 IU/l, and myoglobin 128 ng/ml. Chest X-ray and electrocardiogram appeared normal. Plain CT showed bilateral enlargement of the kidneys without hydronephrosis.

The clinical course is illustrated in Fig. 1. The antihypertensive therapy with losartan and trichlormethiazide was stopped and a new therapy with benidipine was initiated. With a conservative therapy, S-Cr decreased to 1.0 mg/dl and nearly stabilized. Serum uric acid decreased to a subnormal concentration of 0.7–0.8 mg/dl.

A diagnosis of exercise-induced ARF associated with idiopathic renal hypouricemia was made.

After recovery from ARF, magnetic resonance angiography and arteriography demonstrated double renal artery in the left kidney. However, plasma renin activity was 1.7 ng/ml/h and plasma aldosterone concentration was 76 pg/ml. A renal vein sampling during treatment with captopril (37.5 mg/day) showed that the level of plasma renin activity was similar in the right and left renal vein (8.6 and 8.0 ng/ml/h). These results served to rule out the possibility of renovascular hypertension or secondary hypertension.

A renal biopsy was performed on November 11. Light-microscopic examinations revealed the kidney to be recovering from acute tubular necrosis. The histological findings included normal glomeruli, atherosclerotic arterioles and interstitial fibrosis with little cellular infiltration over a wide area. There was no urate deposition (Fig. 2). Pyrazinamide and benz bromarone tests were also performed. Pyrazinamide (3 g) de-
Benzbromarone (100 mg) increased FEUA from 50.3% to 59.3% (Table 2). Based on the results of these tests, we classified the present case as one of presecretory reabsorption defect of uric acid (7).

Discussion

Idiopathic renal hypouricemia is a rare disorder, although its precise incidence is unclear. Hisatome et al. reported that renal hypouricemia was found in 0.15% of individuals in an outpatient Japanese population (6). The incidence of renal hypouricemia in other patient populations is not known, although 50% of case reports of renal hypouricemia involve Japanese patients (14). Exercise-induced ARF in patients with idiopathic renal hypouricemia was first reported by Erley et al. in 1989 (9). Since that time, more than 50 cases of exercise-induced ARF with idiopathic renal hypouricemia have been reported, and most of these were cases from Japan (9–19). Ishikawa et al. reported 13 patients with exercise-induced ARF, and 3 (23%) of these were associated with idiopathic renal hypouricemia (10). In view of these findings, patients with idiopathic renal hypouricemia can be considered to have a 200-fold greater predisposition to exercise-induced ARF than those without renal hypouricemia. Although the long-term prognosis of these patients is not well known, chronic renal dysfunction, as revealed by such conditions as decreased GFR and decreased urine-concentrating ability, has been reported in patients with renal hypouricemia and concomitant exercise-induced ARF (17). Decreased GFR and interstitial fibrosis over a wide area of the kidney were revealed in the present case.

The mechanism of exercise-induced ARF in renal hypouricemia is unclear, although several hypotheses have been proposed. The first hypothesis is that exercise-induced ARF in renal hypouricemia is a result of acute uric acid nephropathy (12, 14). During exercise, the production of uric acid is increased and dehydration concentrates urine. The

Table 2. Pyrazinamide and Benzbromarone Tests

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Serum uric acid (mg/dl)</th>
<th>Serum creatinine (mg/dl)</th>
<th>U-UA/U-Cr (%)</th>
<th>FEUA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrazinamide test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 30–0</td>
<td>0.7</td>
<td>1.0</td>
<td>39.3</td>
<td>56.1</td>
</tr>
<tr>
<td>0–30</td>
<td>0.7</td>
<td>1.0</td>
<td>39.0</td>
<td>55.7</td>
</tr>
<tr>
<td>30–60</td>
<td>0.7</td>
<td>1.0</td>
<td>40.3</td>
<td>57.6</td>
</tr>
<tr>
<td>60–90</td>
<td>0.7</td>
<td>1.0</td>
<td>37.6</td>
<td>53.7</td>
</tr>
<tr>
<td>90–120</td>
<td>0.7</td>
<td>1.0</td>
<td>38.4</td>
<td>54.9</td>
</tr>
<tr>
<td>Benzbromarone test</td>
<td></td>
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</tr>
<tr>
<td>- 60–0</td>
<td>0.8</td>
<td>1.0</td>
<td>40.2</td>
<td>50.3</td>
</tr>
<tr>
<td>0–60</td>
<td>0.8</td>
<td>1.0</td>
<td>43.4</td>
<td>54.2</td>
</tr>
<tr>
<td>60–120</td>
<td>0.7</td>
<td>1.0</td>
<td>41.5</td>
<td>59.3</td>
</tr>
<tr>
<td>120–180</td>
<td>0.7</td>
<td>1.0</td>
<td>39.5</td>
<td>56.4</td>
</tr>
</tbody>
</table>

U-UA, urinary concentration of uric acid; U-Cr, urinary concentration of creatinine; FEUA, fractional excretion of uric acid.

