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【 CASE REPORT 】

A Patient with Acute Kidney Injury Associated with Massive Proteinuria and Acute Hyperuricemia after Epileptic Seizures

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Abstract:
A 25-year-old man presented with acute kidney injury (AKI), massive proteinuria and hyperuricemia after epileptic seizures. His AKI improved along with the disappearance of proteinuria after corticosteroid treatment. A kidney biopsy revealed no significant glomerular abnormalities, but varying degrees of tubular injury, such as proximal tubular simplification, mild distal tubular proliferation, and Tamm-Horsfall protein-like material accumulation with extravasation into the interstitium, were noted. A further analysis revealed the intratubular depositions of uric acid crystals, indicating the involvement of acute uric acid nephropathy associated with seizures. Our patient's condition is rare, and the clinicopathological aspects of the diagnostic challenges are discussed.

Key words: acute kidney injury, minimal change nephrotic syndrome, seizure, uric acid nephropathy

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Introduction

Acute kidney injury (AKI) is a well-known complication of minimal change nephrotic syndrome (MCNS), and a reduction in proteinuria is indispensable for recovery from AKI (1). In addition to prerenal or intrarenal hemodynamic alterations, massive proteinuria has been proposed to contribute to severe AKI due to tubular cell injury and apoptosis in patients with MCNS (2-4).

Seizures carry a potential risk of causing AKI due to rhabdomyolysis (5) or acute hyperuricemia (6, 7). The use of levetiracetam for seizure management can reportedly rarely cause rhabdomyolysis (8) or acute tubulointerstitial nephritis (9), leading to AKI.

We herein report a patient with severe AKI associated with massive proteinuria after epileptic seizures. He was tentatively diagnosed with MCNS-related AKI. However, he also had potential seizure-associated causes of AKI, including moderate rhabdomyolysis and severe acute hyperuricemia. Massive proteinuria following acute uric acid (UA) nephropathy due to seizure was reported in one case report (10). However, our patient's condition is extremely rare, and the clinicopathological aspects of the diagnostic challenges that were encountered in the present patient are discussed. To our knowledge, this is the first report of a kidney biopsy being performed in a patient with acute UA nephropathy due to seizures.

Case Report

A 25-year-old man with a 2-year history of epilepsy that was maintained with lamotrigine was transferred to an outside hospital because of generalized tonic-clonic seizures. A physical examination revealed a Glasgow Coma Scale score of 14/15 (E4V4M6), temperature of 37.8°C, blood pressure

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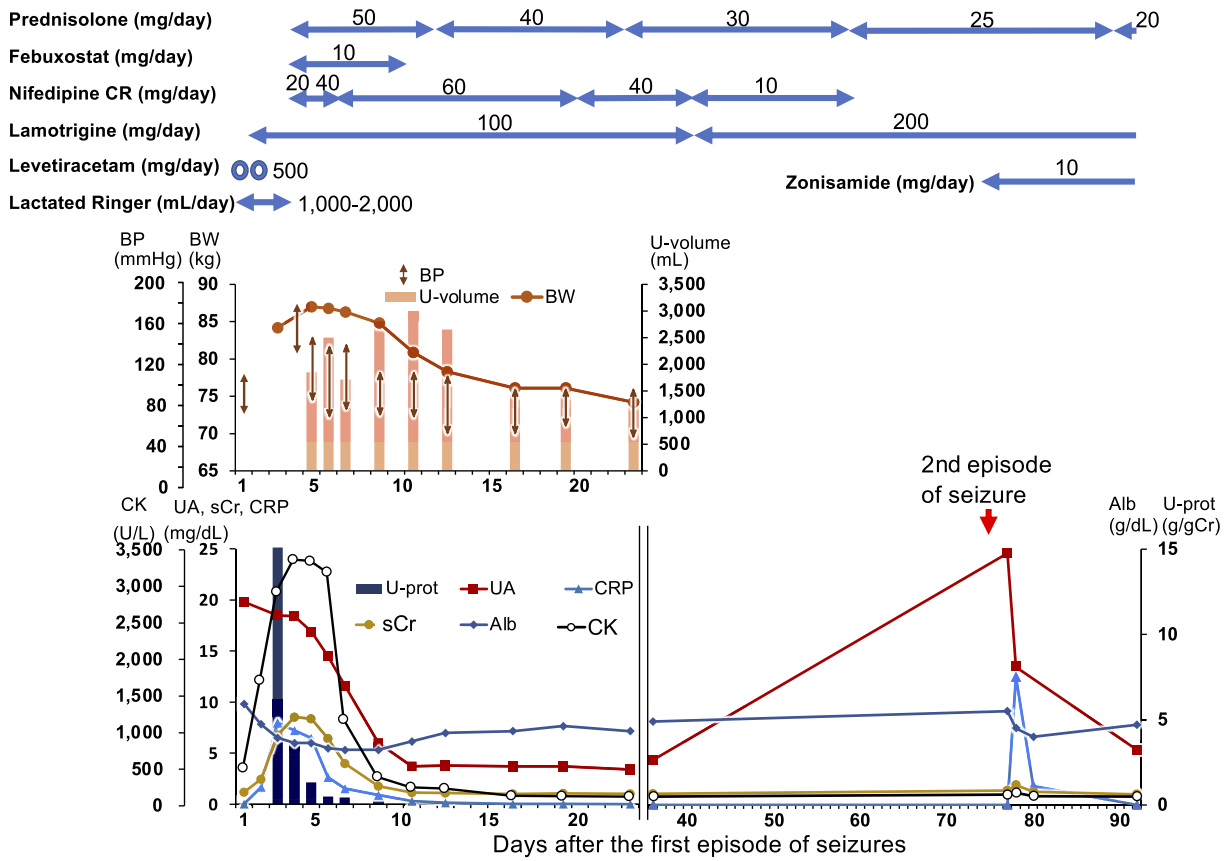

