CASE REPORT

Tubulointerstitial Nephritis and Fanconi Syndrome in Primary Biliary Cirrhosis

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• **Primary biliary cirrhosis is a chronic cholestatic liver disease of unknown cause that predominantly affects middle-aged women. Distal tubular acidosis is the main renal complication of primary biliary cirrhosis. Tubulointerstitial nephritis and Fanconi syndrome have been reported more rarely. We report on 2 patients with primary biliary cirrhosis who presented with tubulointerstitial nephritis and Fanconi syndrome and review similar cases published previously. Serum from 1 patient exerted an inhibitory effect on pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, 2 mitochondrial enzymes that are the main targets of antimitochondrial antibodies in primary biliary cirrhosis. Antimitochondrial antibodies may have a role in the genesis of tubulointerstitial nephritis and Fanconi syndrome, 2 typical renal features of mitochondrial cytopathies. Tubulointerstitial nephritis and Fanconi syndrome have to be added to the spectrum of renal diseases associated with primary biliary cirrhosis. *Am J Kidney Dis* 46:E41-E46.**

INDEX WORDS: Primary biliary cirrhosis; Fanconi syndrome; tubulointerstitial nephritis; antimitochondrial antibodies.

PRIMARY BILIARY cirrhosis (PBC) is a chronic cholestatic liver disease of unknown cause that predominantly affects middle-aged women.[1] The presence of antimitochondrial antibodies (AMAs) is a hallmark of the disease. Distal tubular acidosis (DTA) is the main feature of renal involvement in patients with PBC.[2] It is found in up to 33% of patients, but usually is without clinical consequence. More rarely, tubulointerstitial nephritis (TIN) has been reported in patients with PBC.[3-5] We report 2 cases of TIN associated with PBC and present histopathologic kidney and liver data. Furthermore, the inhibitory effect of circulating AMAs on mitochondrial enzymes in shown. Finally, we compare our findings with the scarce data previously published.

METHODS

We reviewed medical records and pathological data for patients referred from 1990 to 2004 to the Department of Nephrology at Hôpital Necker-Enfants Malades (Paris, France) and Department of Internal Medicine and Nephrology at Hôpital de Valenciennes (France) to identify patients with PBC and renal disease. PBC diagnosis was made based on the presence of at least 3 of the following criteria: alkaline phosphatase or γ-glutamyltransferase level greater than the upper limit of normal; positive AMAs at a titer of 1:20; increased immunoglobulin M (IgM) level; absence of biliary obstruction by means of ultrasonography, computed tomography, or cholangiography; or compatible liver biopsy. Five patients were identified: 4 patients with TIN (Fanconi syndrome was noted in 2 patients) and 1 patient with microscopic polyangiitis. Only the 2 patients with TIN and Fanconi syndrome are presented here.

Fanconi syndrome is defined by the coexistence of hypokalemia, hypophosphatemia with a low renal fractional tubular reabsorption of phosphate, metabolic acidosis, normoglycemic glycosuria, and generalized aminoaciduria. Aminoaciduria was measured by using urinary amino acid chromatography. Glycosuria was detected by using dipsticks and quantified by means of the enzymatic method. Fractional tubular reabsorption of phosphate was estimated as 1 – (U/P) phosphate/(U/P) creatinine, where U and P are urinary and plasma concentrations, respectively.

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Enzyme Studies

We studied the effect of patient 1 plasma (patient 2 plasma was not available) and total IgG on 2 mitochondrial enzymes (pyruvate dehydrogenase [PDH] and α-ketoglutarate dehydrogenase [α-KDH]). These 2 enzymes are major targets of AMAs in patients with PBC. PDH and α-KDH activity was measured spectrophotometrically by following the reduction of the oxidized form of nicotinamide-adenine dinucleotide (NAD^+) at 340 nm in a medium consisting of 0.3 mol/L of mannitol, 5 mmol/L of $MgCl_2$, 10 mmol/L of KCl, 0.1% Triton X-100, 1 mmol/L of freshly prepared cysteine, 240 μmol/L of thiamine pyrophosphate, 200 μmol/L of coenzyme A, 0.5 mmol/L of NAD^+, and 10 mmol/L of KH_2PO_4 (pH 7.4). Each enzyme measurement was started by adding its organic acid substrate, ie, 0.4 mmol/L of pyruvate and 0.5 mmol/L of α-ketoglutarate for the PDH and α-KDH assays, respectively. Measurements of α-KDH activity were performed by using mouse liver mitochondria prepared as previously described.[5] The PDH activity assay was performed on PDH purified from porcine heart (Sigma Chemical Comp, Lyon, France). Protein content was estimated by using the Bradford standard assay.

