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Slowly progressive chronic kidney disease caused by tubulointerstitial nephritis in a patient with primary biliary cholangitis

ABSTRACT

Tubulointerstitial nephritis is a rare complication of primary biliary cholangitis. The most typical presentation is progressive renal disease, and a substantial number of patients have renal tubular acidosis and mild proteinuria. Treatment with steroids is effective, but there are no precise recommendations concerning doses and the duration of therapy.
This article presents a case of a 41-year-old woman with primary biliary cholangitis and slowly progressive chronic kidney disease. Renal tubular acidosis and very high urinary β2 microglobulin excretion but no albuminuria were observed. A kidney biopsy revealed a diffuse interstitial inflammatory infiltrate in both cortex and medulla, dominated by T lymphocytes and macrophages, less numerous B lymphocytes, neutrophils, and eosinophils.
After initiation of steroids, a rapid 10-fold decrease in β2 microglobulin urine excretion and a mild decrease in serum creatinine were observed.
This case shows how mildly symptomatic tubulointerstitial nephritis is in a patient with primary biliary cholangitis. The authors emphasize the importance and crucial role of kidney biopsy.

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Key words: immune-mediated tubulointerstitial nephritis, low molecular weight proteinuria, renal tubular acidosis

INTRODUCTION

Secondary nephropathies constitute a diverse group of disorders. The most common and best known are glomerulopathies related to metabolic (e.g. diabetic nephropathy, renal amyloidosis) and autoimmune diseases (e.g. lupus nephritis, small vessels vasculitis). The kidneys may also be involved in many other diseases — genetic, infectious, vascular, or intoxications. The most vulnerable are glomeruli, therefore, symptoms and signs of glomerulopathies are the best known and arouse most vigilance. The secondary tubulointerstitial involvement can be present in autoimmune diseases with or without glomerulopathies. Chronic tubulointerstitial nephritis (TIN) is associated with a variety of disorders: Sjögren syndrome, sarcoidosis, systemic lupus erythematosus, inflammatory bowel disease, primary biliary cholangitis, anti-tubular basement membrane disease, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, chronic rejection of kidney transplant, and others [1–4].

Tubulointerstitial nephritis is the most typical, although extremely rare, renal manifestation of primary biliary cholangitis (PBC) [5]. The number of cases of biopsy-proven TIN in PBC that has been reported so far is low [3]. The first case was described in 1987 by Macdougall [4]. In 2010, Komatsuda et al. analyzed almost 6000 renal biopsies and found only 4 cases of TIN related to PBC [3]. In 2018, Mizoguchi analyzed 16 cases and presented essential information about the clinical presentation, diagnosis, and treatment of this nephropathy [6].

TIN is most often diagnosed in patients with a previous history of PBC, but in a few cases, nephropathy was diagnosed first, followed by a diagnosis of PBC [4, 7]. Family history is important, as progressive chronic kid-

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ney disease (CKD) due to TIN was reported in two family members (mother and daughter) [5]. All patients described in the medical literature were females [3–10].

Other nephropathies have rarely been diagnosed in patients with PBC. The cases of membranous nephropathy and microscopic polyangiitis in patients with PBC were described with the suggestion that these diseases might share a common pathogenesis [5, 11].

Herein, we present a case of progressive chronic kidney disease in a patient with asymptomatic PBC.

CASE REPORT

In 2021, a 41-year-old female with a history of PBC was observed in the outpatient nephrology clinic due to an increased creatinine level. She had no abnormalities in urinalysis and no changes in renal ultrasound.

PBC was diagnosed in 2014 by a liver biopsy. At that time, the patient complained of weakness but had no pruritus. Typical laboratory abnormalities were present: anemia, elevated erythrocyte sedimentation rate, and high alkaline phosphatase level. In immunological tests, increased IgM, positive anti-nuclear antibodies (ANA), and anti-mitochondrial antibodies (AMA) were present (Tab. 1). The treatment with ursodeoxycholic acid was initiated, but the patient was taking this drug irregularly.