Figure 1. **The clinical course after the first episode of seizures. BP: blood pressure, BW: body weight, U-volume: urine 24-h volume, U-prot: urine protein/creatinine ratio, UA: uric acid, sCr: serum creatinine, CRP: C-reactive protein, CK: creatine kinase, Alb: serum albumin**

of 106/77 mmHg, heart rate of 131 beats/min, and oxygen saturation of 97%. He experienced another convulsive seizure soon after his arrival. His seizure was stopped by intravenous diazepam. Intravenous infusion of levetiracetam at 500 mg was administered on the 1st and 2nd days of admission.

On admission, he showed a serum creatinine (sCr) level of 1.18 mg/dL, UA level of 19.8 mg/dL and creatine kinase (CK) level of 422 U/L. The sCr progressively increased, CK was moderately elevated, and UA was continuously high (Fig. 1). On the 3rd day, the urine protein-creatinine ratio was 15.4 g/gCr, and there were >100 urinary red blood cells/high-power field (HPF) with isomorphic shape, 1 to 4 urinary white blood cells/HPF, and 5 to 9 urinary epithelial cells/HPF. He received acetate Ringer's solution of 2,000 mL on the 1st day, 1,500 mL on the 2nd day, and 1,000 mL on the 3rd day. The patient was aware of his reduced urine output. His body weight was 84.2 kg on the 3rd day of admission. He was then transferred to our hospital for the evaluation of the deterioration of the renal function and massive proteinuria.

On admission to our hospital, a physical examination revealed the following: the patient was alert and had a height of 183.5 cm, a body weight of 87.0 kg, weight gain of 10 kg, temperature of 37.6°C, blood pressure of 168/123 mmHg, heart rate of 83 beats/min, and an oxygen saturation of 97%. His physical examination was unremarkable, except for mild leg edema. A urine examination showed nephrotic range proteinuria, isomorphic microscopic hematuria without pathological sediments or elevated tubular injury markers (Table 1). Blood chemistry showed high sCr and UA levels, moderately increased serum CK levels, and C-reactive protein (CRP) positivity (Fig. 1 and Table 1). No immunological abnormalities were found (Table 1). The fractional excretion of Na was 2.62%, indicating intrinsic AKI. Chest X-ray showed a 52% cardiothoracic ratio. Computed tomography showed mild ground-glass opacities in both lung fields due to interstitial pulmonary edema, ascites as well as slightly enlarged kidneys without hydronephrosis.

