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【 CASE REPORT 】

Acute Kidney Injury and Fanconi Syndrome Caused by a Red Yeast Rice Supplement

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Abstract:

We herein report a case of acute kidney injury and Fanconi syndrome associated with a red yeast rice supplement. A 72-year-old woman's serum creatinine rose from 0.7 to 3.97 mg/dL after starting the supplement, accompanied by metabolic acidosis, proteinuria, hematuria, and glucosuria. A kidney biopsy showed proximal tubular injury without abundant tubulitis. Immunostaining showed dilated tubules that were positive for CD 10, confirming proximal tubule localization. Discontinuation of the supplement and steroid pulse therapy improved the patient's condition. This case highlights the health risks associated with unregulated dietary supplementation.

Key words: red yeast rice, acute kidney injury, Fanconi syndrome, proximal tubule injury, Chinese herb nephropathy, puberulic acid

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Introduction

Health foods and supplements are readily available through over-the-counter (OTC) sales and online purchases, which many people use. Approximately 57.6% of adults in the U.S. and 38.7% in Japan use some form of dietary supplements, and the market is growing (1, 2). However, there are rare instances where health issues may arise.

In Japan, since January 2024, there have been reports of individuals who experienced kidney damage after taking red yeast rice supplement produced by Kobayashi Pharmaceutical, which was marketed to improve dyslipidemia (3-5). This nephropathy shares similarities with nephropathy caused by Chinese herbs, and we highlight the differences between the two conditions.

Case Report

The patient was a 72-year-old woman who had undergone surgery for appendiceal cancer 5 years ago. Apart from that, there were no significant medical history events, and the patient was not on any regular medications. At one point, she had been diagnosed with dyslipidemia during a health checkup and started taking red yeast rice supplements produced by Kobayashi Pharmaceutical. No abnormalities were found in the urine dipstick test. One month after starting the supplement, she visited a surgical clinic for follow-up of appendiceal cancer. Blood tests revealed dyslipidemia, a serum creatinine level of 0.7 mg/dL, and an estimated glomerular filtration rate (eGFR) of 57 mL/min/1.73 m^2. A urine analysis was not performed at that time.

Approximately half a month later, she experienced loss of appetite and vomiting. Subsequently, her symptoms worsened, making oral intake difficult, and she sought medical attention at our hospital. Her height was 158 cm, weight was 54.6 kg, no rash or edema was observed, and her blood pressure was 132/80 mmHg. Laboratory results showed an impaired kidney function, with blood urea nitrogen at 47.0 mg/dL, serum creatinine at 3.97 mg/dL, eGFR 9 mL/min/1.73 m^2, metabolic acidosis (HCO_3^- at 6.0 mmol/L), and abnormal urine findings (urine protein: creatinine ratio 4.66 g/

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Table. Patient's Laboratory Characteristics on Admission.

