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Case Series

Renal Impairment of Proximal Tubular Injury Caused by Red Yeast Rice Supplement: Report of 2 Cases

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Keywords
Red yeast rice supplement · Renal tubular injury · Fanconi syndrome · Renal biopsy · Case report

Abstract
Introduction: Drug-induced tubulointerstitial injury is a common cause of renal impairment. Since the mechanisms of drug-induced tubular injury are diverse, various treatment approaches are needed according to the pathogenesis. Renal biopsy is indispensable to determine not only the pathological diagnosis, but also the underlying mechanism, and to guide appropriate treatment. Most recently, one of the red yeast supplements has been widely highlighted as a novel cause of tubular damage, mainly in Japan and Asia. However, neither detailed pathological findings nor the mechanism of renal impairment has been sufficiently reported. ***Case Presentation:*** Two cases of renal impairment after taking red yeast supplement internally are presented. Both cases showed renal dysfunction with low uric acid, potassium, and phosphorus levels, characteristic features of Fanconi syndrome. The renal biopsy findings of both cases showed severe injury to the proximal tubules with mild inflammatory cell infiltration. The proximal tubules exhibited diffuse loss of the brush border, flattening, and tubular lumen dilation. Immunofluorescence showed no deposition of immunoglobulin and complement in the glomeruli and tubules. Electron microscopic findings indicated proximal tubular damage without crystal deposition. Moreover, immunohistochemistry using the proximal tubular marker CD10 and a marker for distal tubules including the loop of Henle, E-cadherin, collectively

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demonstrated that the focus of renal injury in both cases was mainly the proximal tubules. ***Conclusions:*** The red yeast rice supplement itself, its metabolized product, or other unknown contaminant components might directly induce proximal tubulopathy rather than an allergic reaction-related tubulointerstitial nephritis.

Introduction

Drug-induced acute kidney injury is a well-known cause of renal impairment. Although medications induce various forms of kidney injury, drug-induced acute kidney injury to the tubulointerstitial compartment is the major target and can be classified into several different causes, such as (i) direct injury to tubules, (ii) urinary obstruction due to crystal formation, (iii) alterations in renal hemodynamics, and (iv) allergy or immune-mediated interstitial nephritis [1, 2]. Acute tubular injury resulting from various etiologies is pathologically characterized by phenotypes such as tubular necrosis, tubular injury, tubulitis, and tubulointerstitial nephritis [3]. Though there may be some overlap in the histopathological features of these phenotypes over time, each has distinct characteristics. The treatment and prognosis may vary depending on the pathogenesis, and the presence of allergy or immune-mediated interstitial nephritis may support steroid therapy. Therefore, renal biopsy is needed to identify these pathogeneses for future treatment.

Some people in Japan use "functional labeling foods," which are food product displays showing specific functions or effects of certain nutrients or substances labeled based on appropriate standards based on scientific evidence under the responsibility of the business operator. These foods are believed to help consumers maintain or improve their health in specific ways. In Japan, such supplements are sold after information regarding the safety and evidence of functionality of their specific active ingredients is submitted to and approved by the director-general of the Consumer Affairs Agency. However, they do not receive individual approval from the director-general for each specific product. The red yeast rice (RYR) supplement is one of the functional labeling foods with efficacy for hyperlipidemia [4]. RYR includes monacolin K, which is the same as lovastatin, which has been shown to improve hyperlipidemia. Lovastatin is known to be associated with some adverse effects, such as myopathy and liver injury, and intake of such supplements is not without risk [4].

Recently, it has been widely reported in the media not only in Japan and Asian countries that a certain company's RYR supplement, "紅麹コレステヘルプ®," produced during a specific period, is causing renal injury. However, this information is based on news reports rather than the scientific literature. Recently, 2 cases of renal injury associated with RYR supplements from the same company, both of which clinically showed Fanconi syndrome, which coincides with the report from a survey recently conducted by the Japanese Society of Nephrology (URL: https://jsn.or.jp/en/jsn-news/#4630, JSN News #344), were seen in our hospital. Renal biopsies were performed for both cases, and the details of these cases are presented here because of their importance.