At this time, the AKI was considered to have been caused by MCNS. Therefore, oral prednisolone at 50 mg/day was administered from the day of admission based on a clinical decision. Nifedipine CR at 20 mg/day, febuxostat at 10 mg/day, and sodium bicarbonate were also administered along with lamotrigine. Within 10 days after corticosteroid therapy, the proteinuria disappeared, and the sCr level returned to the basal level compared with his sCr level of 1.12 mg/dL 13 months ago (Fig. 1). Serum UA also normalized within 10 days (Fig. 1).

A kidney biopsy 2 days after corticosteroid treatment revealed minor glomerular abnormalities of 24 glomeruli. Proximal tubular simplification (tubular dilatation and flat-

Table 1. Laboratory Data on Admission.

Urine		
pH	6.0	
Protein	3+	
Occult blood	2+	
Red blood cell	30-49	/high power field
White blood cell	1-4	/high power field
Red-blood-cell shape	Isomorphic	
Uric acid	35.5	mg/dL
Phosphorus	2.9	mg/dL
Calcium	8.0	mg/dL
Creatinine	89.3	md/L
Protein	3.68	g/gCr
NAG	6.6	U/L (0.7 to 11.2)
α1-microglobulin	8.76	mg/L (1.0 to 5.0)
β2-microglobulin	3,434	µg/L (<150)
Complete blood count		
WBC	16,500	/µL
Hb	14.8	g/dL
MCV	80.0	fL
MCHC	35.8	pg
Platelet	16.5×10^4	/µL
Fibrinogen	546	mg/dL
D-dimer	1.2	µg/mL
Blood chemistry		
Total protein	6.0	g/dL
Albumin	3.6	g/dL
Urea nitrogen	56.1	mg/dL
Creatinine	8.53	mg/dL
Uric acid	18.4	mg/dL
Cystatin C	1.91	mg/L
Aspartate aminotransferase	30	IU/L
Alanine aminotransferase	24	IU/L
Total bilirubin	1.75	mg/dL
Alkaline phosphatase	53	IU/L
γ-glutamyltransferase	30	IU/L
Lactate dehydrogenase	365	IU/L
Creatine kinase	3,327	U/L
Na	135	mEq/L
K	4.0	mEq/L
Cl	100	mEq/L
P	5.9	mg/dL
Ca	8.0	mg/dL
HCO_3^-	17.1	mEq/L
Triglyceride	94	mg/dL
Total cholesterol	164	mg/dL
LDL cholesterol	97	mg/dL
Free T3	0.9	pg/mL
Free T4	1.31	ng/dL
TSH	0.226	µIU/mL
estimated GFR (creatinine)	7.4	mL/min/1.73 m^2
estimated GFR (cystatin C)	40.6	mL/min/1.73 m^2
Immunologic test		
IgG	743	mg/dL
IgA	47	mg/dL
IgM	29	mg/dL
CH50	59	U/mL
C3	97	mg/dL
C4	32	mg/dL
C-reactive protein	7.22	mg/dL
Antinuclear antibody	×40>	
Anti-DNA antibody	0.5	IU/mL (<9.0)
MPO-ANCA	1.0>	U/mL (<3.4)
PR3-ANCA	1.0>	U/mL (<3.4)
Cryoglobulin	Negative	
HBs antigen	Negative	
HCV antibody	Negative	

NAG: N-acetyl-β-D-glucosaminidase, TSH: thyroid-stimulating hormone, GFR: glomerular filtration rate, MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase 3-anti-neutrophil cytoplasmic antibody, HBs: hepatitis B surface antigen, HCV: hepatitis C virus

Values in parentheses show the normal range.

