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Case Report

Tubulointerstitial Nephritis Complicated by Fanconi Syndrome and Renal Tubular Acidosis Associated with three autoimmune diseases

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A 45-year-old woman experiencing back pain showed signs of metabolic acidosis and electrolyte imbalances. The results of blood and urine tests indicated Fanconi syndrome and renal tubular acidosis. An x-ray showed vertebral fractures, which were thought to responsible for the back pain. In addition, the patient had proteinuria and renal dysfunction; therefore, renal biopsy was performed, and tubulointerstitial nephritis (TIN) was diagnosed. While investigating TIN, primary biliary cirrhosis and Sjögren's syndrome were also detected. She had been previously diagnosed with chronic thyroiditis. We report a rare case of TIN and 3 autoimmune disorders with review of literature.

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Key words: tubulointerstitial nephritis, primary biliary cirrhosis, Sjögren's syndrome, Fanconi syndrome, renal tubular acidosis

Introduction

Tubulointerstitial nephritis (TIN) either causes acute kidney injury, chronic kidney disease and various symptoms. TIN is most often induced by drugs; however, in other cases, it can be associated with infections or autoimmune disorders (1). Although one autoimmune disorder, such as Sjögren's syndrome (SS) or primary biliary cirrhosis (PBC), complicates TIN in most cases, the case that shows more than 2 autoimmune disorders with TIN is rare. Previously, Takahashi et al. reported the case of a patient with TIN associated with SS and PBC (2). However, to our knowledge, there are no reports of TIN associated with more than 3 autoimmune disorders.

In this report, we describe a case of TIN with Fanconi syndrome and renal tubular acidosis (RTA). As the underlying diseases for TIN, PBC and SS were newly diagnosed, and the patient was previously diagnosed with chronic thyroiditis. This is a rare case of TIN associated with 3 autoimmune disorders (i.e., PBC, SS, and chronic thyroiditis). Furthermore, we also briefly review the cases of TIN with Fanconi syndrome and RTA complicated by PBC, which

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have a course similar to our case.

Case Report

A 45-year-old woman with back pain was referred to our nephrology department. The patient had iron-deficiency anemia and chronic thyroiditis with a positive reaction for microsome test and nearly normal thyroid function for about 10 years. Several months before consultation with our hospital, she began to have back pain. She visited an orthopedic specialist, but spine *x*-ray examinations were normal. Concurrently, she was diagnosed with hypokalemia and proteinuria at a routine medical examination. Therefore, she was referred to our department for further examination.

On the first visit, the patient's height was 157.2 cm and body weight was 52.3 kg. Her blood pressure was 128/73 mmHg, and her thyroid was enlarged and soft but not painful. The breath sounds were normal, and heart sounds were normal with no murmur. The abdomen was soft and flat with no tenderness or mass. There was no pretibial edema. Relevant biological data at referral are listed in Table 1. Fanconi syndrome was suspected due to the presence of metabolic acidosis, hypokalemia, hypouricemia, hypophosphatemia, glycosuria, and panaminoaciduria. In addition, hyperchloremic metabolic acidosis, urine positive anion gap, and elevated urine pH suggested distal renal tubular acidosis. The fractional tubular reabsorption of phosphorus was slightly decreased at 77.6% (normal range, 81-90%), and maximal tubular reabsorption of phosphorus per glomerular filtration rate (Tmp/GFR) was 1.23 (normal range, 2.8-4.4). These results suggested the impairment of phosphorus reabsorption in the proximal tubule. Furthermore, elevated levels of urinary β_2-microglobulin and *N*-acetyl-β-D-glucosaminidase indicated tubulointerstitial injury. She also had moderate renal insufficiency (estimated GFR 52.05 mL/min/1.73 m^2) and a higher level of proteinuria (1.3 g/gCr) than expected for only tubulointerstitial injury. Although the patient tested positive for glycosuria, her blood levels of glucose and hemoglobin A1c were normal. Abnormal liver function was found with high alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (γ-GTP). Antinuclear antibody (ANA) was 320 fold and ANA pattern was homogenous.