Case Presentation

Case 1 was a 66-year-old woman who underwent an annual health check and was diagnosed as healthy. In 2021, Hashimoto's disease was diagnosed; however, it was managed conservatively without treatment. Subsequent periodic health checks in August 2022 and

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February 2023 showed serum creatinine (sCr) levels of 0.61 mg/dL and 0.65 mg/dL, and blood urea nitrogen (BUN) levels of 20.6 mg/dL and 20.6 mg/dL, respectively, indicating satisfactory renal function. From January 2023, the patient began self-administering an RYR supplement, "紅麹コレステヘルプ®" (Fig. 1a), 3 tablets per day. In August of the same year, sCr was 0.62 mg/dL, and BUN was 24.2 mg/dL, without any significant issues noted. In February 2024, the patient reported feeling unwell, prompting a blood test that showed elevated sCr of 1.74 mg/dL and BUN of 21.5 mg/dL. In the middle of March, following reports in the news regarding renal impairment associated with RYR supplement intake, the patient discontinued the supplement. Subsequent testing on day 5 after cessation of the supplement showed an improvement with creatinine levels at 1.09 mg/dL. However, the urinary β2-microglobulin (β2MG) level was markedly elevated at 56,500 μg/L, and urinary NAG levels were also high, 18.5 IU/L, indicating renal tubular dysfunction. In addition, blood tests showed lower potassium, phosphate, and uric acid levels, and urinary glucose 3+, collectively indicating Fanconi syndrome. Detailed data are presented in Table 1. Urinary eosinophils were not detected. No skin rash was observed. The patient was referred to our department for a renal biopsy, which was performed on day 12 after supplement cessation. Light microscopy (Fig. 1b–d), which included 47 glomeruli with 6 showing global sclerosis, showed a severe proximal tubular injury, characterized by flattening of proximal tubular cells, dilatation of the tubular lumen, and diffuse loss of the brush border with moderate interstitial edema and mild interstitial fibrosis. Despite the severity of proximal tubular injury, tubulointerstitial cell infiltration was very mild and highly localized, predominantly around globally sclerotic glomeruli. There was no significant infiltration of eosinophils, and no deposition of substances obstructing the tubular lumen was observed. The glomeruli were within the minor change abnormality. Fluorescence microscopy showed no apparent deposition of immunoglobulins or complement (not shown in the Figure). Electron microscopy did not detect electron-dense deposits in the glomeruli. Prominent flattening of the proximal tubules and loss of the brush border were marked, with no intracellular crystal formation detected (Fig. 1e). After renal biopsy, without the administration of steroid therapy, the Fanconi syndrome improved to the extent that electrolyte administration was no longer necessary, although renal function did not fully recover.

In case 2, a 54-year-old man had never experienced any abnormalities during his annual health checks. In 2021, he was diagnosed with dyslipidemia, and from 2022 onward, he began self-administering an RYR supplement, the same tablets as in case 1, 3 tablets per day (Fig. 2a). This patient was taking magnesium oxide almost daily for constipation. In July 2023, the sCr level was 0.84 mg/dL, but around March 2024, he began experiencing fatigue. No skin rash was observed. In early March, a blood test showed deterioration of sCr to 1.31 mg/dL. Similar to case 1, upon learning about renal impairment associated with RYR through news reports, he discontinued both supplements in the middle of March. Six days after cessation of the supplement, sCr had improved slightly to 1.25 mg/dL, yet urinary protein (TP/Cr) was 0.95 g/gCr, and β2MG was elevated at 59,712 μg/L, prompting further investigation. Subsequently, he was admitted to our hospital for a comprehensive assessment and underwent renal biopsy, which was performed on day 19 after cessation of the supplement. His potassium, phosphate, and uric acid levels were 3.5 mEq/L, 1.6 mg/dL, and 2.1 mg/dL, respectively, and urinary glucose was 3+. He had developed Fanconi syndrome similar to case 1, though uric acid improved to 2.8 mg/dL at the time of renal biopsy. β2MG was also improved to 15,200 μg/L. Detailed data at the time of admission are presented in Table 1. Urinary eosinophils were not detected. Histopathology of the renal biopsy (Fig. 2b–d), similar to case 1, showed proximal tubular injury with diffuse and moderate flattening and loss of the brush border on light microscopy, but the degree of injury was relatively milder than in case 1. Despite the tubular injury, there was scattered tubulointerstitial inflammatory cell infiltration.