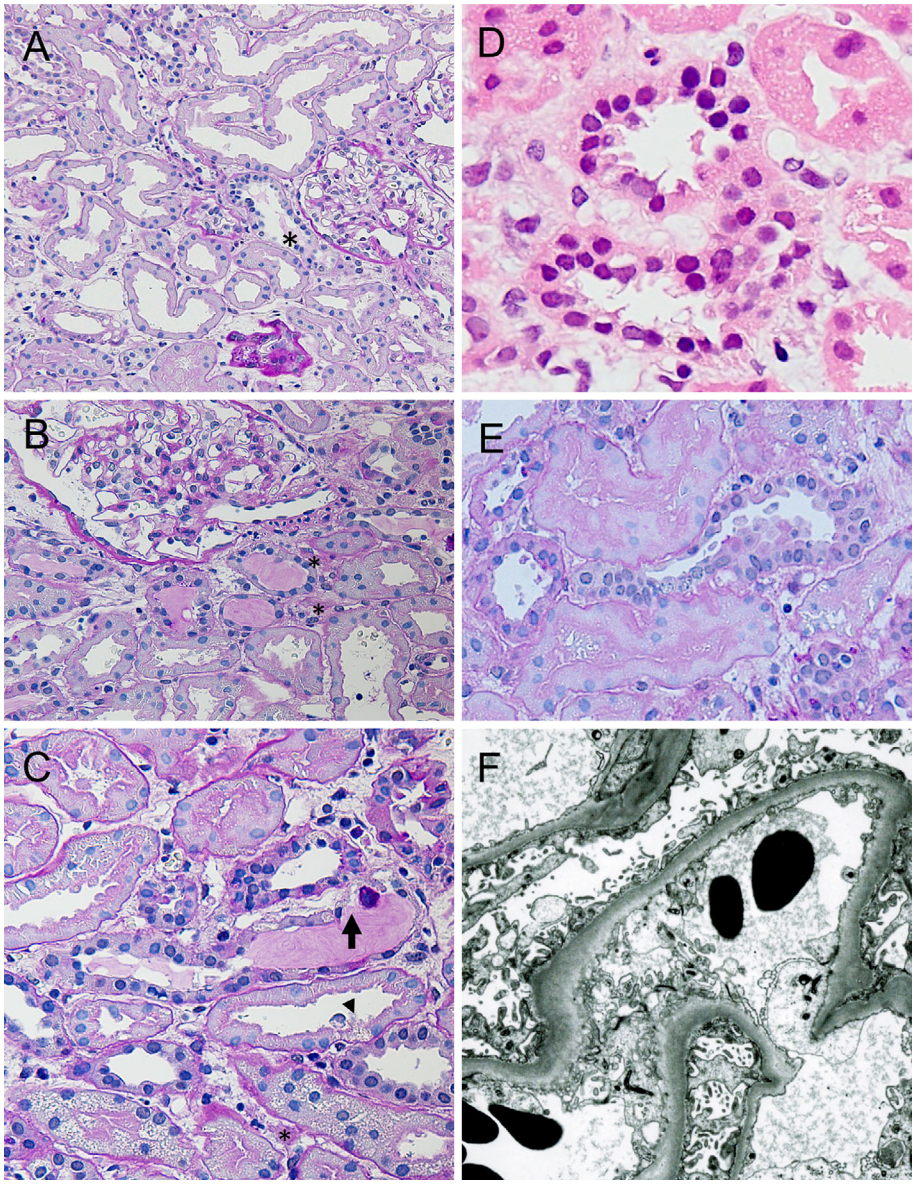

Figure 2. **Kidney biopsy findings. A: On light microscopy, a glomerulus shows a minor abnormality. Proximal tubular simplification (tubular dilatation and epithelial cell flattening) is found in the vicinity of the glomerulus. A distal tubule with sloughed cells (asterisk) is seen. Periodic acid-Schiff (PAS) staining. Original magnification ×200. B: Intratubular PAS-positive Tamm-Horsfall protein-like materials in several distal tubules and their extravasations (asterisks) are found. PAS staining. Original magnification ×200. C: Proximal tubules with blebbing, necrosis (arrowhead) and isometric vacuolization are found. There is a distal tubule with Tamm-Horsfall protein-like material and epithelial cell injury (arrow). Extravasation of Tamm-Horsfall protein-like material in the interstitium (asterisk) is seen. PAS staining. Original magnification ×400. D: There are two damaged distal tubules with a feathery appearance on the apical side of the cells. Hematoxylin and Eosin staining. Original magnification ×400. E: A distal tubule with proliferating epithelial cells and sloughed cells is found. PAS staining. Original magnification ×400. F: Electron micrograph of a glomerulus. There are no electron-dense deposits in the glomerulus. The foot processes show deformation. The glomerular epithelial cells show a mild degree of lipid droplets, pseudocyst formation, and microvillous transformation. Original magnification ×5,000.**

