Exercise-induced acute renal failure in a trainee cyclist without hypouricemia: Successful athletic career post-treatment

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Abstract
Acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise (ALPE) is exercise-induced acute renal failure that occurs without myoglobinuria. We describe a typical case involving an 18-year-old man. Generally, patients with ALPE are advised to avoid anaerobic exercise due to risk of recurrence, but our patient continued and went on to become a professional cyclist without relapse. About 51% of ALPE cases involve patients with renal hypouricemia. His serum uric acid levels were rather high, at 6.4 mg/dL. He is the first patient with ALPE to succeed as a professional athlete in an anaerobic sport.

KEYWORDS
acute kidney injury, acute renal failure, ALPE, exercise, renal hypouricemia

1 | INTRODUCTION
Acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise (ALPE) is known as exercise-induced acute renal injury, without myoglobinuria. We describe a typical case in an 18-year-old male trainee cyclist. Bicycle racing is one of the most vigorous anaerobic sports; therefore, APLE patients are advised to avoid anaerobic exercise. To the best of our knowledge, this is the first reported case of a patient with ALPE who successfully became a professional athlete.

2 | CASE REPORT
An 18-year-old man with nausea, general malaise, and back pain was admitted to our hospital. Past medical history was only relevant for facial bone fracture, and he was not taking any regular medications. Ten days before admission, he had developed a cough, and his temperature was 36.7°C. He visited a nearby clinic, where he was diagnosed with a common cold, and was prescribed 300 mg of cefcapene pivoxil hydrochloride, 75 mg of diprophylline, 75 mg of methoxyphenamine hydrochloride, 15 mg of noscapine, 6 mg of chlorpheniramine maleate, and 1 mg of dequalinium chloride per day for 3 days. Five days before admission, he again visited the clinic due to coughing and was prescribed 500 mg of levofloxacin, 75 mg of diprophylline, 75 mg of methoxyphenamine hydrochloride, 15 mg of noscapine, and 6 mg of chlorpheniramine maleate. Three days before admission, he performed some extremely demanding training (five 500-m sprints) and developed epigastric pain with vomiting that evening. He visited the clinic for a third time, where acute gastroenteritis was diagnosed. Fluid was intravenously administered for 2 days, after which he went back home.

On the day of admission, the clinic doctor found that his creatinine and blood urea nitrogen (BUN) levels were extremely high, and he was referred to our hospital.

His height was 178 cm, and his body weight was 80 kg. His blood pressure was 140/92 mmHg, pulse was 52 beats/min, and body temperature was 37.2°C. He did not have abnormal skin turgor, dry mucous membranes, or edema. Serum creatine kinase levels were normal, and serum creatinine and BUN levels were elevated at 7.51 mg/dL (reference range: 0.40–1.20 mg/dL) and 55.2 mg/dL (reference range: 8.0–20.0 mg/dL), respectively. His serum uric acid (UA) levels were elevated, at 18.3 mg/dL (reference range: 2.0–6.0 mg/dL). Serum myoglobin...
level was 75 ng/mL (reference range: <60 ng/mL). Urinalysis revealed 2+ protein by dipstick, whereas the urinary protein to creatinine ratio was 0.81. The urine occult blood reaction was negative, and urinary myoglobin was undetectable.

Kidney ultrasound showed no abnormalities in their size and shape. However, on the pulse Doppler ultrasound, the resistance indexes of the interlobar arteries were over 0.8 on both kidneys, suggesting low perfusion at the level of the interlobar arteries of kidneys (Figure 1A).

Based on the typical symptoms, such as bilateral back pain, and findings from the pulse Doppler ultrasound, we made the diagnosis of ALPE.

Along with oral intake, intravenous potassium-free fluid (Solita-T No.1®, AY PHARMACEUTICALS CO., LTD, Tokyo, Japan) was administered by 500 mL/day over the next 4 days. He had an adequate urinary output exceeding 1000 mL/day, and his nausea and loin pain remitted.

When serum creatinine level decreased to 1.5 mg/dL, 40 mL of iodine contrast dye was administered, and 24 hours later, we performed noncontrast CT. This delayed CT scan showed patchy, wedge-shaped, high-density areas on both kidneys, due to a delay in excretion of contrast (Figure 1B).

The patient’s symptoms fully resolved and he was discharged 12 days after admission. The time course of his biochemical measurements is shown in Figure 2.

3 | DISCUSSION

On admission, the fractional excretion of sodium was 0.46% and the fractional excretion of urea nitrogen was 30.6%, both lower than the normal range. This was suggestive of dehydration, possibly caused by reduced appetite because of nausea. On the other hand, his inferior vena cava had a respiratory change in diameter of 18-5 mm on abdominal echogram and was not collapsed. His urinary-specific gravity was 1.011, which was within the normal range. In addition, he gained 1.3 kg due to intravenously administered fluid at the clinic. The cardiothoracic ratio on chest X-ray was 44%, which was not small compared with that 1 year later (42%). For the above reasons, dehydration was unlikely to be the main cause of acute kidney injury (AKI).