To examine the cause of renal dysfunction and proteinuria, a renal biopsy was performed. Light microscopic findings showed severe TIN characterized by lymphocytic infiltration in the interstitium (Figure 1a). Tubular atrophy was remarkable, and vacuolar change and detachment of epithelial cells were visible. There was no finding of interstitial macrophage infiltration and tubular cell hyperplasia which were shown in hypokalemia nephropathy (3). Most glom-

Table 1. Patient's characteristics

<Peripheral blood>		<Immunological findings>		<Blood gas (vein)>	
White blood cell	5100/μL	Anti-nuclear antibody	320fold	pH	7.34
Red blood cell	$489\times10^4/\mu$L	(homogenous pattern)		pCO_2	36.1mmHg
Hemoglobin	9.0 g/dL	Anti-ss DNA antibody	33.0 IU/mL	HCO_3	18.7mmol/L
Platelet	$37.1\times10^4/\mu$L	Anti-ds DNA antibody	1.2IU/mL	BE	-6.0
<Serum chemistry>		Anti-Ro/SS-A antibody	0.5		
Na	140mEq/L	Anti-La/SS-B antibody	1.1	<Urialysis>	
K	2.9mEq/L	Anti-M2 antibody	95	pH	8.0
Cl	112mEq/L	C3	84.3mg/dL	U-P/U-Cr	1.3g/gCr
Ca	9.2mg/dL	C4	19.1mg/dL	Glucose	(3+)
P	2.5mg/dL	IgG	1750mg/dL	Red blood cell	1~2/HPF
Blood urea nitrogen	14mg/dL	IgG4	<3.0mg/dL	Tubular epithelial cell	1~2/HPF
Creatinine	0.93mg/dL	IgM	614mg/dL	Granular cast	5~10/WF
eGFR	52.05mL/min/1.73m^2	IgA	273mg/dL	U-NAG	35.8IU/L
Uric acid	1.6mg/dL			U-β_2-MG	80728μg/L
Total protein	8.2g/dL	<Thyroid function>		Pan-aminoaciduria	(+)
Albumin	4.3g/dL	FT3	2.95ng/dL	%TRP	77.6
Aspartate aminotransferase	25IU/L	FT4	0.77ng/dL		
Alanine aminotransferase	27IU/L	TSH	4.85mg/dL		
Alkaline phosphatase	583IU/L				
Total-bilirubin	0.4mg/dL				
γ-glutamyltransferase	77IU/L				
Fasting blood sugar	92mg/dL				

Anti-ss DNA antibody: anti-single stranded DNA antibody, Anti-ds DNA antibody: anti-double stranded DNA antibody, Anti-M2 antibody: Anti-mitochondrial M2 antibody, eGFR : estimated glomerular filtration rate, FT3: free triiodothyronine, FT4: free thyroxine, TSH: thyroid stimulating hormone, U-P/U-Cr: urine protein/urine creatinine, U-NAG: urine N-acetyl-β-D-glucosaminidase, Urine β_2-MG: urine β_2-microglobulin, %TRP: the fractional tubular reabsorption of phosphorus

eruli were normal, and 2 sclerotic glomeruli were observed in 14 obtained glomeruli. Immunofluorescence staining for immunoglobulin and complement was negative. Based on these results, TIN, not glomerulonephritis, was considered to cause renal dysfunction, and the cause of proteinuria was considered to be derived from renal tubules.

Regarding the cause, there was no possibility of drug-induced TIN, since no drugs had been prescribed. From the high ALP, γ-GTP, and serum IgM levels, we suspected PBC as an underlying disease. Testing for antimitochondrial M2 antibody was positive. Liver biopsy was performed to diagnose PBC, and the findings revealed portal inflammation with epithelioid cells (Figure 1b). Therefore, the patient was diagnosed with PBC at stage 1.

In addition, we performed detailed examination for SS, which is associated strong with TIN, although she had no clinical manifestation of SS, such as dry eye or dry mouth. First, the patient was diagnosed with keratoconjunctivitis sicca at an ophthalmological clinic. Although anti-SSA and SSB antibodies were negative, Schirmer's test and Saxon test were positive, and a lip biopsy showed lymphocytic infiltration around the salivary glands with focus score 3 (Figure 1c). Finally, she was diagnosed with SS, based on the revised Japanese Ministry of Health criteria for the diagnosis of SS (1999) and American College of Rheumatology Classification Criteria for Sjögren's Syndrome (4, 5).