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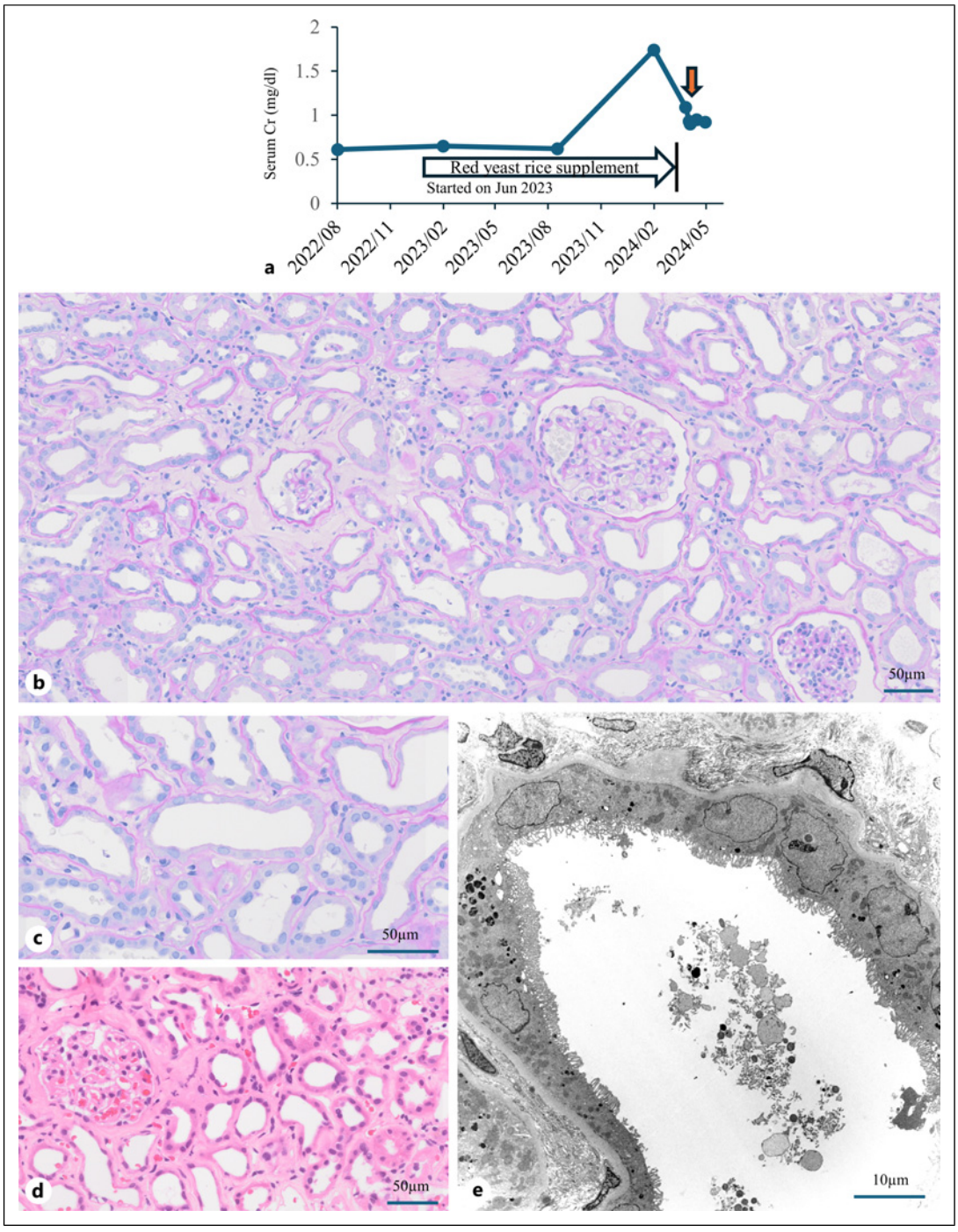

