INTERNAL MEDICINE

□ CASE REPORT □

Acute Renal Failure with Severe Loin Pain and Patchy Renal Vasoconstriction in a Patient without Hypouricemia, Provoked by Epileptic Seizure

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Abstract

A 26-year-old Japanese man without hypouricemia and with 3 previous episodes of seizures concurrent with acute kidney injury (AKI) was admitted due to an epileptic seizure, lower back pain and AKI. His creatinine kinase levels were slightly elevated. Patchy renal ischemia on contrast-enhanced computed tomography and persistent residual contrast medium was observed, consistent with acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise (ALPE). Diffusion-weighted imaging (DWI) demonstrated signal changes in the corresponding area. ALPE should be considered a cause of AKI following seizures. We recommend DWI as an alternative diagnostic modality.

Key words: acute kidney injury (AKI), seizure, persistent nephrogram, patchy renal ischemia, acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise (ALPE), diffusion-weighted imaging (DWI)

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Introduction

Acute renal failure with loin pain and patchy renal ischemia after anaerobic exercise (ALPE) is a type of acute kidney injury (AKI) characterized by patchy renal hypoperfusion on contrast-enhanced computed tomography (CT) and by residual contrast medium in corresponding lesions on delayed-enhancement CT (1). A diagnosis is made based on clinical findings, including imaging studies. Clinical manifestations, including severe low back pain and nausea, are attributed to the transient vasoconstriction of arteries in the kidney, resulting in acute tubular necrosis. Most cases of ALPE develop after strenuous exercise such as short-distance sprinting, and recurrent AKI occurs in one-quarter of patients (2). While renal hypouricemia is a known predisposing factor for recurrent episodes of non-myoglobinuric AKI, significant proportions of patients suffer from this condition without renal hypouricemia (1, 3). Although the pathogenesis of ALPE remains unclear, free radicals or myogenic toxins are assumed to cause renal damage (4).

We herein report the case of a patient with recurrent attacks of ALPE without renal hypouricemia presenting as kidney dysfunction after each epileptic seizure. Two of 4 episodes presented with elevated creatinine kinase levels above 5,000 IU/L, which is generally considered rhabdomyolysis. Multiple wedge-shaped lesions in the kidneys were identified on CT and magnetic resonance imaging (MRI) during the recovery phase of AKI, leading to the diagnosis. The clinical course of recurrent AKI following convulsion demonstrated an altered boundary between ALPE and rhabdomyolysis.

Case Report

A 26-year-old Japanese man with three previous episodes of epileptic seizure with concomitant acute kidney injury presented to the emergency room after a generalized seizure. Five months before presentation, epilepsy was diagnosed from electroencephalography during the third seizure attack,

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Table. Laboratory Data on Admission.

Urianalysis		Blood chemistry		Serological study	
SG	1.015	TP	7.8 g/dL	CRP	0.36 mg/dL
pH	5.0	Alb	4.7 g/dL	IgG	1,204 mg/dL
Protein	2+	Na	141 mEq/L	IgA	144 mg/dL
Blood	1+	K	3.6 mEq/L	IgM	77 mg/dL
Glucose	-	Cl	104 mEq/L	C3	96 mg/dL
β_2-macroglobulin	10,600 μg/L	BUN	23 mg/dL	C4	22.6 mg/dL
Myoglobin	10,000 ng/mL	Cr	1.59 mg/dL	CH50	55.2 U/mL
RBC	1-4/hpf	CK	686 U/L	ANA	negative
		AST	26 U/L	Anti-DNA-Ab (RIA)	negative
Blood cell count		ALT	13 U/L	Anti-SS-A-Ab	negative
WBC	28,190/μL	LDH	266 U/L	RF	negative
(Seg 3%, Band 88%, Lym 3%, Mo 4%, Eos 1%)		γGTP	14 U/L	PR3-ANCA	negative
		GLU	107 mg/dL	MPO-ANCA	negative
RBC	541×10^4/μL				
Hb	15.9 g/dL			Venous Blood Gas	
MCV	83.0 fL			pH	7.346
MCH	29.4 pg			PCO_2	38.6 mmHg
MCHC	35.4%			HCO_3^-	20.6 mmol/L
Plt	27.4×10^4/μL			Lac	9 mg/dL

with no marked findings in the brain on CT or MRI. He had been treated with levetiracetam since that time. His baseline kidney function had been recorded 2 years prior, with a serum creatinine level of 0.82 mg/dL and an estimated glomerular filtration rate (eGFR) of 96 mL/min/1.73 m^2 (5). He had no family history of epilepsy, kidney disease, or hypouricemia.

