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CASE REPORT

Fanconi syndrome in an elderly patient with membranous nephropathy during treatment with the immunosuppressant mizoribine

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Abstract

We report on an 80-year-old man diagnosed with Fanconi syndrome induced by mizoribine after 4 weeks of administration to treat membranous nephropathy. Mizoribine is an oral immunosuppressant that inhibits inosine monophosphate dehydrogenase and is widely used in Japan for the treatment of autoimmune diseases and nephrotic syndrome, as well as after renal transplantation. Acquired Fanconi syndrome is often caused by drugs (antibacterial, antiviral, anticancer, and anticonvulsant drugs) and is sometimes caused by autoimmune diseases, monoclonal light chain-associated diseases, or heavy metal poisoning. In our patient, hypokalemia, hypophosphatemia, glucosuria, hypouricemia, and severe proteinuria resolved gradually after discontinuation of mizoribine administration, despite oral administration of prednisolone followed by a single intravenous injection of rituximab. The patient was ultimately diagnosed with Fanconi syndrome induced by mizoribine based on his clinical course and his typical laboratory data with the absence of proximal tubular acidosis. To our knowledge, this is the first report of Fanconi syndrome possibly induced by mizoribine. Although the precise mechanism by which mizoribine induces proximal tubular dysfunction is unknown, we suggest that nephrologists should be aware of the onset of Fanconi syndrome, a rare complication during mizoribine treatment.

Keywords Fanconi syndrome · Mizoribine · Nephrotic syndrome · Membranous nephropathy · Drug induced · Immunosuppressive drugs

Introduction

Fanconi syndrome (FS) is a generalized dysfunction of the proximal tubule [1], leading to hypophosphatemia, metabolic acidosis, glucosuria, aminoaciduria, and hypouricemia. FS occurs in both inherited and acquired forms. Acquired FS is caused by various conditions, including autoimmune disease (Sjögren syndrome) [2, 3], monoclonal light chain-associated diseases [4, 5], heavy metal exposure [6, 7], Chinese herbs [8], drugs (antibacterial, antiviral, anticancer, anticonvulsant and, rarely, immunosuppressive drugs) [9–13], coronavirus infection [14, 15] and tubulointerstitial nephritis with IgM-positive plasma cells (IgMPC-TIN) [16].

Mizoribine (MZR) is an oral immunosuppressant that selectively inhibits lymphocyte proliferation by inhibiting inosine monophosphate dehydrogenase in a de novo pathway [17]. MZR is widely used in Japan for the treatment of rheumatoid arthritis [18–20], systemic lupus erythematosus [21, 22], nephrotic syndrome (NS) [23, 24] and IgA nephropathy [25] as well as after renal transplantation [26], and is noted for its low incidence of side effects. In addition, several recent studies have shown that a combination of steroids and MZR is effective in patients with membranous nephropathy (MN) [27–29]. In this report, we describe the case of an elderly patient diagnosed with FS during MZR monotherapy prior to the addition of prednisolone for the treatment of MN.

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Case report

In August 2017, an 80-year-old man was referred to our hospital with FS, acute kidney injury (AKI), and severe proteinuria (15 g/gCr). He was diagnosed with hypertension 15 years earlier and was prescribed an angiotensin receptor blocker (ARB; azilsartan) and a calcium channel blocker. Several years earlier, he had been diagnosed with hyperuricemia, dyslipidemia, and diabetes mellitus, for which febuxostat and pitavastatin were prescribed. In June, 2 months before this admission, the patient was diagnosed with primary MN positive for the phospholipase A2 receptor (PLA2r) without involvement of light chain deposition disease based on the results of a renal biopsy; no FS was found at that time. Light microscopic examination of 24 glomeruli revealed two sclerotic, almost collapsing glomeruli and no crescent formation. The thickness of the glomerular basement membrane (GBM) was almost normal (Fig. 1A), without spike formation. A small area of tubular atrophy and interstitial fibrosis was observed (Fig. 1B, C). The arterioles and small arteries showed thickening. Electron microscopy revealed subepithelial deposits on the outer aspect of the GBM (Ehrenreich and Churg depiction; stage I) (Fig. 1D). Immunofluorescence microscopy revealed significant granular positivity for the IgG and phospholipase A2 receptor (Figs. 1E and F) and no obvious linear deposition of kappa and lambda along the tubular basement membrane (Figs. 1G and H). The patient and his wife chose outpatient treatment due to his mild age-related dementia. Oral administration of MZR (100 mg/day, Asahikasei Pharma Co.) was started before prednisolone administration, which was started in July. One month later, his serum creatine increased rapidly from 1.9 to 2.7 mg/dL with nephrotic proteinuria. Furthermore, serum albumin had decreased to 1.1 g/dL and various abnormalities in his laboratory data, including glucosuria, hypokalemia, hypophosphatemia, and hypouricemia, were confirmed. The patient had no history of exposure to heavy metals or administration of any other drug, including Chinese medicines.