Fig. 1. a Clinical time course of sCr levels of case 1. The renal biopsy was performed on day 12 after cessation of the RYR supplement (orange arrow). **b–d** Light microscopy and electron microscopy findings of the renal biopsy of case 1, performed on day 12 after cessation of the RYR supplement. PAS (**b**, **c**) and HE (**d**) staining show proximal tubular injury with flattening, diffuse loss of the brush border, and tubular dilatation with interstitial edema and mild fibrosis. Only a few inflammatory cell infiltrates are found. **e** Electron microscopy shows diffuse loss of microvilli and flattened proximal tubular cells. Bar in (**b–d**): 50 μm, (**e**): 10 μm.

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Table 1. Data at the time of admission

Blood	Case 1	Case 2
WBC, /μL	5,800	6,800
Neutrophil, %	61.1	57.9
Eosinophil, %	2.4	3.5
Hb, g/dL	12.6	14.4
Plt, $\times 10^4$/μL	30.8	30.0
Total protein, g/dL	5.5	6.1
Albumin, g/dL	3.4	3.9
Total bilirubin, mg/dL	0.3	0.5
AST, U/L	18	19
ALT, U/L	16	14
BUN, mg/dL	16.9	13.1
Cr, mg/dL	0.93	1.23
Uric acid, mg/dL	1.4	2.8
CPK, mg/dL	127	116
T-Cho, mg/dL	242	245
LDL-Cho, mg/dL	122	149
HDL-Cho, mg/dL	75	78
Triglyceride, mg/dL	334	192
HbA1c, %	4.6	6.1
Na, mEq/L	138	142
K, mEq/L	3.6	3.5
Cl, mEq/L	108	106
Corrected Ca, mg/dL	8.6	8.5
P, mg/dL	1.0	3.1
Mg, mg/dL	3.1	2.6
CRP, mg/dL	<0.03	0.04
Antinuclear Ab	<40 times	<40 times
Urine		
pH	7.5	6.5
Protein	1+	–
Glucose	3+	–
Blood	±	–
Urobilinogen	±	±
Bilirubin	–	–
Keton	–	–
Total protein, mg/dL	53	7
Creatinine, mg/dL	51	28
TP/Cre, g/g Cr	1.04	0.25
NAG, IU/L	18.5	4.5
β2MG, μg/L	56,500	15,200