tened epithelium) was found in the vicinity of the glomeruli (Fig. 2A). Periodic acid Schiff-positive proteinaceous casts (possible Tamm-Horsfall protein) were found in some distal tubular lumens with or without tubular cell injury (Fig. 2B, C). Extravasation of such proteins was also found in the interstitium (Fig. 2B, C). Some proximal tubules showed isometric vacuolization and blebbing, and very limited proximal tubular cells showed necrosis (Fig. 2C). There were injured cells, proliferating cells, and sloughed cells in a relatively large number of distal tubules

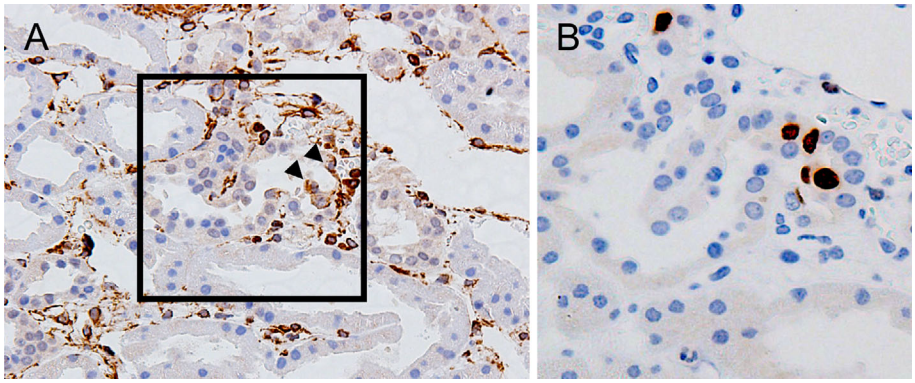

Figure 3. **Indirect immunohistochemistry findings for vimentin- and Ki67-positive cells. A: Vimentin is observed in the mesangium and peritubular capillaries, as in normal human adult kidneys. Simplified proximal tubules are negative for vimentin. Vimentin-positive injured cells (arrowheads) are found in a distal tubule. Original magnification ×200. B: The area of the square in (A) shows that Ki67-positive proliferating or regenerating cells are found in the distal tubule with vimentin-positive cells. Original magnification ×400. The primary antibodies, including murine monoclonal anti-vimentin antibody (clone V9; Sigma Aldrich, St Louis, USA) or murine monoclonal anti-human Ki67 antibody (clone MIB-1; Dako Denmark, Glostrup, Denmark), were used.**

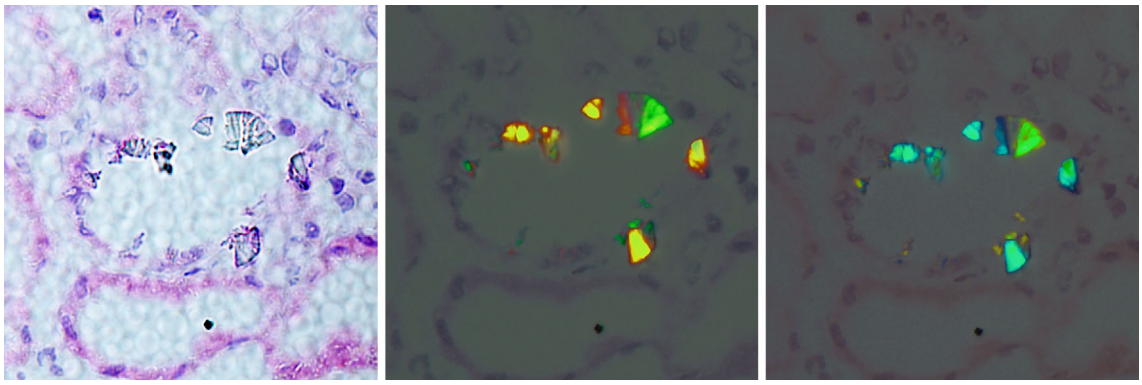

Figure 4. **Findings in a Hematoxylin and Eosin staining, alcohol-fixed frozen section. A: Retained crystals appear lightly basophilic to translucent in a distal tubule. B, C: Crystals are yellow when parallel with the γ-axis (B) and blue when perpendicular to the γ-axis (C) under a polarized light examination with a gout analyzer U-GAN.**