Early one morning, he noted abrupt involuntary movements of the extremities just before losing consciousness, and he was brought to the emergency room. After a rapid recovery from a brief period of impaired consciousness, he developed abdominal pain, severe nausea and vomiting, severe low back pain, and myalgia in the lower extremities. His vital signs included a blood pressure of 126/76 mmHg, heart rate of 85 beats/min, and a low-grade fever. A physical examination revealed bilateral costovertebral angle (CVA) tenderness. Laboratory findings on admission showed a decreased kidney function: serum creatinine, 1.59 mg/dL; blood urea nitrogen (BUN), 23 mg/dL; and creatine kinase (CK) slightly elevated at 686 U/L (Table). A urinalysis showed a 2+ result for protein and a 1+ result for occult blood. Blood tests and urine culture yielded negative results. Ultrasonography showed diffuse enlargement of both kidneys without stones or hydronephrosis.

On the third day, the concentrations of serum creatinine, uric acid, and CK rose to 3.91 mg/dL, 11.0 mg/dL, and 24,640 U/L, respectively (Fig. 1). Wedge-shaped areas of decreased enhancement in both kidneys were noted on contrast-enhanced CT with 40 mL of iopamidol (300 mg iodine/mL) at the time serum creatinine was 1.88 mg/dL (eGFR, 38.2 mL/min/1.73 m^2) during the recovery phase of AKI (Fig. 2a). Twenty-four hours later, unenhanced CT revealed residual contrast medium in the corresponding areas (Fig. 2b). Each lesion consisted of a patchy aggregation of striated-enhanced areas, appearing as linear bands parallel to the axis of the collecting system. Renal MRI showed multifocal wedge-shaped areas of signal hyperintensity on diffusion-weighted imaging (DWI) (Fig. 2c), with the same areas appearing slightly hyperintense on T2-weighted imaging. No significant findings were detected on T1-weighted imaging, and the apparent diffusion coefficient (ADC) was not increased in the corresponding regions on DWI. A renal biopsy revealed acute tubular necrosis with normal glomeruli showing no deposition of urate crystals (Fig. 3). We diagnosed ALPE provoked by epileptic seizures, associated with severe muscle injury.

Non-oliguric AKI recovered with fluid resuscitation, and the renal function had returned to baseline (creatinine, 0.91 mg/dL; eGFR, 84.4 mL/min) by 2 weeks later. Five weeks after this AKI episode, the serum uric acid concentration was 5.5 mg/dL, with fractional excretion of urate at 4.2%, implying an absence of renal hypouricemia (6). Even though the patient had taken the antiepileptic agent as directed, epileptic seizures accompanied by kidney dysfunction recurred during the antiepileptic therapy as described, so the dose of levetiracetam was increased from 1,000 to 1,500 mg/day. However, dose reduction was needed due to mood instability and suicidal behavior; the patient was referred to the epileptic center to seek better seizure control. No evidence of progressive kidney dysfunction was seen during levetiracetam treatment. As such, drug-related kidney dysfunction seemed unlikely. Two months later, contrast-enhanced CT showed no hypoattenuated areas in either kidney and no persistent enhancement 1 hour after contrast administration.