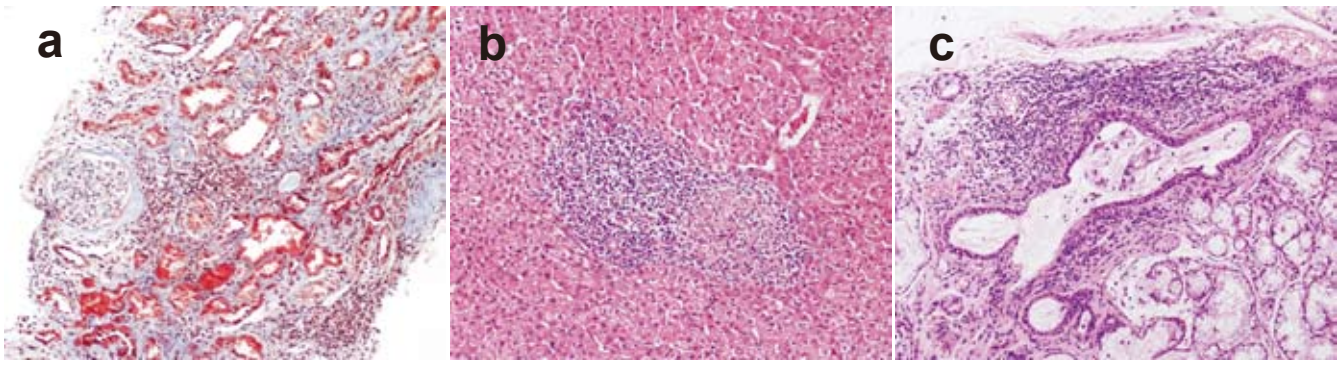

Figure 1. (a) Light microscopic findings of a renal biopsy (Masson's trichrome staining, x100). Lymphocytic infiltration in the interstitium and tubular atrophy were observed. (b) Light microscopic findings of a liver biopsy (hematoxylin eosin (HE) staining, x100). The findings revealed portal inflammation with epitheloid cells. (c) Light microscopic findings of a lip biopsy (HE staining, x100). Lymphocytic infiltration was observed around the salivary glands.

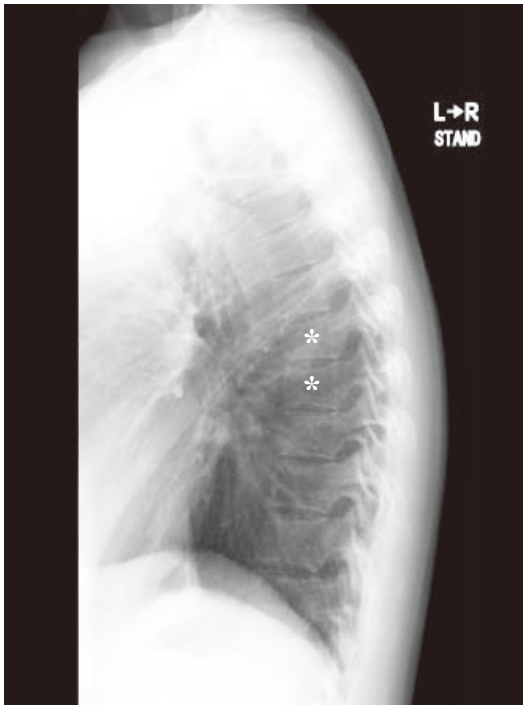

Figure 2. A spine *x*-ray scan. A spine *x*-ray scan showed vertebral fractures of Th7 and Th8 (white asterisks).

When we investigated the cause of her back pain, a spine *x*-ray scan showed vertebral fractures of Th7 and Th8 (Figure 2), although bone mineral density (BMD) was normal. We suspected that her back pain resulted from these vertebral fractures.

Based on these findings, she was newly diagnosed with TIN, PBC, and SS complicated by RTA and Fanconi syndrome, in addition to the previously diagnosed chronic thyroiditis.

For RTA and hypokalemia, she was treated with orally administered sodium bicarbonate (1.5 g/day), potassium citrate/sodium citrate (3 g/day), and potassium l-aspartate (600 mg/day). In addition, she was started on glucocorticoid therapy (20 mg/day of prednisolone orally) for TIN. She was also administered ursodeoxycholic acid for PBC. As prevention for osteoporosis induced by prednisolone and PBC, oral vitamin D (0.25 μg/day of calcitriol) and bisphosphonate were started. One year after beginning steroid therapy, serum creatinine slightly decreased to 0.86 mg/dL, and proteinuria and urinary β_2-microglobulin markedly decreased