(Fig. 2A, C, D and E). Some damaged distal tubules showed a feathery-like appearance on the apical side of the cells (Fig. 1D). Periodic acid Schiff-stained microcalcifications with epithelial cell injuries were found in a few tubular lumens (data not shown). Significant inflammatory cell infiltration was not found in the tubulointerstitium. Edema and fibrosis were found in approximately 10% of the cortical areas. Immunofluorescence showed negative staining for IgG, IgA, IgM, C3, and C1q. Electron microscopy revealed no electron-dense deposits in the glomerulus (Fig. 2F). The foot process effacement was approximately 20%, and many of the foot processes showed deformation (Fig. 2F). The glomerular epithelial cells showed a mild degree of lipid droplets, pseudocyst formation, and microvillous transformation (Fig. 2F).

A further examination of the renal tissues by immunohistochemistry showed that simplified proximal tubules were negative for vimentin (Fig. 3A). Vimentin-positive injured cells were sporadically found in the proximal and distal tubules (Fig. 3A). Ki67-positive proliferating or regenerating cells were rarely found in the distal tubules with vimentin-positive cells (Fig. 3B). The Hematoxylin and Eosin staining, alcohol-fixed frozen section showed that a few retained rhomboid- or bar-shaped crystals appeared lightly basophilic to translucent (Fig. 4A), which was compatible with UA crystals (11). In addition, the crystals were yellow when parallel with the γ-axis and blue when perpendicular to the γ-axis under a polarized light examination with a U-GAN gout analyzer (Olympus, Tokyo, Japan) (Fig. 4B, C), suggesting UA crystals, according to the manufacturer's instructions.

Febuxostat treatment was stopped prior to discharge. The dose of prednisolone began to be tapered two weeks after treatment. Two months after discharge, the patient had another episode of epileptic seizures and was admitted to our hospital for four days. On admission, he was alert and had a

fever of 37.8°C without any infectious signs. The serum UA level was 24.6 mg/dL, the sCr level was 1.4 mg/dL, and the CK level was not increased (Fig. 1). The next day, sCr peaked at 1.95 mg/dL, and serum UA was 13.5 mg/dL (Fig. 1). The fractional excretion of Na was 0.78%, indicating prerenal AKI. His proteinuria level remained within the normal range, and all the abnormal levels spontaneously returned to basal values (Fig. 1). Zonisamide at 10 mg/day was added to lamotrigine for seizure management. The patient remained well with prednisolone at 25 mg/day, lamotrigine, and zonisamide, and his sCr, UA, and proteinuria levels were 1.08 mg/dL, 6.1 mg/dL, and 0.02 g/gCr, respectively, 6 months after corticosteroid treatment.

Discussion

We encountered a patient with AKI, massive proteinuria, moderately high CK levels, and severe acute hyperuricemia after epileptic seizures. While we cannot be certain, according to the trend in serum albumin levels, nephrotic-range proteinuria likely developed after seizures (Fig. 1). The patient showed 10-kg body weight gain on admission to our hospital, suggesting overhydration due to AKI (Fig. 1). This may have contributed to the development of hypertension. AKI was alleviated with the reduction in proteinuria; however, whether or not the massive proteinuria disappeared spontaneously or by corticosteroid treatment was not clear. The kidney biopsy two days after corticosteroid therapy did not show diffuse foot process effacement; however, glomerular epithelial cell findings, such as deformity of foot processes and microvillous transformation, reflected the ultrastructures of MCNS. The patient may not have developed full-blown nephrotic syndrome and simply been in the process of recovering from massive proteinuria, as indicated by the partial foot process effacement. However, it was reported that patients with focal segmental glomerulosclerosis secondary to hyperfiltration did not develop hypoalbuminemia despite the presence of massive proteinuria (12). Glomerular hyperfiltration is considered to be linked to increased glomerular perfusion and glomerulomegaly with podocyte injury. Glomerular hyperfiltration/hypertension increases the filtration pressure and filtrate flow. Pressure causes distension stress, and flow causes shear stress. Among the filtration barrier components, the podocyte is the most susceptible to mechanical challenges from flow-derived factors (13). The renal pathology in our patient did not show glomerulomegaly, probably because of the short-term hyperfiltration period. However, the partial foot process effacement and foot processes deformation might have been due to glomerular hyperfiltration/hypertension.