In 2016, the patient gave birth to a healthy child, and in 2017 for the first time, a mild increase in creatinine level (1.17 mg/dL) was found. There were no changes in urinalysis except for low urine specific gravity of 1005––1010. Urine pH was 6.5–7.0. Biochemical tests did not show any electrolyte abnormalities. Slow progression of kidney disease was observed in the next years. In March 2021, eGFR Cr was 37 and eGFR Cys-C 44 mL/min.

In June 2021, the patient was in good state, without pruritus or any gastrointestinal symptoms. She had no skin changes, Raynaud syndrome, joint pains, or any sickness symptoms. She had polyuria of 3–3.5 L/day and did not complain of dysuria. To exclude other conditions than PBC and autoimmune disease, additional immunological tests were performed (Tab. 1).

Family history revealed that the patient's mother also had PBC and her aunt (mother's sister) had rheumatoid arthritis, but both without renal involvement.

In the physical examination, there were no edema, jaundice, or skin abnormalities. Blood pressure was 107/67–110/70 mmHg, heart rate 74–83 betas/min, and weight 57.3 kg.

Table. 1. Immunological tests

Year	Measurements
2014	Elevated IgM: 10.83 g/L Positive AMA and ANA (1:320)
2020	Positive ANA index: 6.7 Normal complement components C3 111.67 mg/dL and C4 18.57 mg/dL Normal serum protein electrophoresis
2021	Elevated IgM 9.66 g/L Positive AMA and ANA (1:320) ANA immunoblot: positive AMA M2 (+++) Negative rheumatoid factor (< 20.0 IU/mL) Negative SSA (Ro) and SSB (La) Negative anti-centromere antibody (< 1: 80) Normal IgG1 6.35 g/L; IgG2 3.39 g/L; IgG3 1.96 g/L and IgG4 0.31 g/L

AMA — anti-mitochondrial antibodies, ANA — anti-nuclear antibodies

The biochemical examination revealed elevated serum creatinine (1.64/mg/dL), metabolic acidosis, and increased urinary beta-2-microglobulin excretion (8.29 mg/L, 30.28 mg/24 h). Albuminuria was repeated several times and was always below 5 mg/L.

TUBULOPATHY

The patient had hyperchloremic metabolic acidosis (pH 7.3, HCO3 16.9 mmol/L, Cl 111 mmol/L). Normal urine pH 7 suggested distal renal tubular acidosis (dRTA). An acidification test with furosemide (40 mg) and fludrocortisone (1 mg) was performed [12]. In urine taken after 2 hours, pH decreased to 5. The urine anion gap decreased and after 6 hours was negative, which is typical of increased ammonium ion excretion. Both these results excluded dRTA and suggested proximal RTA (pRTA).

Fractional excretion of bicarbonate after sodium bicarbonate loading was not performed. Isolated pRTA was observed without other signs of Fanconi syndrome, as the patient had no glucosuria or hypophosphatemia. She had no serum electrolyte abnormalities and no changes in urinary electrolytes excretion: FeK was 19.7%; FeNa was 1.7%; FePO4 was 0.211%, and the uCa/uCr ratio was 0.17g/g (Tab. 2).

KIDNEY BIOPSY

In September 2021, a kidney biopsy was performed and revealed a diffuse interstitial inflammatory infiltrate in both cortex and medulla, dominated by T lymphocytes and macrophages, less numerous B lymphocytes, neu-

Table. 2. Urine acidification test with furosemide and fludrocortisone

Value	03.08.2021	24.09.2021						
		8:30	9:30	10:30	11:30	12:30	13:30	14:30
Urine pH	7	7	7	5	6.5	6.5	6	6.5
UAG	+ 6.7	n/a	n/a	n/a	+2.4	n/a	n/a	–6.7
Blood pH	7.3	7.323	n/a	n/a	n/a	n/a	n/a	7.37
Blood HCO_3	16.9	16.9	n/a	n/a	n/a	n/a	n/a	18.2