Discussion

In the present case, the clinical symptoms and characteris-

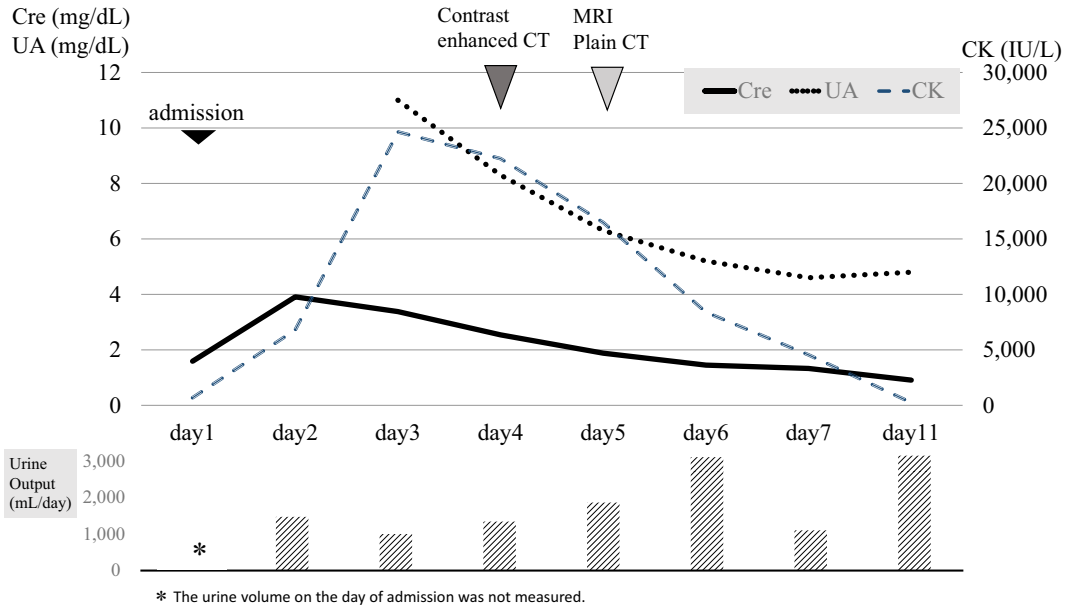

Figure 1. Clinical course. The kidney function deteriorated rapidly, and the creatinine kinase concentration was markedly elevated after admission. Cre: creatinine, UA: uric acid, CK: creatine kinase

tic radiographic findings on CT were diagnostic of a form of exercise-induced AKI, termed "acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise". DWI also demonstrated wedge-shaped lesions in the kidney. Of note was the finding of severe muscle injury concurrent with ALPE in two of the four episodes of AKI, and that grand mal seizures repeatedly induced AKI.

ALPE should be differentiated from acute urate nephropathy and rhabdomyolysis, both of which are associated with generalized seizures. There are several case reports on AKI precipitated by grand mal seizure, in which acute urate nephropathy and rhabdomyolysis were the implicated etiologies. Warren et al. reported that seven patients were admitted for seizures complicated by AKI, and that renal dysfunction in those patients was attributed to acute urate nephropathy because severe hyperuricemia had developed before the increases in blood urea (7). Although patients with convulsions have been documented to frequently develop hyperuricemia, since convulsions cause muscle injury leading to tissue hypercatabolism and urate production (8), only a small proportion of patients with severe hyperuricemia as a complication of convulsions develop AKI. In such cases, acute urate nephropathy is diagnosed without pathological evidence on a renal biopsy indicating the clinical diagnosis. Rhabdomyolysis is also known as a frequent complication of seizures (9). Chang reported the cases of five patients with severe muscle injury caused by seizure (10), of whom four with seizure-related muscle injury developed AKI, implying that convulsion-induced rhabdomyolysis resulted in kidney dysfunction. Nielsen et al. also reported the development of kidney dysfunction in 9 of 13 patients admitted for generalized seizures (11). Those reports suggested that renal impairment in patients might have been related to rhabdomyolysis, but only slight elevations in concentrations of muscle enzymes in plasma were documented, suggesting the involvement of other pathogenetic mechanisms. Clinicians should consider ALPE as a differential diagnosis in the presence of AKI following seizure, even when complicated by muscle injury and hyperuricemia, although no previous reports appear to have described cases of ALPE induced by seizure.