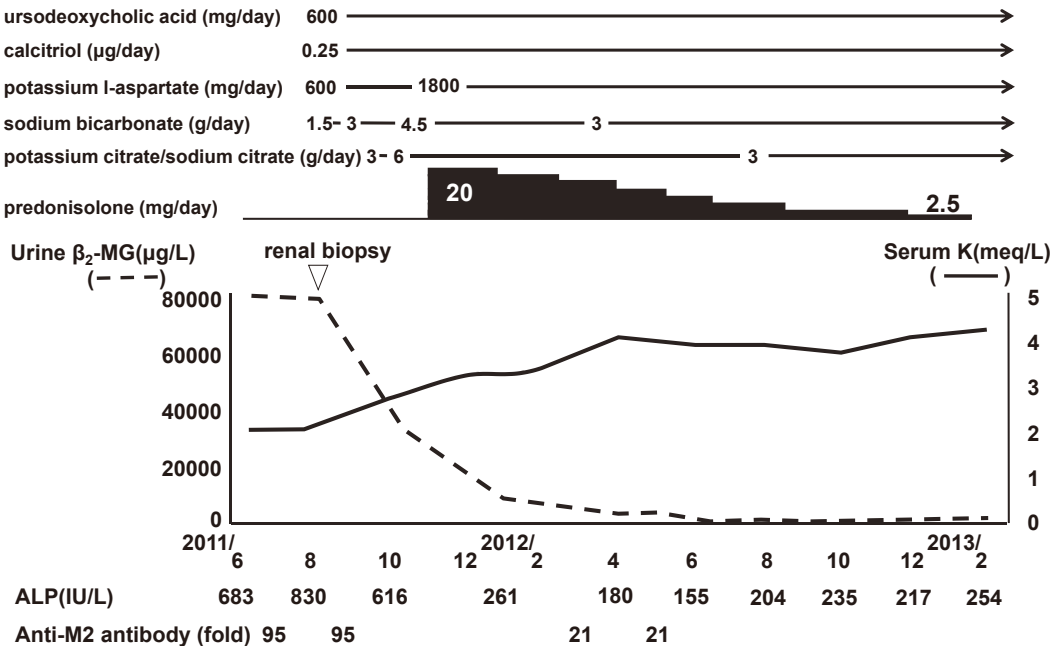

Figure 3. Clinical courses. ALP: alkaline phosphatase, Urine β_2-MG: urine β_2-microglobulin, Anti-M2 antibody: antimitochondrial M2 antibody

to 0.10 g/gCr and 2659 mg/dL. Venous blood gas analysis revealed pH 7.353, pCO_2 42.8 mmHg, and bicarbonate 23.2 mmol/L. Serum potassium was 4.0 mEq/L. Serum ALP, γ-GTP, and the titer of anti-mitochondrial M2 antibody also decreased within the normal range (Figure 3).

Discussion

In this case, TIN complicated by Fanconi syndrome and RTA was discovered with a chief complaint of back pain, and it was associated with 3 autoimmune disorders (i.e., PBC, SS, and chronic thyroiditis).

Regarding the association of a single autoimmune disorder and TIN, TIN has been known to be complicated in more than 50% cases of SS (6). Meanwhile, PBC has rarely been reported in association with TIN, but TIN is an important complication of PBC as extrahepatic disorders (Table 2) (7). Furthermore, only a single case has been reported of TIN occurring along with chronic thyroiditis (8). To date, there is only one report on the case with 2 autoimmune disorders (PBC and SS) complicating TIN (2). Therefore, as far as we know, our case is the first report of a patient with 3 autoimmune disorders complicating TIN.

Histological characteristics of TIN associated with SS reveal focal or diffuse lymphocytic infiltration, predominantly CD4-positive T cells, in the interstitial tissue (4). Although it is unknown why TIN tends to be associated with SS, it is reported that lymphocytic infiltration is induced by autoantigens, and TIN develops in SS (9). On the other hand,

Table 2. Previous reported cases of TIN in patients with PBC

Age	Sex	s-Cr (mg/dl)	Ccr (ml/min)	IgM	SjS	FS	RTA	M2A	Tx	References
50	F	1.96	32	630	-	-	-	ND	PSL, KCl, NaCl	[19]
58	F	2	25	ND	+	-	D	ND	PSL, KCl	[20]
36	F	0.8	84	1260	-	+	M	-	-	[21]
51	F	1.4	32	ND	-	+	D	800	PSL, VitD	[10]
68	F	1.35	41	ND	-	+	D	640	PSL, KCl, VitD	[10]
39	F	0.85	55.8	1040	+	+	D	30.9	PSL	[2]
44	F	0.93	52.1	614	+	+	D	95	PSL, KCl, VitD	This case