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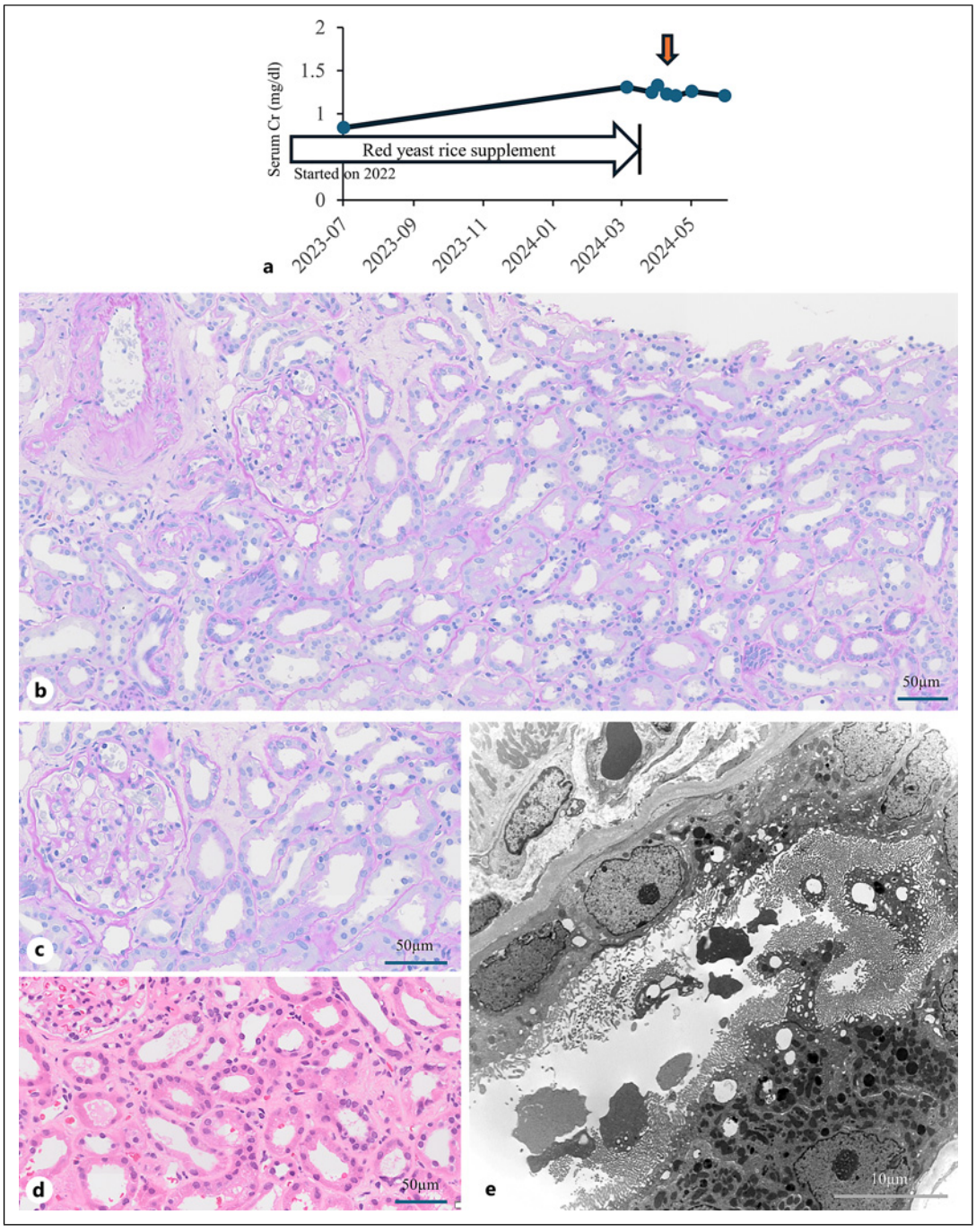

Fig. 2. a Clinical time course of the sCr level of case 2. The renal biopsy was performed on day 19 after cessation of the RYR supplement (orange arrow). **b–d** Light microscopy and electron microscopy findings of the renal biopsy of case 2, performed on day 19 after cessation of the RYR supplement. PAS (**b**, **c**) and HE (**d**) staining show proximal tubular injury with flattening, partial loss of the brush border, and tubular lumen dilatation with interstitial edema and mild fibrosis. Only a few inflammatory cell infiltrates are found. **e** Electron microscopy shows partial loss of microvilli and moderately flattened proximal tubular cells. Bar in (**b–d**): 50 μm, (**e**): 10 μm.

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The renal biopsy specimen contained 16 glomeruli, all of which exhibited morphology within the normal range. Fluorescence microscopy showed no apparent deposition of immunoglobulins or complement (not shown in the Figure). Electron microscopy (Fig. 2e) showed injured proximal tubules with flattening and loss of the brush border partially observed, but the degree of injury was relatively milder than in case 1. No intracellular crystal formation was observed. After the renal biopsy, without steroid therapy, similar to case 1, the Fanconi syndrome improved to the extent that electrolyte administration was no longer necessary, although renal function did not fully recover.