UAG — urine anion gap, n/a — not available

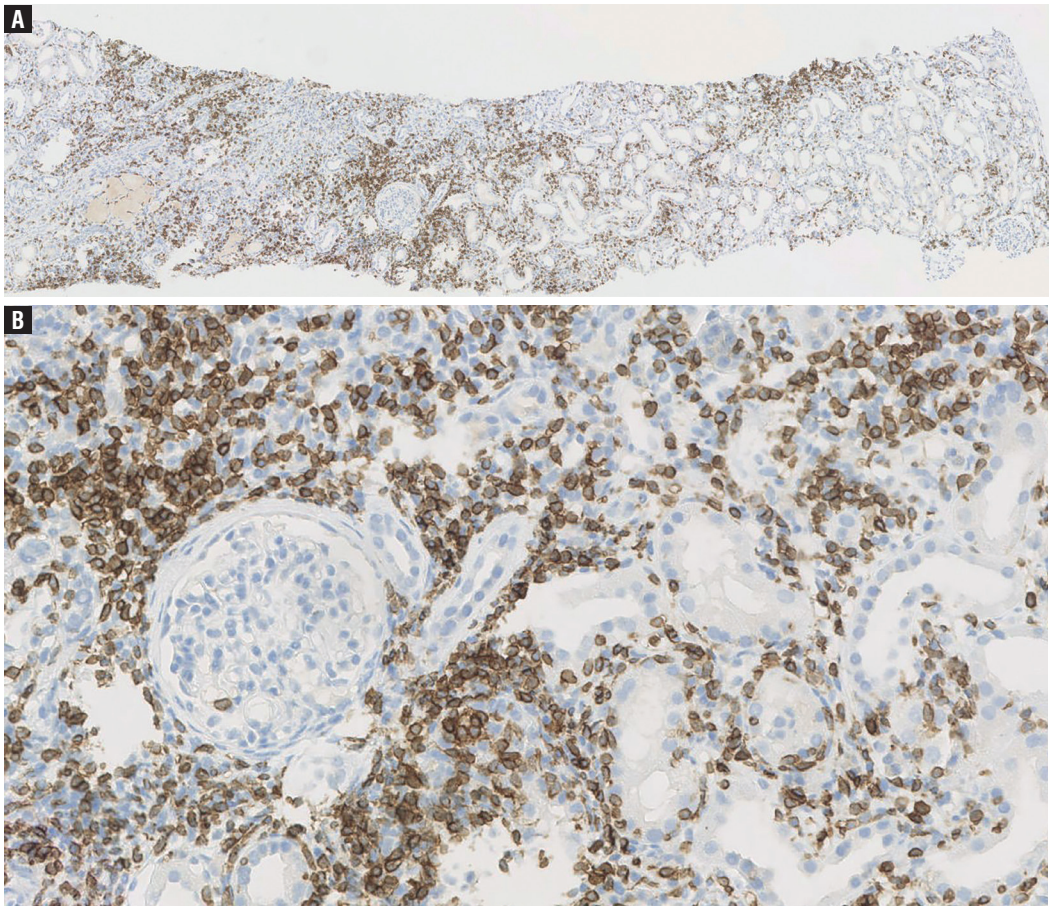

Figure 1. Kidney biopsy. Diffuse interstitial inflammatory infiltrate in both cortex and medulla, dominated by T lymphocytes (CD3+). **A.** Lower magnification. **B.** Higher magnifiation

trophils, and eosinophils (Figs. 1–3). There was no inflammation within the tubular epithelium, only morphologically mild epithelial injury manifested by focal loss of a brush border and epithelial flattening. There was no interstitial fibrosis and only mild focal tubular basement membrane thickening reflecting an early phase of tubular atrophy.