Fig. 2. Light micrograph of the renal biopsy specimen obtained from the present patient. Staining was done with hematoxylin-eosin. Magnifications are ʷ 100 (upper) and ʷ 400 (lower). The histological findings included normal glomeruli, atherosclerotic arterioles, and interstitial fibrosis with little cellular infiltration over a wide area. There was no urate deposition.
concentration of uric acid in urine is markedly increased in a patient with renal hypouricemia, and this may result in acute uric acid nephropathy. In this regard, Erley et al. (9) reported that acute tubular necrosis with intratubular urate crystals was found in a renal biopsy specimen, whereas no other reports have identified this crystal in such specimens. The second hypothesis, proposed by Murakami et al. (13), emphasizes the role of uric acid as an antioxidant. The renal handling of uric acid seems to be a protective mechanism against the renal injury by oxygen free radicals. Both the uric acid pool and the total amount of uric acid mobilized into the proximal tubular cells are very small in patients with renal hypouricemia. Renal perfusion is diminished during exercise, and reperfusion is achieved after exercise, which mimics ischemia-reperfusion injury. In this state, an excessive production of oxygen free radicals may lead to extensive kidney damage. It has also been proposed that an intrarenal perfusion defect due to regional vasoconstriction participates in the mechanisms of this type of ARF. Ishikawa et al. (10) reported that renal CT revealed a delayed wedge-shaped patchy contrast enhancement during exercise-induced ARF in patients with idiopathic renal hypouricemia. Hasegawa et al. (15) reported that renal CT showed the delayed wedge-shaped patchy contrast enhancement after exercise in a patient with idiopathic renal hypouricemia, even though the level of exercise did not induce ARF. At present, the dehydration, excessive production of oxygen free radicals, and regional vasoconstriction are considered to participate in the mechanism of exercise-induced ARF in renal hypouricemia.

The appropriate antihypertensive therapy for patients with renal hypouricemia has not been discussed previously. Diuretics are not suitable antihypertensive drugs for these patients because they can induce dehydration, which is considered to participate in the mechanism of exercise-induced ARF. In the present case, the patient had been treated with trichlormethiazide and losartan. The combination therapy with diuretics and angiotensin converting enzyme (ACE) inhibitors or AII receptor antagonists has not only a stronger antihypertensive effect, but also a higher risk of dehydration as compared with monotherapy with either drug. Therefore, it is possible that the combination therapy with losartan and trichlormethiazide might have played a role in the development of exercise-induced ARF in the present case. Calcium antagonists are suitable drugs for patients with renal hypouricemia, because they appropriately maintain the renal circulation and prevent regional vasoconstriction after exercise, in addition to their safety-of-use in cases of severe renal dysfunction (3). ACE inhibitors and AII receptor antagonists may also be suitable drugs, provided they do not induce dehydration. These drugs reduce proteinuria in cases of diabetic and non-diabetic renal disease and have protective effects on the kidney (3). It has also been reported that AII activates URAT1 expressed in Xenopus oocytes (8) and urate transport in the brush-border membrane of the human kidney (22). In addition to these uricosuric drugs, losartan also inhibits URAT1 (8) and urate transport in the brush-border membrane of the human kidney (23). Benzbromarone and probenecid can increase FEUA in patients classified as having a presecretory reabsorption defect of uric acid (7), who constitute the majority of cases of exercise-induced ARF (12–19). Therefore, it is possible that losartan may increase FEUA even in patients with idiopathic renal hypouricemia. In this regard, other AII receptor antagonists are considered to be more safe for the patients with idiopathic renal hypouricemia, because these drugs have no uricosuric property (23, 24).

Although idiopathic renal hypouricemia is a rare disorder, it can be associated with exercise-induced ARF and chronic renal dysfunction. Careful antihypertensive therapy and follow-up evaluation of renal function might be necessary for hypertensive patients with idiopathic renal hypouricemia. Antihypertensive drug regimens for these patients will need to be further investigated.

References

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