When the patient was admitted to our hospital a few days later, he was 155 cm tall and weighed 55.6 kg. His blood pressure was 104/57 mmHg, his pulse rate was 93/min with sinus rhythm, and his body temperature was 36.4 °C. He had severe lower leg edema with other abnormal physical findings. Laboratory tests showed the following: serum total protein 5.5 g/dL, albumin 1.4 g/dL, blood urea nitrogen 23 mg/dL, creatinine 2.19 mg/dL, uric acid 2.1 mg/dL, sodium 143 mEq/L, potassium 3.1 mEq/L, chloride 109 mEq/L, calcium 7.4 mg/dL, inorganic phosphorus 2.6 mg/dL, estimated GFR 23.4 mL/min/1.73 m^2, LDL cholesterol 154 mg/dL and triglyceride 163 mg/dL. The results of the serological tests for hepatitis C and human immunodeficiency virus (HIV) antibodies were negative. Although antibodies against the surface and core antigens of hepatitis B were positive, hepatitis B DNA was not detected. Immunological tests, including antinuclear antibodies, rheumatoid factor, anti-DNA antibodies, anti-SS-A/SS-B antibodies, antineutrophil cytoplasmic antibodies, cryoglobulin, antistreptolysin O and M protein, were all within normal limits or negative. Serum C3 and C4 levels were within normal limits and serum complement activity (CH50) increased slightly at 53 (30–45) U/ml. Although not at the onset of FS, blood levels of MZR 5 days after discontinuation of oral administration were below the detection sensitivity (< 0.08 μg/mL). Urinalysis revealed obvious glucosuria (4 +), severe proteinuria (4 +) with oval fat bodies and various casts. The protein-to-creatinine ratio in urine and urine protein concentration for 24 h were 9.24 g/gCr and 16.4 g/day, respectively. Urinary beta2-microglobulin and *N*-acetyl-*β*-D-glucosaminidase were 61,368 (< 271) μg/L and 21.7 (< 11.5) U/L, respectively. Blood gas analysis did not show abnormalities. The fractional tubular reabsorption of phosphate decreased by 49% (60–90%) and urinary amino acids increased. Based on these findings, the patient was diagnosed with FS. These abnormal features of FS were not observed during his earlier admission or renal biopsy. A detailed description of the laboratory data of the patient at admission is shown in Table 1. A chest radiograph did not show cardiomegaly or pleural effusion, and his electrocardiogram did not show abnormalities.

Clinical course

Oral MZR administration was discontinued for this patient just before this admission. Instead, he was treated with daily oral administration of 30 mg of prednisolone (Fig. 2). After an additional single intravenous rituximab treatment (375 mg/m^2) on his 24th day of hospitalization, urinary protein began to gradually decrease and his hypouricemia, hypokalemia, glucosuria and hypophosphatemia improved. He was ultimately diagnosed with MZR-induced FS based on this clinical course and typical laboratory findings, except for the absence of proximal tubular acidosis (RTA). As oral prednisolone was reduced, the biochemical parameters remained within normal limits (Fig. 2). Furthermore, renal function gradually improved from Cr 2.19 to 1.66 mg/dL on his 59th day of hospitalization (Fig. 2). The patient was discharged on day 61.