DIAGNOSIS, TREATMENT, AND FOLLOW UP

Finally, tubulointerstitial nephritis related to PBC was diagnosed. Treatment with steroids was initiated in September 2021 at a dose equivalent to 40 mg of prednisone (methylprednisolone 32 mg). The patient also received 1.0 g of sodium bicarbonate, 600 mg of potassium chloride, pantoprazole, and ursodeoxycholic acid.

During the next three months, a mild decrease in creatinine and a rapid 10-fold decrease in beta-2-microglobulinuria (β2m) were observed. Steroid doses were tapered to 8 mg (Tab. 3 and Fig. 4).

DISCUSSION

The case of nephritis secondary to PBC presented here is interesting for several reasons. The patient had no classical indications

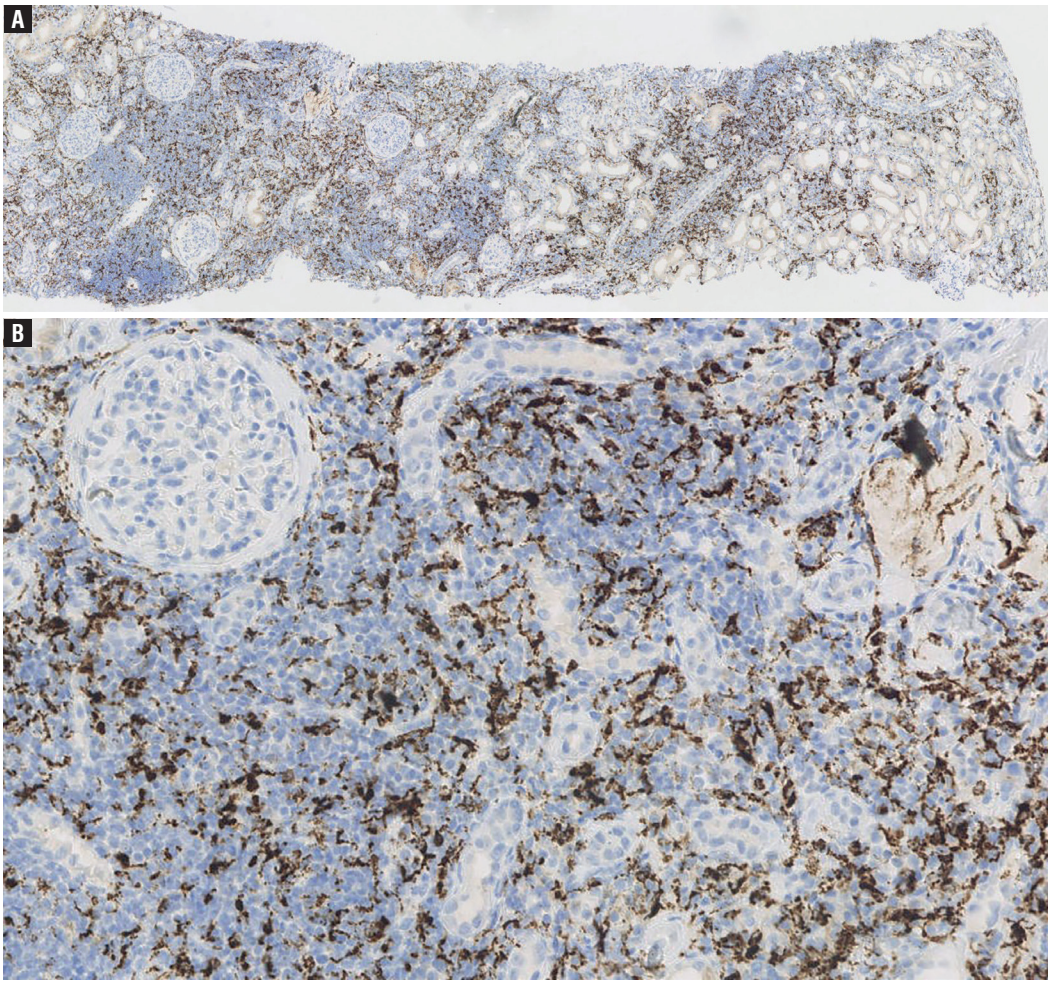

Figure 2. Kidney biopsy. Diffuse interstitial inflammatory infiltrate in both cortex and medulla by macrophages (CD 68+). **A.** Lower magnification. **B.** Higher magnification

for kidney biopsy, and the only changes concerning kidney function were a mild increase in creatinine, high urine β2m excretion, and renal tubular acidosis. All these issues are briefly discussed below.