	Result	Reference range
Blood test		
White blood cells (/μL)	10,000	3,300-8,600
Neutrophil (%)	85.2	41.8-73.8
Lymphocyte (%)	10.9	18.3-47.5
Monocyte (%)	3.7	2.5-7.3
Eosinophil (%)	0.0	0.0-5.6
Basophil (%)	0.2	0.1-1.3
Hemoglobin (g/dL)	15.3	11.6-14.8
Platelets (10^3/μL)	271	158-348
Total protein (g/dL)	8.2	6.6-8.1
Albumin (g/dL)	4.2	4.1-5.1
Blood urea (mg/dL)	47	8-20
Creatinine (mg/dL)	3.97	0.46-0.79
Sodium (mmol/L)	138	138-145
Potassium (mmol/L)	2.6	3.6-4.8
Chloride (mmol/L)	113	101-108
Calcium (mg/dL)	10.2	8.8-10.1
Phosphate (mg/dL)	3.6	2.7-4.6
Uric acid (mg/dL)	3.2	2.6-5.5
Total cholesterol (mg/dL)	265	142-248
Triglyceride (mg/dL)	173	30-117
HDL-cholesterol (mg/dL)	65	48-103
Blood glucose (mg/dL)	97	73-109
IgG (mg/dL)	1,981	820-1,740
IgG4 (mg/dL)	36	11-121
IgA (mg/dL)	349	90-400
IgM (mg/dL)	63	52-270
Monoclonal protein	Negative	Negative
FLC kappa:lambda ratio	1.12	0.26-1.65
C3 (mg/dL)	160	80-140
C4 (mg/dL)	58.8	11-34
CH50 (U/mL)	67	30-45
Blood pH	7.07	7.35-7.45
Bicarbonate (mmol/L)	6.0	21.2-27.0
Anti-nuclear antibody	Negative	Negative
Anti-SS-A/Ro antibody	Negative	Negative
MPO-ANCA	Negative	Negative
PR3-ANCA	Negative	Negative
Anti-GBM antibody	Negative	Negative
Urinary test		
Urine pH	5.5	7.5
Specific gravity	1.013	
Glucose	3+	-
Protein:creatinine ratio (g/gCr)	4.66	<0.15
Red blood cells (/HPF)	1-4	<5
White blood cells (/HPF)	50-99	<5
Granular casts (/WF)	1-4	
Hyaline casts (/WF)	1-4	
β2-microglobulin (μg/L)	5,276	<289
NAG (U/L)	18.5	<11.5

HDL: high density lipoprotein, FLC: free light chain, MPO-ANCA: myeloperoxidase antineutrophil cytoplasmic antibody, PR3-ANCA: proteinase 3 antineutrophil cytoplasmic antibody, GBM: glomerular basement membrane, HPF: high power field, WF: whole field, NAG: N-acetyl-beta-D-glucosaminidase

gCr, red blood cells 1-4/high power field, urine glucose 3+) (Table). Computed tomography (CT) scans from the neck to the pelvis showed no significant lymph node enlargement or other abnormalities. Suspecting rapidly progressive glomerulonephritis, we initiated steroid pulse therapy and corrected the acidemia after admission to the hospital. We had her stop taking the red yeast rice supplements.

An ultrasound-guided percutaneous kidney biopsy was performed on the day after admission. Light microscopy revealed diffuse interstitial fibrosis with an enlarged renal tubular lumen (Fig. 1A). A total of 30 glomeruli were observed, four of which exhibited global sclerosis, while the preserved glomeruli showed mild enlargement with minor glomerular abnormalities (Fig. 1B). In the tubulointerstitium (Fig. 1C), flattening and simplification of the proximal epithelial cells were observed along with widening of the lumen. Masson's trichrome staining showed a significant decrease in red epithelial cells, representing the mitochondria in the proximal tubules. These findings suggested proximal tubule dysfunction. CD10, a marker for proximal tubules (Fig. 1D, E), and epithelial membrane antigen (EMA), a marker for distal tubules (Fig. 1F), were immunohistochemically stained. Dilatated injured renal tubules were positive for CD10 (Fig. 1D, E), and unaffected renal tubules were positive for EMA (Fig. 1F). In the damaged tubules, several types of damaged epithelial cells were observed, such as severe vacuolar degeneration, red granule accumulation in Masson's trichrome stain, enlarged cells with large nuclei and nucleoli, flattening and simplification of the proximal epithelial cells with loss of brash borders, and shedding of epithelial cells (Fig. 1G, H). Mild inflammatory cell infiltration in the interstitium without abundant tubulitis was also observed, indicating no apparent development of tubulointerstitial nephritis (Fig. 1I). Electron microscopy findings of damaged tubular epithelial cells showed various types of epithelial cytoplasmic clear vacuolation, such as large vacuoles, accumulated small isometric vacuoles in epithelial cells, and numerous electron-dense granules in lysosomes in epithelial cells (Fig. 1J-L). Immunofluorescence staining did not reveal a significant deposition of immunoglobulins (data not shown).