In MCNS patients with AKI, redistribution of the renal blood flow from cortical to juxtaglomerular nephrons and a decrease in the capillary filtration coefficient (Kf) were reported to contribute to AKI (14). Massive proteinuria has also been proposed to contribute to AKI due to proximal tubular cell injury and apoptosis in patients with MCNS (2-4). Our previous study demonstrated that MCNS patients with AKI showed proximal tubular simplification in the vicinity of the glomeruli, and the areas of vimentin-positive simplified proximal tubules were significantly larger in MCNS patients with AKI than in MCNS patients without AKI (15). In our patient, proximal tubular simplification was found in the vicinity of the glomeruli; however, the tubular cells in the simplified tubules were negative for vimentin. Furthermore, there were significant distal tubular cell injuries, as indicated by vimentin positivity, and proliferation was indicated by Ki 67 positivity. Thus, these mechanisms may have been additional or alternative causes of AKI.

In our patient, the CK level was high 4 days after seizures (3,327 U/L), which is when the sCr value was near its peak level (Fig. 1). Both seizures (16) and levetiracetam (8) can induce rhabdomyolysis-induced AKI. In rhabdomyolysis-induced AKI, tubule obstruction of myoglobin occurs principally at the level of the distal tubules, and direct tubule cytotoxicity by myoglobin occurs mainly in the proximal tubules, showing acute tubular necrosis (17). However, the renal pathology in our patient did not show acute tubular necrosis. Acute tubulointerstitial nephritis has also been reported in levetiracetam-induced AKI (9); however, this was not found in our patient.

Acute UA nephropathy may occur in conditions causing increased serum UA levels, typically ≥10-15 mg/dL, and is characterized by oliguric AKI (18). Crystal-independent mechanisms by which UA contributes to AKI were reported to include renal vasoconstriction, activation of proinflammatory cells, microvascular injury, and altered renal autoregulation (19). Glomerular afferent arteriolar vasoconstriction might also have contributed to the sudden increase in blood pressure and AKI in our patient. Persistent or repetitive contraction of the muscle during seizures may cause direct nucleotide breakdown. This breakdown produces increased levels of adenosine, which is then converted by xanthine oxidase in the liver to UA (20). To our knowledge, patients with acute UA nephropathy due to seizures have been described in two case series (6, 7) and four case reports (10, 21-23). A kidney biopsy was not performed in any reported cases; however, serum UA levels were unproportionally high compared with secondary hyperuricemia due to renal dysfunction. Our patient clearly showed severe acute hyperuricemia just after seizures without high CK levels or severe renal dysfunction (Fig. 1). According to the 4 previous case reports (10, 21-23) (Table 2), the mean peak serum UA level was 15.3 mg/dL (13.1-20.2 mg/dL) within 48 h after seizures, and in 3 cases, the patient was treated with either or both allopurinol or rasburicase. The mean peak sCr level was 6.2 mg/dL (2.4-9.2 mg/dL) within 72 h after seizures. The mean peak CK level was 2,134 U/L (663-4,489 U/L), which is generally insufficient to cause rhabdomyolysis-induced AKI. Of note, two cases showed nonoliguric AKI, similar to our case. Two patients required hemodialysis; however, all patients recovered their renal function. Although not all reported cases showed these find-

Table 2. Reported Cases of Acute Uric Acid Nephropathy Due to Seizure.