PBC

Primary biliary cholangitis (PBC), previously known as primary biliary cirrhosis, is an immune-mediated chronic cholestatic liver disease, characterized by the presence of AMA antibodies [5, 8]. Extra-hepatic autoimmune disorders arise in 60–70% of patients with PBC [8, 13].

The most common comorbidities of PBC are Sjögren syndrome, observed in 30% of patients, followed by Raynaud's phenomenon in 18%, autoimmune thyroiditis, systemic sclerosis, rheumatoid arthritis, and HLA-B27 enthesopathy. Autoimmune hepatitis (AIH)-PBC overlap syndrome is found in 10% of adults with AIH [6, 13]. TIN due to PBC was reported only in women aged from 28 to 77 [6].

The case presented here was a 41-year-old woman without other co-morbidities but with a family history of other autoimmune disorders.

KIDNEY BIOPSY

The only examination that helps to diagnose the majority of renal diseases precisely is kidney biopsy. The classical indications for native kidney biopsy are nephrotic and nephritic syndromes. Those two are not subject to discussion. The isolated components of these syndromes: proteinuria, erythrocyturia, and acute kidney injury are also indications for kidney biopsy, albeit relative, and before kidney biopsy, other causes of these abnormalities must be excluded.

Patients with PBC and TIN do not have typical indications for kidney biopsy. Most of the patients described previously had mild proteinuria (1–2 g/g), in some cases also hematuria [3, 6]. Only in one patient, proteinuria was not reported [5]. The main clinical presentation was slowly progressive kidney disease, which