Blood tests and renal pathology did not indicate findings suggesting anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis or anti-glomerular basement membrane (GBM) disease. The drug-induced lymphocyte stimulation test for the supplement was negative, and the renal histological findings showed no significant inflammatory cell infiltration in the tubulointerstitial area, with no substantial evidence suggesting tubulointerstitial nephritis.

Gradually, the patient's self-reported symptoms improved and kidney function showed a positive trend. However, the hypokalemia and hypophosphatemia became more pronounced, necessitating supplementation. Considering the limited benefit of continued steroid therapy, the dosage was gradually reduced, and the patient was discharged. After discharge, the patient visited an ophthalmologist, and no abnor-

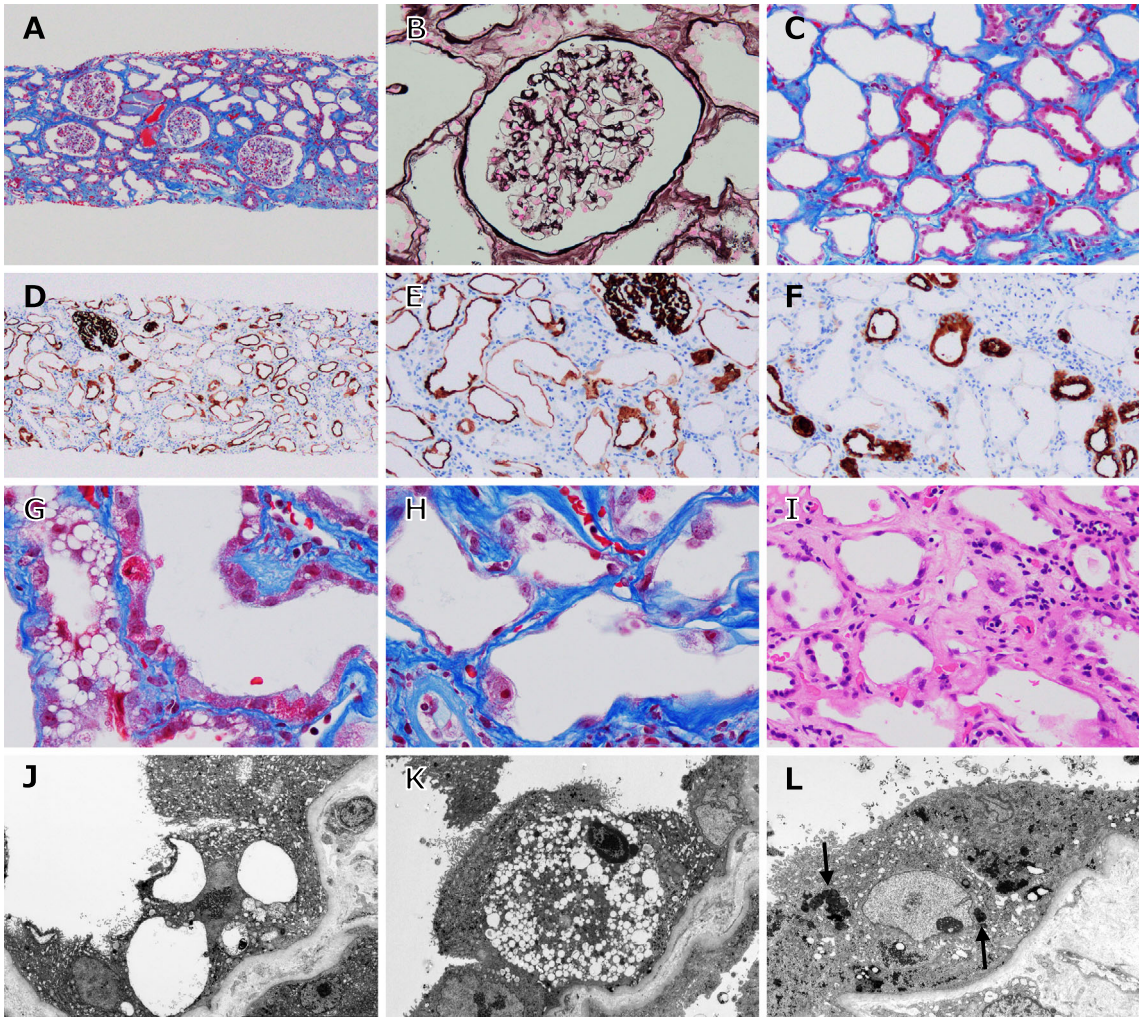

Figure 1. **The pathological findings of renal biopsy specimens. A: Diffuse interstitial fibrosis with enlarged renal tubular lumens. B: The glomeruli were within the range of minor glomerular abnormalities. C: Enlargement of tubular lumens occurs with flattened tubular epithelial cells. D: CD10-positive cells are expressed in dilated renal tubules. E, F: Injured tubules with dilatation showed expression of CD10, and non-dilated renal tubules showed expression of epithelial membrane antigen (EMA) in serial sections. G, H: Several types of damaged epithelial cells were observed. I: Mild inflammatory cell infiltration in the interstitium without tubulitis was observed. J, K: Various types of vacuolar degeneration of tubular epithelial cells were observed. L: Numerous electron-dense