Immunohistochemistry of the Renal Biopsies in Both Cases

Renal biopsy tissue samples from both patients were examined immunohistochemically using anti-CD10 antibody (Ab) as a convoluted and straight proximal tubular marker, anti-E-cadherin Ab as loop of Henle, distal tubule, and collecting duct marker, and anti-Ki67 Ab as a cell proliferation marker (Fig. 3). CD10 is normally strongly expressed diffusely in the cytoplasm of proximal tubular cells, including the brush border. In case 1, CD10 was expressed only in the brush border and not in the cytoplasm (Fig. 3a, d). In case 2, compared to case 1, CD10 was observed to be slightly but markedly more strongly expressed, with its distribution seen not only in the brush border, but also within the intracellular compartment (Fig. 3g, j). In comparison, the expression of E-cadherin was preserved in both cases (Fig. 3b, e, h, k). The proliferation marker, Ki-67, was slightly more frequently observed in case 1 than in case 2 (Fig. 3c, f, i, l).

Discussion

The findings common to both cases were as follows: (i) Fanconi syndrome, (ii) renal biopsy-proven proximal tubular injury, (iii) scattered infiltrating inflammatory cells, (iv) no skin rash, (v) no eosinophilia, urinary eosinophils, or eosinophil infiltration on renal biopsy specimen examination, and (v) marked loss of the proximal tubular marker CD10, with preservation of the distal tubule marker E-cadherin, in renal biopsy tissue. Collectively, these findings indicate that proximal tubular injury occurred due to direct damage to the proximal tubules, rather than through an allergic or immune-mediated mechanism. In addition, these two cases had a renal biopsy at different times after cessation of RYR supplement intake, 12 days in case 1 and 19 days in case 2. In line with that, in case 2, compared with case 1, there seemed to be less severe tubular damage, the brush border appeared more preserved, and uric acid and β2MG improved without any treatment, which may mean that case 2 was on the way to recovery. Furthermore, the expression of Ki-67 was more abundant in case 1, suggesting that cellular proliferation, indicative of the recovery process following injury, was more pronounced in case 1. As announced in the press conference from the company making this RYR supplement through social media, renal impairment was occurring only in products manufactured during a specific period, and the present two cases, despite long-term ingestion, recently developed renal impairment, as shown by sCr elevation and indicated by mild interstitial fibrosis on renal biopsy specimen examination, as well. This suggests a high likelihood of these renal conditions being associated with supplements produced during a specific recent period. Furthermore, the absence of notable medical history, conditions, or medication usage other than the supplement further strengthens this hypothesis.

In the present cases, proximal tubular injury could be presumed to have occurred due to direct injury to tubular cells rather than allergies or urinary obstruction. However, importantly, there was no direct evidence that this RYR supplement induced such severe damage.