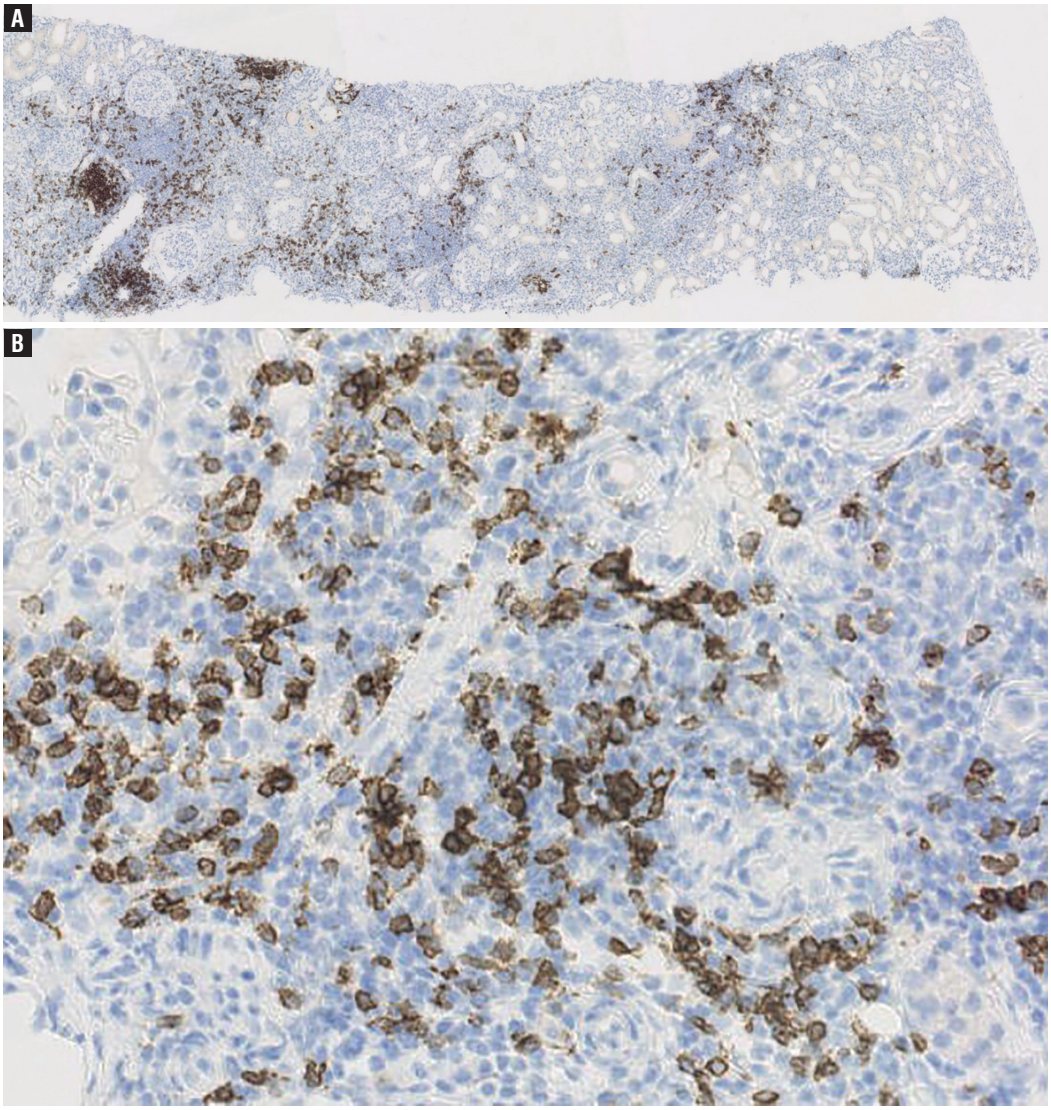

Figure 3. Kidney biopsy. Diffuse interstitial inflammatory infiltrate in both cortex and medulla by B lymphocytes (CD20+). **A.** Lower magnification. **B.** Higher magnification

Table 3. Laboratory measurements

	2014	01. 2020	10. 2020	03. 2021	07. 2021	08. 2021	09. 2021	10. 2021	11. 2021	03.01. 2022	31.01. 2022	28.02. 2022	04.04. 2022
sCr mg/dL	1.08	1.09	1.45	1.49	1.64	1.53	1.69	1.57	1.34	1.51	1.41	1.55	1.42
eGFR (mL/min)	58	56	40	39	35	37	34	36	44	38	41	37	41
uβ2m mg/L						8.902	8.297		2.104	0.677	0.945	1.45	0.778
uAlb mg/L						< 5	< 5		< 5	< 5	< 5		
Hgb g/dL	12	12.4	12.7	11.4	12.5	12	12.1	12.6	13.4	13.5	13.4	12.6	13.5
pH						7.3	7.32	7.41	7.46	7.43	7.38	7.38	7.37
HCO_3 mM/L						16.9	16.9	20.6	23.4	24.1	21.3	20.7	19.8
Steroids mg/day								32	24	16	12	10	8

sCr — serum creatinine, uβ2m — urinary beta-2-microglobulin, uAlb — urinary albumin, Hgb — hemoglobin