granules were observed in the lysosomes of epithelial cells (arrows). (A, C, G, H: Masson's trichrome stain, B: Periodic Acid-Methenamine silver stain, D, E: Immunohistochemistry for CD10, F: Immunohistochemistry for EMA, I: Hematoxylin and Eosin staining, J-L: Electron microscopy; A, D: ×90, B, G, H: ×400, C: ×200, E, F: ×120, I: ×250, J, L: ×1,200, K: ×1,500).**

malities, including uveitis, were identified.

Kobayashi Pharmaceutical, announced a voluntary recall of its red yeast rice supplements because of reports of renal dysfunction among users. Although our patient's kidney function and urinalysis results improved, she still required potassium and phosphate supplementation, and her urinary β 2-microglobulin level remained high three months after our initial consultation (Fig. 2).

Discussion

The present patient experienced acute kidney injury and Fanconi syndrome due to proximal tubular damage after several months of taking red yeast rice supplements produced by Kobayashi Pharmaceutical. Using immunohistochemistry, we demonstrated that this supplement primarily caused proximal tubular epithelial lesions.

According to Japan's Ministry of Health, Labour and Welfare, as of the end of November 2024, 2,628 people had sought medical attention due to health problems caused by this supplement, 540 people required hospitalization, and 397 deaths might be related. This has become a significant societal concern. The Japanese Society of Nephrology reported an investigative survey titled "Questionnaire Survey

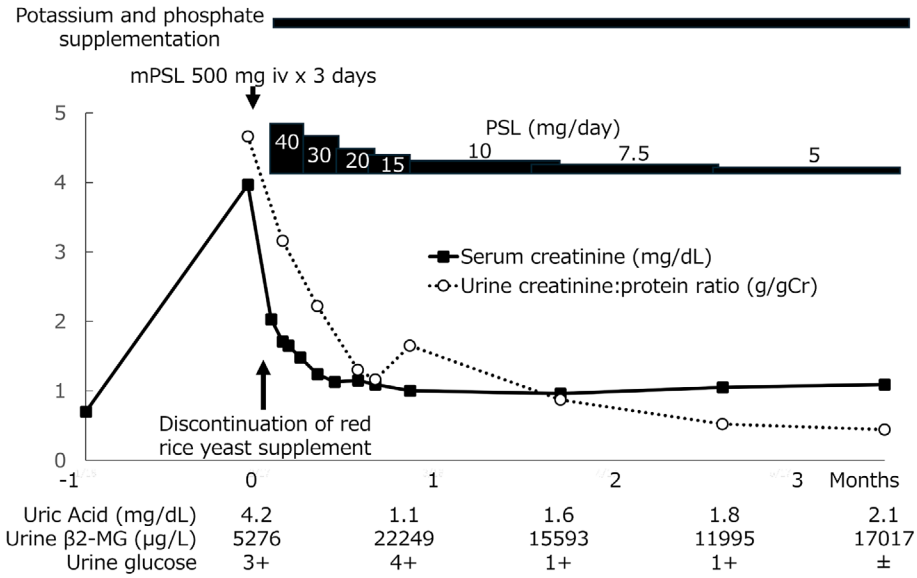

Figure 2. **Clinical course. β2-MG: β2-microglobulin, mPSL: methylprednisolone, iv: intravenous, PSL: prednisolone**