Exercise-induced AKI has two types: AKI with myoglobinuria and without myoglobinuria. ALPE is a type of ARF developing after
anaerobic exercise, without myoglobinuria, which typically presents in young males, and was first reported by Ishikawa et al.\(^2\) in 1982.\(^3\) Ishikawa and coauthors first used the term “patchy renal vasoconstriction (PRV)” to describe a case of ARF with typical findings on a CT scan.\(^4\) Various medical terms, such as exercise-induced ARF with PRV and exercise-induced ARF without rhabdomyolysis, have been used.

The diagnostic criteria for ALPE are shown below:\(^5\):

1. Episodes of vigorous exercise (especially anaerobic exercise such as sprinting).
2. Severe loin pain often developing 1-48 hours after exercise.
3. Serum creatine kinase levels within normal range, or only slightly elevated (no more than 9 times higher than the upper limit of normal).

The third is an essential diagnostic criterion, but a few cases do not meet the first or the second.

Also suggestive of ALPE are serum myoglobin levels within normal range, or no more than 6 times higher than the upper limit, and the observation of a wedge-shaped high-density area on delayed CT.\(^1\)

Our case matched all the above criteria.

In accordance with previous cases, he should have been advised to subsequently avoid anaerobic exercise. Unfortunately, he was about to enter the Japan Keirin School, which is the only school in Japan that trains professional cyclists. Because of the risk of recurrence and a lack of precedent, he was not admitted to the school.

Although the precise mechanism of ALPE is unknown, 51% of ALPE cases have been reported to involve patients with renal hypouricemia,\(^3\) in whom a higher risk of recurrence exists compared with those without hypouricemia.\(^1\) Ames et al.\(^5\) have suggested that UA levels in plasma functions as a powerful antioxidant and free radical scavenger. Strenuous exercise triggers a sequential increase in free radical levels.\(^6\) Therefore, compared with those without renal hypouricemia, patients with renal hypouricemia are thought to be at a much higher risk for kidney damage through free radicals after exercise due to poor scavenging activity.

On the other hand, those without hypouricemia also have ALPE. UA levels in our patient were not low after AKI. In fact, they were rather high at 6.4 mg/dL and 6.9 mg/dL 1 year later.

Analgesics, such as acetaminophen and aspirin, and some diuretics have been associated with PRV in other studies.\(^6,7\) Severe alcohol drinking, analgesic intake, and upper respiratory infections were found in patients with no history of exercise before experiencing pain.\(^8\) Our patient had never taken nonsteroidal anti-inflammatory drugs, supplements, or illegal drugs. Ten days before admission, he had taken 300 mg of cefcapene pivoxil hydrochloride, 75 mg of diprophylline, 75 mg of methoxypenamine hydrochloride, 15 mg of noscapine, and 6 mg of chlorpheniramine maleate. He had taken these drugs several times, both before and after the AKI. Five days before admission (2 days before AKI), he had started taking levofloxacin. It was the first time that he had taken levofloxacin.

Levofloxacin-induced acute renal failure due to hypersensitivity reaction or direct toxic effects, such as allergic interstitial nephritis and crystal nephropathy, has been reported.\(^9\) However, our patient suffered back pain, while pulse Doppler ultrasound showed low perfusions at the level of the interlobar arteries in both kidneys. He did not show signs of rash with eosinophilia. Urinalysis showed no sign of hematuria, proteinuria, or abnormal sedimentations, while acute tubular necrosis was unlikely. We presumed another mechanism for AKI.

Levofloxacin has been known to induce arrhythmia.\(^10\) Levofloxacin induces transient ST elevation on ECG without coronary occlusion.\(^11\) Although the relation between levofloxacin and ALPE has not been reported, levofloxacin may induce vasoconstriction of the renal arteries through an increase in free radicals after strenuous exercise. This is the only new factor that could induce PRV.

After resolution, 20% of these cases experienced recurrence, and this rate increased to thirty percent in patients with renal hypouricemia. Only one of the 221 cases reported developed chronic renal failure.\(^12\) We explained these data to our patient and his family.

Our patient strongly wanted to become a professional cyclist, and he requested the school to allow him admission, on the condition that he would leave if he relapsed with another AKI. He was advised to avoid physical exercise when sick, dehydrated, or taking new medications. One year after the episode of ALPE, he made his debut as a professional cyclist and continued his career since then without relapse for more than 3 years.

To the best of our knowledge, this is the first reported case of a patient with ALPE becoming a professional athlete in an anaerobic sport. His UA levels were not low; in fact, they were rather high at 6.4 mg/dL prior to discharge and 6.9 mg/dL (serum creatinine: 1.04 mg/dL) 1 year later.

For such patients in future, full explanation about the risk of relapse and avoidance strategy will be necessary, and cautious follow-up will also be important.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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