As shown in the present case, ALPE can occur concomitantly with moderate to severe muscle injury. It seems reasonable to consider that all four AKI episodes in our patient were attributable to ALPE with various levels of muscle injury, rather than two episodes of ALPE with mild muscle injury and two other episodes of AKI induced by severe muscle injury. ALPE was originally defined as AKI without severe muscle injury in order to clearly differentiate exertional rhabdomyolysis from this form of kidney dysfunction (1). Ishikawa et al. proposed that unknown nephrotoxins from injured muscle tissue other than myoglobin may cause renal vasoconstriction, resulting in acute tubular necrosis and the deterioration of the renal function (1). However, a recent study on ALPE advocated a pathophysiological basis of free radicals produced by exercise leading to renal vasoconstriction and ischemic damage (4), indicating that the pathophysiology of ALPE is independent of muscle injury. Since the epileptic seizures in the present patient resolved spontaneously before he reached our emergency room, hypoxemia was not documented. However, in the first episode of seizure-induced AKI when he was transported to our emergency room just after the epileptic seizure, a blood gas analysis showed severe lactic acidosis, suggesting the presence of intra-ictal hypoxia. Convulsions were presumed to act as anaerobic exercise, which might produce some vasoactive mediators in the patient. Furthermore, another case exhibited AKI complicated with loin pain, nausea, patchy

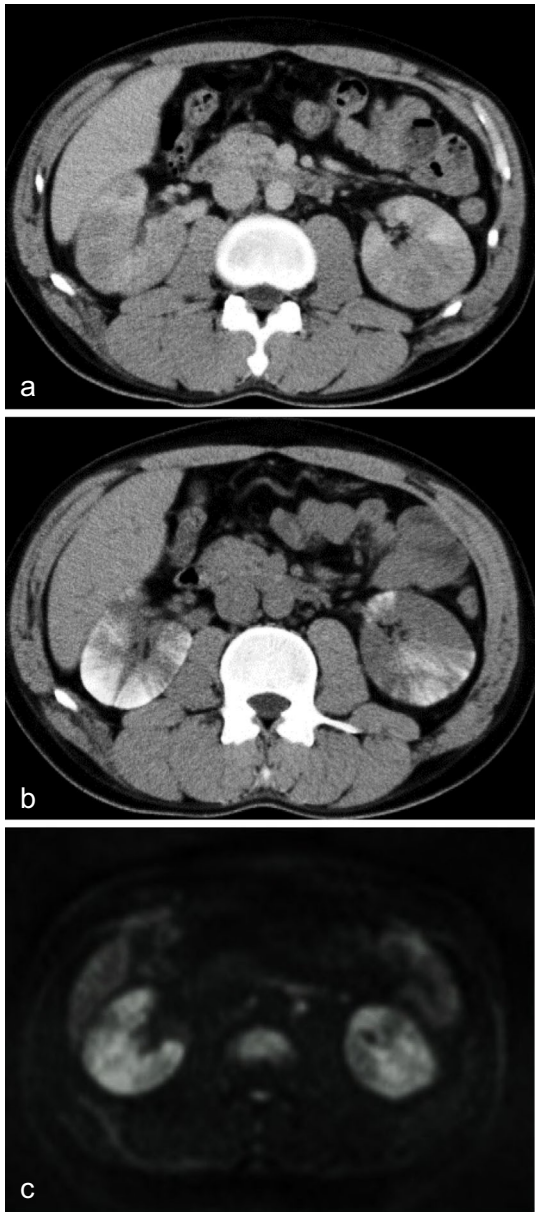

Figure 2. **(a) Contrast-enhanced computed tomography with 40 mL of iodine contrast agent performed during an episode of acute kidney injury. A nephrographic-phase image at 120 s after contrast administration shows patchy areas of hypoattenuation in both kidneys. (b) Computed tomography 24 h after contrast administration demonstrates persistent enhancement in the patchy areas, which correspond to the hypoattenuated areas on nephrographic-phase CT. The wedge-shaped areas comprise multiple linear bands of contrast enhancement. (c) Diffusion-weighted imaging shows signal hyperintensity in the hypoattenuated areas on contrast-enhanced computed tomography.**

renal ischemia, and severely elevated CK levels (12); this may have been a case of ALPE developing concurrently with rhabdomyolysis.

The appearance of patchy renal ischemic lesions on imaging is relatively specific to ALPE, contrasting with the kidney imaging results of rhabdomyolysis, which generally show diffuse hypoattenuation on contrast-enhanced CT (1).