on Renal Injury Associated with BeniKoji (Red Yeast Cholesterol Help®) for Members of the Japanese Society of Nephrology (Interim Report)" (6). According to this report, most patients, predominantly 40-69 years old and slightly more often women than men, begin experiencing symptoms such as fatigue, anorexia, abnormal urine, and renal dysfunction. Laboratory findings were strongly indicative of Fanconi syndrome, with common abnormalities, including hypokalemia, hypophosphatemia, hypouricemia, metabolic acidosis, and glucosuria. A renal biopsy revealed tubulointerstitial nephritis, tubular necrosis, and acute tubular injury. Discontinuation of the supplement led to significant improvements in the renal function in many patients, with steroids being used selectively based on biopsy findings. Although electrolyte and urinary abnormalities improved in most cases, some patients showed limited recovery, emphasizing the need for caution.

The health problems caused by this supplement appear to be characterized by Fanconi syndrome with acute kidney injury. Fanconi syndrome is a group of disorders characterized by generalized solute transport dysfunction in the proximal tubules that leads to excessive urinary loss of substances normally reabsorbed there (7). Impaired reabsorption of solutes, such as amino acids, glucose, bicarbonate, and phosphate, leads to metabolic acidosis, electrolyte abnormalities, dehydration, growth retardation, and rickets. Causes include congenital and acquired factors. Congenital factors include cystinosis, mitochondrial disease, Wilson's disease, galactosemia, Lowe syndrome, and Dent disease. Acquired factors are most commonly drug-induced but can also result from heavy metals, such as lead and cadmium, as well as diseases causing tubulointerstitial damage, including multiple myeloma, amyloidosis, Sjögren's syndrome, and chronic interstitial nephritis (8). The causative drugs include valproic acid, antibiotics, and chemotherapeutic agents. In drug-induced Fanconi syndrome, drugs accumulate in the proximal tubular cells and adversely affect cellular metabolism, leading to damage to the proximal tubules. The mitochondria within proximal tubular cells may become enlarged or morphologically altered because of the toxic effects of drugs. As damage to the proximal tubules progresses, fibrosis may develop in the tubulointerstitial areas. However, these findings are nonspecific, making a definitive diagnosis based solely on the renal histology difficult.

Red yeast rice, which contains the cholesterol synthesis inhibitor monacolin K, is used as a supplement to improve cholesterol levels (9). However, some red yeast rice strains produce citrinin, which is associated with kidney toxicity and carcinogenicity (10). Consequently, in some countries, selling food products containing red yeast rice is considered illegal due to this risk. According to Kobayashi Pharmaceutical, these supplements utilize red yeast rice strains that lack the ability to synthesize citrinin. Their announcement stated that even in the 2024 ingredient analysis, citrinin was not detected in the raw materials.

Although red yeast rice supplements were launched in April 2021, approximately three years before the reports of adverse events, reports of health issues emerged only in January 2024. Contamination with unintended substances, rather than the inherent renal toxicity of red yeast rice, causes kidney damage. On September 18, 2024, the Ministry of Health, Labour and Welfare announced findings regarding causative substances (11). Three compounds, including puberulic acid, were detected in batches of supplements linked to health issues but were absent in the unaffected batches. It was discovered that the blue mold *Penicillium adametzioides*, which resides in the supplement manufacturing facility, produces puberulic acid. Animal experiments have confirmed that puberulic acid induces degeneration and necrosis of proximal tubules. Investigations of other substances are

ongoing. Health damage is suspected to be partly caused by contamination of the supplement with blue mold in the factory, which leads to the inclusion of puberulic acid.