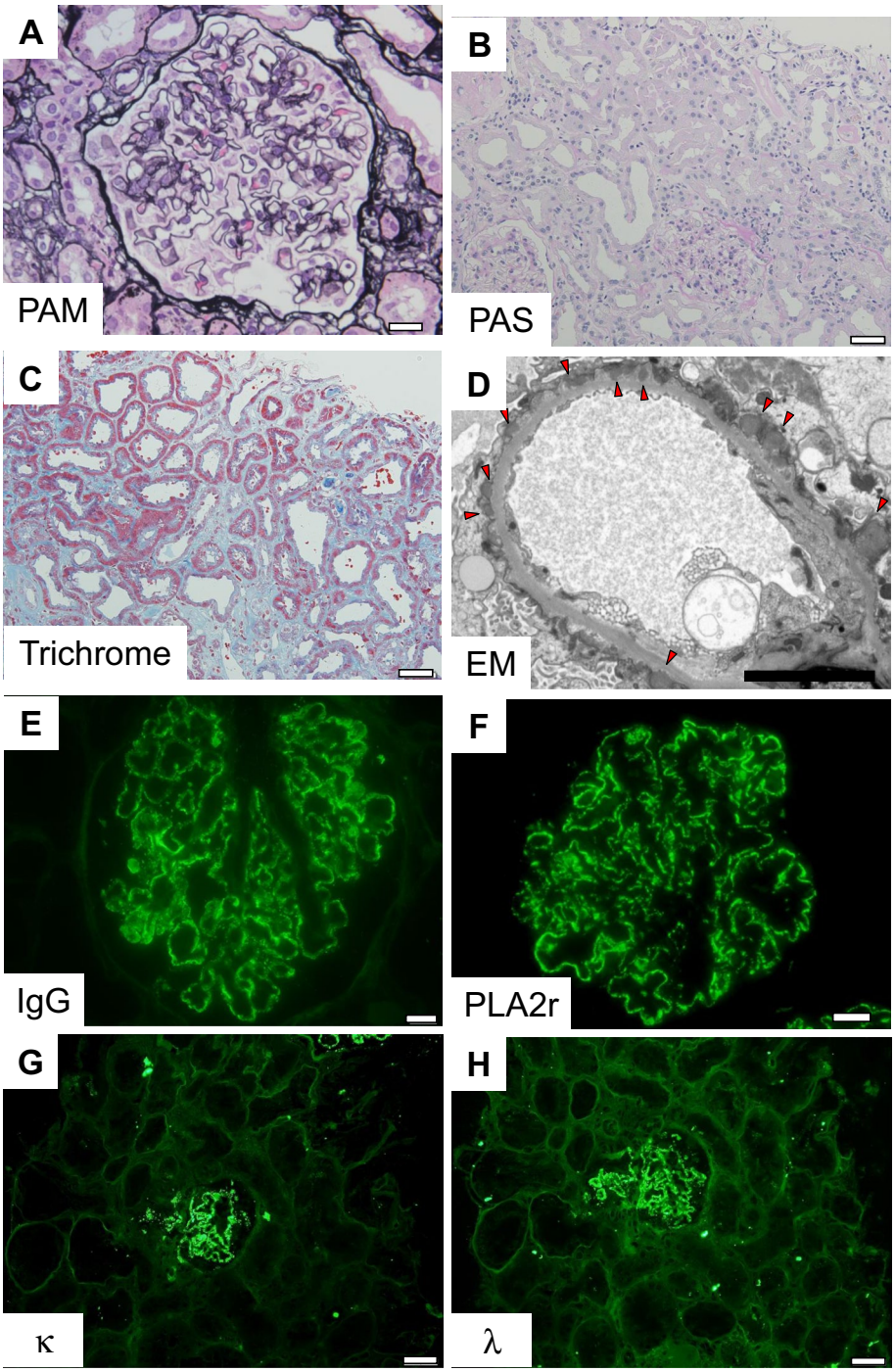

Fig. 1 Renal biopsy specimens. **A** Light microscopy shows a glomerular basement membrane (GBM) with normal thickness and no spike formation in (PAM). Bar = 20 µm. **B**, **C** A small area of tubular atrophy and interstitial fibrosis was observed (PAS and trichrome) Bar = 50 µm. **D** Electron microscopy revealed subepithelial deposits (red arrowheads) in the GBM (Ehrenreich and Churg; stage I). Bar = 5 µm. **E**–**H** Immunofluorescence microscopy revealed fine granular IgG (**E**) and phospholipase A2 receptor (PLA2r) (**F**) staining along the GBM (Bars = 20 µm) and no obvious linear deposition of kappa and lambda along the tubular basement membrane (**G**, **H**) (Bars = 50 µm)

Discussion

We made two important clinical observations with this patient: (1) immunosuppressive MZR can be a rare cause of acquired FS and (2) MZR-induced FS is not accompanied by proximal RTA.