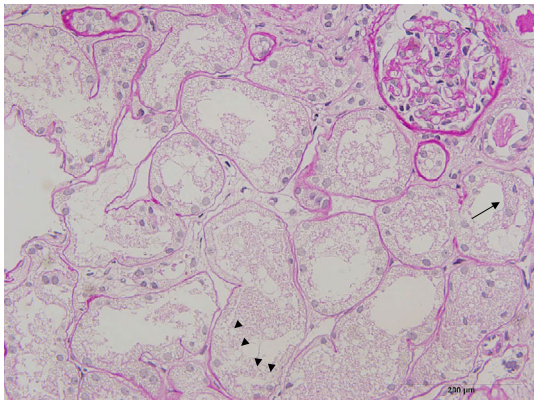

Figure 3. **Pathological findings of the renal biopsy specimen. Cellular injury of the tubular epithelial cells (arrows) and the loss of brush borders (arrowheads) are evident. In contrast, at least one glomerulus appears normal. Periodic acid-Schiff staining (400×), Scale bar 200 μm.**

Global or cortical enhancement on CT is the typical manifestation of contrast-induced nephropathy, whereas striated enhancement of the kidneys on CT is uncommon (13). A small number of case reports have described striated kidney enhancement in conditions such as pyelonephritis (14) and renal ischemia caused by life-threatening systemic hypoperfusion (15). In an infected kidney, the localized persistence of contrast in the lesion is attributed to an underlying pathophysiology of tubular obstruction caused by inflammatory debris within the lumen, interstitial edema, and vasospasm (14). Such situations reduce the tubular flow of contrast agent and cause accumulation, induced by the reabsorption of water and electrolytes, resulting in poor enhancement on nephrographic-phase imaging on CT and residual contrast medium after a few hours to days (14). In most cases of ALPE, this characteristic wedge-shaped attenuation in contrast-enhanced CT and striated persistence of contrast in patchy areas are detected in both kidneys (1, 3). A previous study showed that the greater the deterioration in the renal function, the broader the area of contrast persistence on kidney imaging (1). We speculate a putative pathophysiology of altered hemodynamics over time in the affected kidney. Most peripheral arteries in the kidney are constricted at the time of onset, so the gradual resolution of vasospasm releases trapped contrast medium in a patchy manner as the renal function improves.

Contract-enhanced CT can show the characteristic findings of ALPE in the recovery phase of renal dysfunction, but concerns remain about the risk of contrast-induced kidney dysfunction. We therefore recommend performing imaging with a minimal dose of contrast medium after confirming that the renal function has recovered sufficiently from severe kidney dysfunction. To prevent additional kidney dysfunction, other imaging methods for evaluating the renal circulation in ALPE patients have been explored. Based on case studies, ^{99m}Tc-methylene diphosphonate bone scintigraphy (16), color Doppler sonography with ultrasound contrast

agent (17), and MRI (1, 3) have been confirmed as imaging modalities allowing the detection of wedge-shaped renal ischemic lesions.

Given the time required to perform these studies and concerns about the risk of radiation exposure, MRI may represent the most promising and practical modality. This alternative imaging study can also avoid the administration of potentially nephrotoxic contrast medium. Little is currently known about MRI findings during AKI induced by crystal or pigment, but some studies evaluating MRI in renal disease, especially DWI, have demonstrated signal alteration in patients with acute or chronic kidney disease, and the authors of those studies did not mention any patchy signal changes in the kidney (18-22). Two other case reports of patients with rhabdomyolysis showed diffuse signal changes on MRI of the kidneys (23, 24). Previous studies of ALPE have noted the high sensitivity of T1-weighted imaging; for example, one case series noted localized signal hyperintensity in four of six patients (1), and another found signal hyperintensity in the kidneys of all three cases evaluated (3). A report of two pediatric ALPE patients showed clear wedge-shaped hyperintensity on DWI and slight signal hyperintensity on T2-weighted MRI (25), as seen in our case.

In summary, this is the first report of ALPE provoked by convulsions, and the ALPE was associated with rhabdomyolysis. Contrast-enhanced CT demonstrated multiple wedge-shaped hypoperfused areas in both kidneys and persistent enhancement in the corresponding lesions with delayed enhancement CT. In addition, DWI also clearly showed multiple patchy lesions in the kidneys. We suggest that ALPE be considered as a cause of AKI following seizure, and recommend DWI as a potential alternative diagnostic imaging modality.

Author's disclosure of potential Conflicts of Interest (COI).
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