Reference	Age (years)/ Sex	Peak UA (mg/dL)/ Days after seizure	Peak Cr (mg/dL)/ Days after seizure	Peak CK (U/L)/ Days after seizure	Urine UA to Cr ratio	Treatment for hyperuricemia	Others
(10)	35/M	13.2/2	7.2≤/3	2,760/3	1.2	Allopurinol rasburicase	Anuric, transient HD urine UA crystals urine protein 6.2 g/gCr recovered
(21)	21/M	20.2/1	9.2/3.5	4,489/1			37.8°C reduced urine output transient HD Rhabdomyolysis and hyperuricemia contributed to AKI recovered
(22)	28/M	15.0/2	6.1/2	663/2	1.2	Rasburicase	Nonoliguric AKI urine UA crystals recovered
(23)	26/M	13.1/1	2.4/1	15,240/3	0.57 (3 days after seizure)	Allopurinol	Nonoliguric AKI recovered
Our case	25/M	19.8/1	8.61/4	3,327/4	0.75 (2 days after seizures)	Febuxostat	Nonoliguric AKI recovered

M: man, UA: uric acid, Cr: creatinine, CK: creatine kinase, HD: hemodialysis, AKI: acute kidney injury

ings (Table 2), UA crystals in urine and a urine UA-to-creatinine ratio of more than 1 were reported to be highly suggestive of acute UA nephropathy (24). However, a urinalysis may be normal if there is no output from the obstructed nephrons (19). Therefore, a clinical diagnosis of UA nephropathy could not be excluded in our patient. These reported cases did not show a common morbid state. However, all reported cases, including our case, were young men (Table 2), a population that tends to have a high muscle volume. This can thus cause high levels of nucleotide breakdown during seizures, leading to increased serum UA levels and acute UA nephropathy.

Pathologically, acute UA nephropathy shows obstruction of the distal nephron by intraluminal clusters of UA crystals in tubules, usually collecting ducts, which can cause dilatation, inflammation, and obstruction of proximal tubules (18, 25). The crystals can be observed as needle-like clefts in conventional light microscopic tissues, but UA crystals are dissolved during tissue processing (25). A kidney biopsy in our patient did not include a sufficient volume of the medullary collecting ducts. However, the possible intratubular accumulation of Tamm-Horsfall proteins and their extravasation into the interstitium together with proximal tubular dilatation suggest obstruction at the distal part of the nephron in our patient. The feathery damage at the luminal side of some distal tubules is also suggestive of the effects of distal tubular obstruction. In addition, although intratubular retained crystals observed on alcohol-fixed, frozen sections were not typical needle-like shapes but instead rhomboid- or bar-shaped, their characteristics were compatible with gout crystals under a polarized light examination. The shapes of intratubular crystals in our patient resembled those of urine UA crystals, showing a rhomboid or bar shape. One reported case with UA nephropathy due to seizure showed barrel- or diamond-shaped UA crystals in urine sediments (22). Interestingly, UA crystals in urine sediments span a wide morphological spectrum and include shapes that are frequently observed (e.g., rhomboid plates and barrel-like structures), infrequently observed (e.g., hexagons, prisms, rosettes, cubes, drum sticks, and rolling pins), and very unusual (needle- and pencil-like) (26). These findings may support the pathology of acute UA nephropathy in our patient.

Given the clinicopathological findings, it is possible that our patient had acute UA nephropathy due to seizures. Of interest, one of the described patients presented with the development of nephrotic range proteinuria just after acute UA nephropathy due to seizures (10). The authors speculated that the relationship between massive proteinuria and some glomerular and tubular injuries had been caused by acute hyperuricemia. Unfortunately, they did not have any long-term follow-up data on their patient; thus, whether or not proteinuria ceased after resolution of AKI and the relationship between hyperuricemia and massive proteinuria are unclear. However, the experimental evidence showed that hyperuricemia was able to induce glomerular afferent arteriolopathy, which impairs the autoregulatory response (19). Therefore, the glomeruli supplied with blood through the afferent arterioles with altered autoregulatory response under high blood pressure might develop glomerular hypertension, leading to massive proteinuria. This mechanism might explain the massive proteinuria in our patient. However, to our knowledge, there have been no reported cases of massive proteinuria after acute hyperuricemia due to tumor lysis syndrome.

In summary, after the occurrence of seizures, patients may have several potential risk factors for AKI. The exact cause of AKI in our patient was not apparent; however, both MCNS-related AKI and acute UA nephropathy may have contributed to the development of severe AKI after epileptic seizures. The relationship between acute hyperuricemia and massive proteinuria remains unclear. Since rasburicase, a recombinant urate oxidase, can be safely and effectively used, the diagnosis of acute hyperuricemia after seizures should

not be delayed or overlooked to prevent severe AKI.

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

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