Acquired FS is caused by various conditions, including Sjogren's syndrome (autoimmune disease) [2, 3] and IgMPC-TIN [16]; exposure to monoclonal light chain (light chain tubulopathy) [4, 5], heavy metals (heavy metal nephropathy) [6, 7] or Chinese herbs (aristolochic acid nephropathy) [8]; and drugs, including antibacterial agents (gentamicin [30]), antiviral agents (tenofovir [31, 32]), anticancer agents (cisplatin, ifosfamide) [33, 34], anticonvulsants [35] and rarely immunosuppressants (methotrexate and apremilast) [12, 13]; as well as coronavirus infection [14, 15]. In this patient, we suspected that FS was caused by MZR because he had no autoimmune disease, no serum or

Table 1 Laboratory data on admission

Complete blood count		
WBC	7600/μL	3300–8600
RBC	3.92×10^6/μL	$4.35–5.55\times10^6$
Hb	12.1 g/dL	13.7–16.8
Plt	42×10^4/μL	$15.8–34.8\times10^4$
Blood chemistry		
Na	143 mEq/L	138–145
K	3.1 mEq/L	3.6–4.8
Cl	109 mEq/L	101–108
Ca	7.4 mg/dL	8.8–10.1
IP	2.6 mg/dL	2.7–4.6
Cre	2.19 mg/dL	0.65–1.07
UN	23 mg/dL	8–20
UA	2.1 mg/dL	3.7–7.8
TP	5.5 g/dL	6.6–8.1
Alb	1.4 g/dL	4.1–5.1
AST	21 U/L	13–30
ALT	17 U/L	10–42
LD	253 U/L	124–222
LDLC	154 mg/dL	65–163
TG	163 mg/dL	40–234
CRP	0.35 mg/dL	0–0.14
BS	154 mg/dL	73–109
HbA1c	6.6%	4.9–6.0
eGFR	23.4 mL/min/1.73m^2	> 60
Serology		
C3	106 mg/dL	73–138
C4	30.6 mg/dL	11–31
CH50	53 U/mL	30–50
IgG	877 mg/dL	861–1747
IgA	425 mg/dL	93–393
IgM	113 mg/dL	33–183
ANA	< 40	< 40
MPO-ANCA	< 0.1 IU/mL	< 3.5
PR3-ANCA	< 0.1 IU/mL	< 3.5
Free light chain κ/λ ratio	2.014	0.248–1.804
M protein	(−)	(−)
HBs antigen	(−)	(−)
HBs antibody	(+)	(−)
HBc antibody	(−)	(−)
HBV-DNA	(−)	(−)
HCV antibody	(−)	(−)
HIV antibody	(−)	(−)
Venous gas analysis		
pH	7.365	
PCO_2	45.4 mmHg	
HCO_3^-	25.3 mEq/L	
BE	0.3 mEq/L	
Urinalysis		
pH	6.5	5.0–7.5
Protein	4 +	(−)
Occult blood	3 +	(−)
Sugar	4 +	(−)
Sediment		
WBC	< 1/HPF	
RBC	10–19/HPF dysmorphic	
Cast		
Hyaline	5 +	
Epithelial	1 +	
Granular	1 +	
Fatty	2 +	
Urinalysis chemistry		
U-Na	46 mEq/L	
U-K	52.4 mEq/L	
U-Cl	52 mEq/L	
U-IP	72 mg/dL	
U-Cr	119 mg/dL	
U-TP/Cr	9.24 g/gCr	< 0.14
NAG	21.7 U/L	1.3–6.1
B_2MG	61,368 μg/L	< 200
Bence-Jones protein	(−)	(−)
%TRP	49%	60–90
Selectivity index	0.44	

urinary monoclonal light chains upon immunofixation, no linear deposition of kappa or lambda light chains along the tubular basement membrane (Figs. 1G and H), no history of exposure to heavy metals or herbs, and no coronavirus infection. MZR was the only new drug that was started before the onset of FS. Furthermore, although this patient was treated with corticosteroids and intravenous rituximab, MZR withdrawal led to a gradual recovery of proximal tubular function (Fig. 2), increasing the likelihood of a diagnosis of FS due to MZR in this patient.