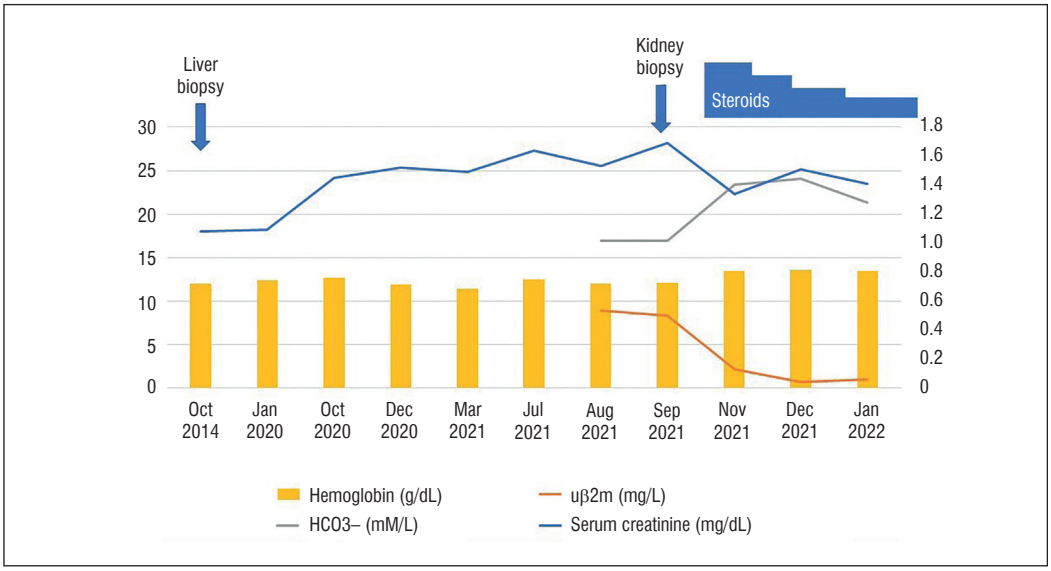

Figure 4. Laboratory measurements and steroid treatment

can sometimes be interpreted as a relative contraindication for kidney biopsy. Therefore, TIN can be easily overlooked in patients with PBC.

TIN can lead to albuminuria, but more typical is low molecular weight proteinuria. In TIN, due to PBC, increased excretion of β2m and N-acetyl-β-D-glucosaminidase (NAG) have been commonly observed [3, 6].

Our patient was somehow unique because she had no changes in urine at all. Albuminuria was checked several times and was always below < 5 mg/L. Urine excretion of β2m was typically high.

RENAL TUBULAR ACIDOSIS

Both dRTA and pRTA have been reported in TIN due to PBC. pRTA was usually present with other signs and syndromes typical for Fanconi syndrome (normoglycemic glycosuria, pan-aminoaciduria, hypokalemia, hypophosphatemia, bone fractures, or pains) [3, 9]. In the medical literature, also dRTA with Fanconi syndrome and a mixed type of renal tubular acidosis were reported [4, 7, 9]. It was also shown that one-third of patients with PBC had incomplete RTA without clinical consequences and biopsy-proven TIN [3, 5].

In the case presented here, we used a urine acidification test with furosemide and fludrocortisone, which is an easy alternative to the classic Wrong Davies test [12]. The results suggested isolated pRTA.

TREATMENT, FOLLOW-UP, AND PROGNOSIS

There are no recommendations concerning treatment. In previously published case reports, treatment with an initial dose of steroids ranging from 20 to 60 mg of prednisone was proposed. All patients responded well to steroid therapy [3, 4], but it is not clear how long steroids should be continued. In some cases, kidney function deteriorated when steroids were withdrawn [5] although the risk of relapse of TIN after steroid tapering is probably low [6]. In the case presented here, treatment with 32 mg of methylprednisolone was initiated with a positive effect. The serum creatinine level and urine excretion of β2m decreased. The patient reported an improvement in well-being, and her hemoglobin level increased from 11.8 to 13.4 g/dL. The dose of steroids was tapered.

Mandai et al. suggested that anti-centromere antibodies (ACA), typically positive in patients with systemic sclerosis are an independent risk factor for CKD in PBC [14]. In our patient, these antibodies were not present.

CONCLUSIONS

TIN after PBC is an extremely rare but important extrahepatic complication of PBC. There are no recommendations concerning diagnosis and treatment. Slowly progressive renal disease, low molecular weight proteinuria, and renal tubular acidosis are the most common abnormalities. Therefore, they should be monitored in patients with PBC. Kidney biopsy is crucial for diagnosis. The previously described cases show that steroids are effective, but the optimal duration of this treatment is unknown.

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