Our patient had no medical history other than that of surgically treated appendiceal cancer. Apart from dyslipidemia identified during a health checkup, no other issues were noted, and the patient was not taking any regular medications before starting the supplement. She presented with renal dysfunction, metabolic acidosis, hypokalemia, and abnormal urinalysis results at the initial consultation. As the renal function improved, hypophosphatemia and hypouricemia became apparent. Hypophosphatemia and hypouricemia are characteristic findings of Fanconi syndrome, but the absence of these abnormalities at the time of the visit was likely due to renal dysfunction. Initially, we suspected rapidly progressive glomerulonephritis and initiated steroid therapy. However, renal biopsy findings did not support the diagnosis of proximal tubular injury, although the glomeruli were within the range of minor glomerular abnormalities, and there was no evidence of interstitial nephritis. In the present case, the results of renal histopathology and the negative consequence of the drug-induced lymphocyte stimulation test suggest that the renal injury caused by this supplement is not mediated through an allergic mechanism but rather by direct toxicity to the proximal tubular epithelium. The attending physician continued steroid treatment for several months, believing that the steroids had a therapeutic effect. However, based on the pathological findings, it is possible that steroids were unnecessary, and discontinuing the supplement alone would have been sufficient. According to a survey by the Japanese Society of Nephrology, steroids were used in only 20% of cases (6). This indicates that discontinuing the supplement alone may lead to improvements in some cases.

Our patient presented with renal dysfunction accompanied by Fanconi syndrome and proximal tubular damage identified by a renal biopsy, although the cause was initially unknown. She was not taking any medications other than the supplement, and while heavy metal levels were not measured, blood tests and imaging studies did not reveal the cause of her condition. After the patient was discharged, reports linking the supplement to kidney damage emerged, leading us to conclude that the supplement was the causative agent.

In this instance, symptoms appeared within two months of starting the supplement, and rapid onset of renal dysfunction was evident. Although the patient's eGFR had been 57 mL/min/1.73 m^2 just under a month earlier, she presented with severe renal impairment and metabolic acidosis upon admission. The decline in the renal function in this patient is thought to be due not only to direct kidney damage caused by the supplement but also to renal kidney failure resulting from decreased oral intake caused by electrolyte imbalances associated with Fanconi syndrome.

The renal impairment caused by this supplement shares similarities with nephropathy caused by the Chinese herb. Chinese herbal nephropathy is recognized as a distinct renal disease that occurs after the ingestion of herbal medicines and was initially identified primarily in Belgium (12). Chinese herb nephropathy, caused by herbal medicine marketed as a slimming supplement in the 1990s, has gained attention in Japan and internationally for its association with Fanconi syndrome and kidney injury. In Japan, re-exposure to Chinese crude drugs has been reported to lead to relapse of acquired Fanconi syndrome (13). A pathological examination revealed characteristic hypocellular tubulointerstitial fibrosis, accompanied by atrophy and loss of tubules, predominantly located in the superficial cortex (14). Several companies that manufactured suspected drugs ceased production, leading to a decrease in the cases reported in Japan.

The causative agent was identified as aristolochic acid. No cases of Chinese herbal nephropathy have been reported in recent years. Of note, this supplement and Chinese herb nephropathy share several common features: both cause kidney injury through supplement intake, the primary site of damage is the proximal tubules, and both can be associated with Fanconi syndrome. However, there were notable differences between the two. Chinese herbal nephropathy is characterized by a chronic course of interstitial fibrosis in the renal tubules. Even after discontinuing the causative agent, the renal function progressively deteriorates, steroid treatment is ineffective, and many patients eventually require dialysis. In contrast, kidney injury caused by the supplement followed an acute course, characterized by acute tubular injury without interstitial fibrosis. Discontinuation of the supplement is adequate, and in some cases, steroid therapy may also be successful in improving the renal function. However, it may not always return to the pre-treatment levels.

Only a few academic papers have addressed renal disorders caused by this supplement (3-5), and accumulating cases and establishing effective treatment strategies are crucial for future research.

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

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