However, since there are no reports of FS during MZR therapy, which is widely used in Japan, it is more likely due to other factors, e.g., elevated MZR blood levels. Possible causes of elevated MZR blood levels include coexisting AKI due to nephrotic syndrome and interactions with other oral medications. Unfortunately, we were unable to prove elevated levels of blood MZR because our stored serum was 5 days after discontinuation of MZR. However, it is quite possible that the levels were abnormally high at the onset of FS in this patient.

Regarding drug interactions, this patient was taking Febuxostat, Piravastatin, Azilsartan, and Nifedipine in addition to MZR at the onset of FS, and the interaction between MZR and these drugs may have increased the concentration of MZR in the blood. The metabolic pathway of MZR in humans is not well understood, but when

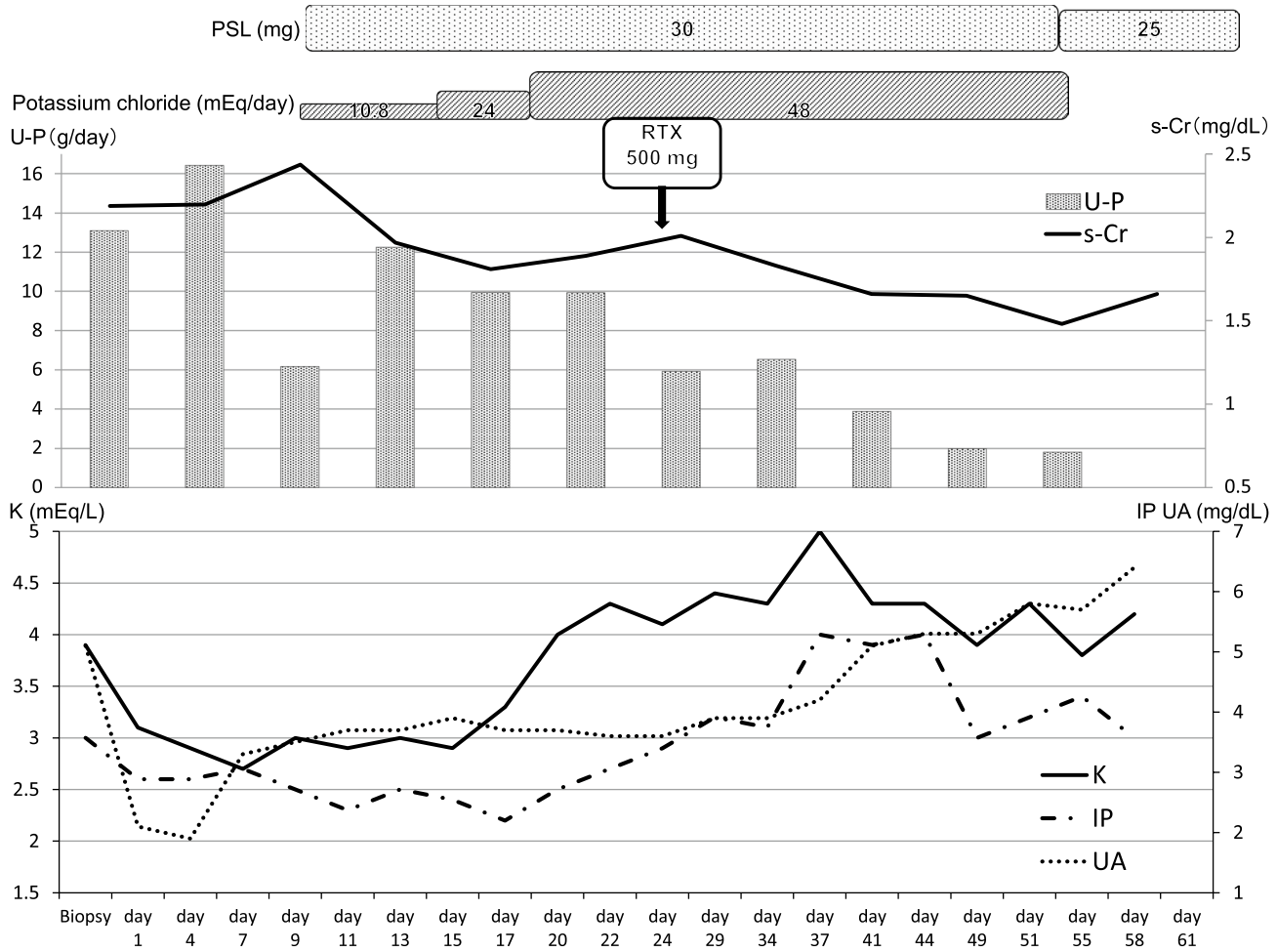

Fig. 2 Clinical course of the patient. After administration of prednisolone and rituximab, biochemical markers gradually improved. Hypokalemia, hypophosphatemia, and hypouricemia disappeared and proteinuria decreased. *PSL*, prednisolone; *s-Cr*, serum creatinine; *U-P*, urinary protein; *IP* inorganic phosphorus; *UA*, uric acid; *RTX*, rituximab

MZR was administered to rats, it was rapidly absorbed and reached maximum blood concentration in 1.5 h, and 85% of the dose was excreted unchanged in the urine within 24 h after administration [36], it appears to be poorly metabolized in the body. Similarly, the effect of human CYP450 enzymes on MZR metabolism has not been studied, but in rats, the activities of aminopyrine demethylase and aniline hydroxylase did not show significant changes in the MZR group compared to the control group. However, it cannot be ruled out that an unknown drug interaction between the concomitant drug above and MZR may have induced proximal tubular damage.

Generally, the proposed mechanisms that could potentially underlie drug-induced FS include (1) abnormal fluidity of the apical membrane, (2) impaired endocytosis and receptor recycling, (3) lysosomal dysfunction, (4) antioxidant glutathione depletion, (5) mitochondrial toxicity with decreased ATP synthesis, (6) inhibition of Na^+, K^+-ATPase and (7) back leakage of solutes through the paracellular pathway or through the apical membrane [10]. Immunosuppressant methotrexate (MTX) has been reported to inhibit ATIC transformylase and reduce inosine monophosphate and its downstream ATP production (supplementary Fig. 1) [37]. Intraperitoneal administration of MTX to rats induces FS that is reported to be caused by mitochondrial dysfunction with a decrease in ATP content. On the other hand, MZR is an inosine monophosphate