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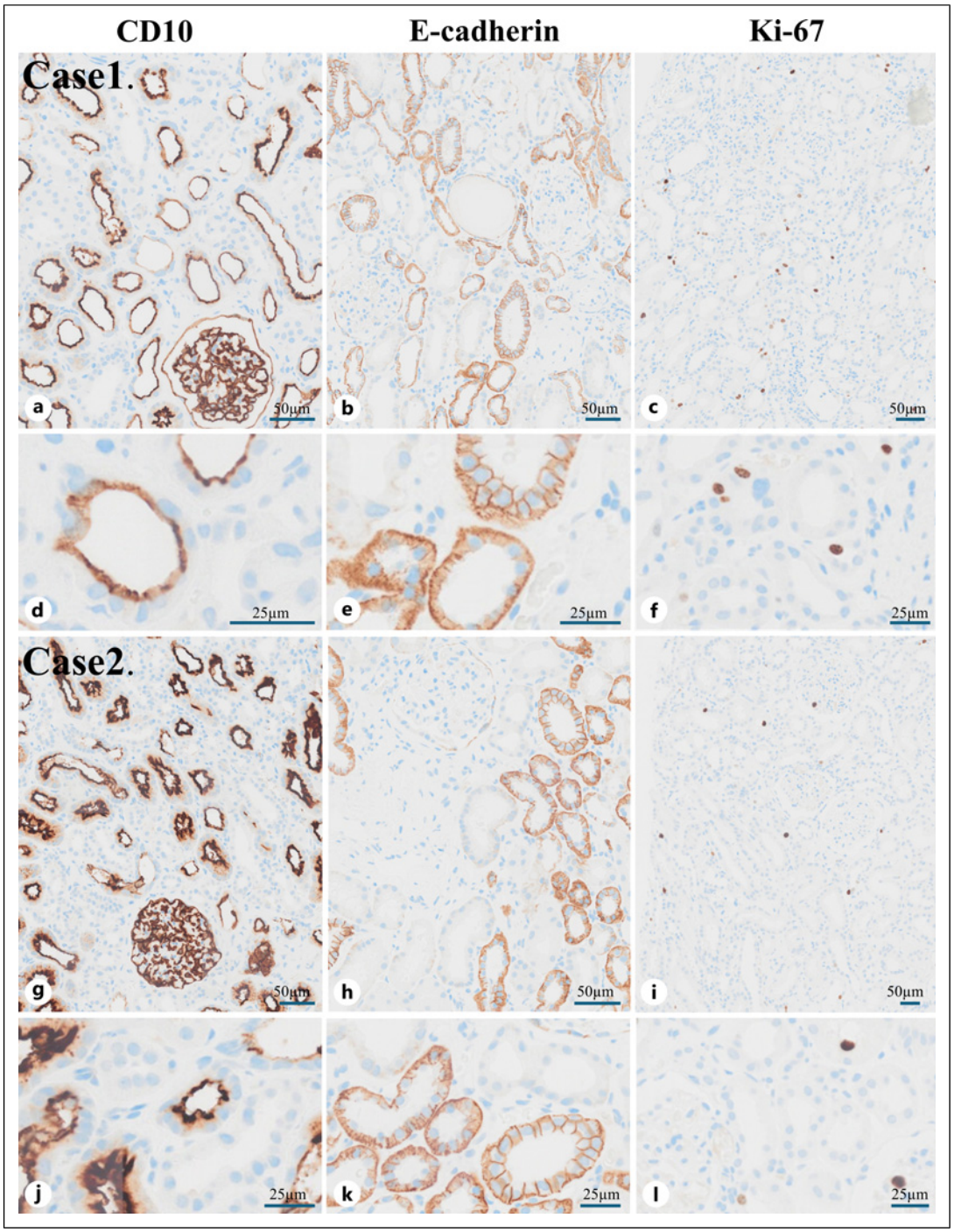

Fig. 3. Immunostaining of the 2 cases (case 1: **a–f**, case 2: **g–l**) using Abs against CD10 (**a**, **d**, **g**, **j**), a marker for proximal tubules, E-cadherin (**b**, **e**, **h**, **k**), a marker for distal tubules including the loop of Henle, and Ki-67 (**c**, **f**, **i**, **l**), a marker for cell proliferation. Low (**a–c**, **g–i**) and high magnification (**d–f**, **j–l**) fields are shown, respectively. CD10 expression is markedly decreased in the cytoplasm and expressed only in the brush border in case 1 (**a**, **d**). In comparison, in case 2, CD10 is expressed not only in the brush border, but also in the cytoplasm, although its expression pattern deviates significantly from the normal expression observed in proximal tubules (**g**, **j**). The expression of E-cadherin in both cases is preserved (**b**, **e**, **h**, **k**). Expression of Ki-67 is observed in both cases, but appears slightly more abundant in case 1 (**c**, **f**, **i**, **l**). Bar in (**a–c**) and (**g–i**): 50 μm. Bar in (**d–f**) and (**j–l**): 25 μm.