D: distal type, FS: Fanconi syndrome, F: female, M: mixed type, M2A: anti-M2 antibody, ND: No Date, PSL: predonisolone, RTA: renal tubular acidosis, SjS: Sjogren's syndrome, Tx: treatment

the clinical features in cases of TIN complicated with PBC are reported that serum IgM was high, and the infiltrating cells in the interstitium were composed of IgM-positive plasmacytoid lymphocytes immunohistochemically (2). Recently, Iwakura et al. reported that the electron-microscopic findings showed various sized and shaped mitochondria with irregular cristae and some lucent matrices in proximal tubules of patient with TIN and PBC (10). Regarding the pathogenesis of TIN associated with PBC, Lino et al. suggested that abnormal antigen expression, such as mitochondrial antigen, which is the cause of PBC, may occur in renal tubular cells and lead to infiltration of the renal interstitium by autoreactive T cells (11). Meanwhile, the mechanism that TIN is complicated with chronic thyroiditis is unclear. In our case, renal biopsy showed diffuse lymphocytic infiltration in the interstitial tissue with high levels of serum IgM. However, the infiltrating lymphocytes did not appear to be plasmacytoid cells morphologically in the interstitium. In addition, electron-microscopic findings showed no mitochondrial alternation in proximal tubules as reported previously (10). We could not examine whether the infiltrating cells were positive for IgM, which is reported to be characteristic of PBC-related TIN. Therefore, it is difficult to identify which autoimmune disease caused TIN dominantly.

In our case, Fanconi syndrome and RTA were first discovered by back pain, and subsequently, TIN and the other autoimmune diseases were found. Distal RTA is associated with more than 30% of cases and less commonly with proximal RTA (Fanconi syndrome) in SS (12, 13). Meanwhile, the cases of TIN with PBC showed high comorbidity rate with Fanconi syndrome or RTA, although TIN is a rare complication of PBC (2). In the cases of TIN with PBC as far as we checked, 4 of 6 cases had Fanconi syndrome and 5 of 6 cases had distal or mixed (distal and proximal) type RTA (Table 2). Thus, we should consider autoimmune disorders as underlying diseases when Fanconi syndrome and RTA are diagnosed. In the present case, PBC might be dominantly involved in the pathogenesis of Fanconi syndrome and RTA, considering the comorbidity rate.

As an etiology of back pain, which was the chief complaint in this case, we suspected that it resulted from the vertebral fractures found on *x*-ray scan. Both Fanconi syndrome and RTA are known to cause osteomalacia by renal phosphate wasting and increased calcium loss due to metabolic acidosis (14, 15). Osteomalacia easily leads to pathological fracture and often produces pain in bones where fractures have occurred. In patients diagnosed with Fanconi syndrome, most chief complaints have been reported to be bone pain, as in our case, followed by fatigue and asymptomatic renal insufficiency (16). Although the definitive diagnosis for osteomalacia could not be established in our case because bone biopsy was not performed, it is possible that vertebral fractures resulted from osteomalacia by Fanconi syndrome and RTA. Meanwhile, osteoporosis is a characteristic bone disorder in PBC, and it often causes bone fracture (17). Although the patient showed BMD within the normal range at the beginning of therapy, we started oral vitamin D and bisphosphonate to prevent new bone fractures. Furthermore, we needed to be cautious about the development of secondary osteoporosis by glucocorticoid therapy and PBC, examining BMD routinely during therapy.

Finally, oral prednisolone was started as a treatment for TIN and was effective in decreasing proteinuria and urinary β_2-microglobulin in our case. For SS patients, glucocorticoids are generally administered for the treatment of severe manifestations, such as cutaneous or neurologic lesion, vasculitis and TIN (18). On the other hand, glucocorticoid therapy is not considered to be effective in PBC because of adverse effects, including osteoporosis (19). However, glucocorticoids were often used for the treatment of patients with TIN associated with PBC as far as we searched (Table 2), although the effect has not been certain (2, 11, 20-22). Dhanda et al. recently reported that lymphocytes in patients with PBC were sensitive to glucocorticoid *in vitro* (23). In this case, since serum ALP, γ-GTP, and the titer of antimitochondrial M2 antibody also decreased after the initiation of glucocorticoid therapy and ursodeoxycholic acid, glucocorticoid therapy might be effective for not only TIN but also PBC.

In summary, we reported a case of TIN with Fanconi syndrome and RTA, which was associated with 3 autoimmune diseases. In cases of patients who complain of bone pain, we should remember Fanconi syndrome or RTA as a cause of this symptom and consider autoimmune disorders, including PBC or SS, as underlying diseases. Furthermore, we need to explore the possibility that multiple autoimmune diseases can exist simultaneously.

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