dehydrogenase inhibitor, which in turn inhibits GMP and GTP production [17, 37]. Because MTX decreases both ATP and GMP production, as shown in supplementary Fig. 1, it may be that GMP depletion is involved in MTX-induced FS. Furthermore, GTP depletion has been identified as an important inducer of apoptosis after ischemic injury [38, 39]. In our patient, elevated blood levels of MZR may have induced GTP depletion and apoptosis within the proximal tubules. Because we did not perform a second renal biopsy at the beginning of FS, we cannot

be sure whether necrosis, apoptosis, or tubulitis [16] of the proximal tubules had occurred, which is a limitation of this report. Although we have presented several possibilities, the precise molecular mechanism underlying MZR-induced FS in this patient remains unknown.

FS is generally characterized by pan-proximal tubular dysfunction and is therefore often complicated by proximal RTA. However, FS with or without RTA has been reported, depending on the associated drug [40]. Our observation with this patient suggests that MZR, like ifosfamide, is responsible for FS without RTA. Furthermore, differences in the segment of proximal tubule damage caused by MZR may also explain why only RTA does not appear. Generally, proximal RTA is thought to be caused by loss of function of the Na^+/H^+ exchanger (NHE3) or the Na^+, HCO_3^--cotransporter (NBCe1). NHE3 is located in the apical membrane of all proximal tubular segments, extending from the S1 and S2 segments (convoluted tubule) to the S3 segment [41]. In the S1 and S2 segments of the proximal tubulus, NHE3 contributes to the reabsorption of Na^+, water, and bicarbonate, while in the S3 segment, it is important for the reabsorption of Na^+, Cl^- and water without significant relevance to bicarbonate titration. On the other hand, NBCe1 is also located in the convoluted proximal tubule [42]. In other words, if MZR-induced proximal tubular damage occurs mainly in the S3 segment, it is assumed that FS without RTA can develop. In the future, a large number of cases will be needed to determine whether the absence of RTA is a characteristic feature of MZR-induced FS.

To our knowledge, this is the first report to demonstrate MZR-induced FS. Given these findings, we suggest that nephrologists should be aware of possibility, although rare, of the onset of FS during MZR treatment.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13730-022-00715-0.

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Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki of 1964 and its subsequent amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient described in this case report.

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