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RYR is commonly used as a supplement for hyperlipidemia, and its main lipid-lowering component is known to inhibit the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase. Though it is widely known that the use of statins can lead to rhabdomyolysis, it was reported that the RYR caused a rhabdomyolysis-induced acute kidney injury [5]. However, it is totally different from the present cases because they had not developed rhabdomyolysis. The raw material of RYR is produced by cultivating Monascus fungi on rice, followed by processes such as heating and grinding to create the final product. During this process, something may have contaminated and caused renal injury. One possibility is puberulic acid, but since we have not had a chance to test this component, its involvement is currently unknown. In addition, mycotoxins, known to be components of RYR, are also known to induce proximal tubular injury, and they may be considered as one potential cause in these cases [6]. However, none of these hypotheses has been substantiated, and further research is eagerly awaited in the future.

As in the present 2 cases, toxic drug-induced tubular injury due to tenofovir and cisplatin and other drugs is well known to cause proximal tubular necrosis with Fanconi syndrome. Tenofovir is known to induce apoptosis by inhibiting mitochondrial DNA polymerase γ, reducing the content of mitochondrial DNA, and causing structural changes in mitochondria resulting in tubular injury [7]. In contrast, the free form of cisplatin is taken up by cells via organic anion transporter 2, OCT2, located on the basolateral side of proximal tubules, resulting in accumulation of free-type cisplatin within the renal tubular epithelial cells, which directly binds to DNA, leading to tubular cell damage and necrosis [8]. The mechanism of these renal impairments commonly involves the induction of apoptosis of renal tubular epithelial cells through mitochondrial damage, oxidative stress, and inflammatory cytokines. In the present cases, tubular dysfunction associated with these mechanisms probably occurred, but the detailed mechanisms remain unclear, and further investigation is necessary.

Interestingly, though magnesium (Mg) levels are typically low in Fanconi syndrome, in the present 2 patients, one of whom was taking magnesium oxide as a laxative, serum Mg levels were higher than the normal range. As a widely recognized fact, in cisplatin nephrotoxicity, Mg supplementation is considered an important therapeutic strategy due to the decrease of Mg associated with tubular damage related to Fanconi syndrome [9]. Mg is known to be reabsorbed not only in the proximal tubules, but also in the thick ascending limb and distal convoluted tubules [10]. Our experience suggests that the RYR supplement may cause more localized tubular injury. Therefore, it was hypothesized that these segments were working to compensate for the function of the proximal tubules and acute renal dysfunction, together leading to elevated levels of Mg, although this remains unknown.

In conclusion, the histopathological cause of renal impairment in patients affected by RYR supplements produced during a specific period was considered to be proximal tubular injury not accompanied by an immune reaction, but rather directly caused by tubular toxicity. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000540258).

Statement of Ethics

Ethical approval was not required for this study in accordance with local or national guidelines. Written, informed consent was obtained from the patients for publication of the details of their cases and any accompanying images.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

Kazuhiro T., Sayumi K., Yukihiro W., Emi S., Hideaki K., Akira S., and Yasuo T. designed the overall framework of the study, and Kazuhiro T., Sayumi K., Yukihiro W., Emi S., and Hideaki K. wrote the manuscript with input from all authors. Kazuhiro T., Sayumi K., Yukihiro W., Shun S., Tomomi M., Naohiro K., Hiroyuki O., Shokichi N., Togo A., and Yasuo T. directly treated the patient and performed the renal biopsy. Kazuhiro T., Emi S., Hideaki K., Togo A., and Akira S. mainly assessed the renal pathology. Togo A. mainly performed electron microscopy examination. All authors were responsible for implementation of the study, critically revised the report, commented on drafts of the manuscript, and approved the final report.

Data Availability Statement

All data generated or analyzed during this study are included in this published article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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