CASE REPORTS

Patient 1

A 51-year-old woman was referred for the evaluation of chronic renal failure diagnosed 3 years earlier. At that time, serum creatinine (SCr) level was 1.4 mg/dL (121 μmol/L; creatinine clearance [CrCl], 40 mL/min [0.67 mL/s]). Hypophosphatemia (phosphate, 1.9 mg/dL [0.62 mmol/L]), hypouricemia (uric acid, 1.74 mg/dL [104 μmol/L]), and mild proteinuria (protein, 1 g/d) were noted. Hematuria was absent. A renal biopsy performed at that time showed TIN with a marked lymphocytic ($CD3^+$) infiltrate. Two years later, the patient reported bone pain affecting mainly the ribs and hips. Rheumatological workup, including bone biopsy, led to the diagnosis of osteomalacia complicating Fanconi syndrome. Relevant biological data at referral are listed in Table 1. Fanconi syndrome was diagnosed based on hypouricemia, hypophosphatemia, generalized aminoaciduria, and normoglycemic glycosuria. A salivary gland biopsy was unremarkable. Immunologic test results were negative except for the presence of antinuclear antibodies (1/160) and high-titer (>1/800) type 2 AMAs. Test results for hepatitis B and C virus were negative. Kidney and liver biopsies were performed (Fig 1A-D).

The patient was started on calcitriol therapy (0.25 μg for 2 days), and phosphatemia normalized. She subsequently was administered ursodeoxycholic acid and a course of steroid therapy (0.5 mg/kg/d, with progressive tapering over 6 months), which led to a transient improvement in renal function (SCr, 1.35 mg/dL [120 μmol/L]). At last follow-up, 1 year after referral, SCr level was 1.58 mgdL (140 μmol/L; CrCl, 36 mL/min [0.6 mL/s]).

Patient 2

This 68-year-old woman had been given a diagnosis of PBC (stage 2 on liver biopsy) 2 years before her referral to the nephrologist. High-titer (1/640) type 2 AMAs were present. Xerostomia was noted, and mild lymphocytic infiltrate was present in a salivary gland biopsy. One year later, she presented with bone fractures. Hypophosphatemia and hypocalcemia were noted. Osteomalacia was suspected, but could not be formally confirmed on bone biopsy. At that time, SCr level was 1 mg/dL (90 μmol/L) and rapidly increased to 1.35 mg/dL (120 μmol/L) 4 months later.

On admission, blood pressure was 135/74 mm Hg. Physical examination was unremarkable. Relevant laboratory test results are listed in Table 1. Fanconi syndrome was diagnosed based on hypokalemia, hypouricemia, hypophosphatemia, generalized aminoaciduria, and normoglycemic glycosuria. Test results for type 2 AMAs were positive (1/640), with low-titer antinuclear antibodies (1/40) in the absence of antiextractable nuclear antigen antibodies, including anti-SSA and anti-SSB antibodies. Serological test results for hepatitis B and C were negative. A renal biopsy was performed (Fig 1F). The patient was started on therapy with sodium bicarbonate calcitriol and potassium chloride oral supplementation. Despite a course of steroids (0.5 mg/d with gradual tapering), renal failure progressed, and at last follow-up, SCr level was 2.29 mg/dL (203 μmol/L).

Table 1. Relevant Biological Data at the Time of Diagnosis of TIN in 2 Patients With PBC

	Patient 1	Patient 2
SCr (mg/dL)	1.77	1.3
CrCl (mL/min)	32	41
Serum potassium (mEq/L)	3.9	3.3
Serum phosphate (mg/dL)	1.17	2.41
Total carbon dioxide (mEq/L)	21.5	21.8
Uricemia (mg/dL)	2.01	2.85
Total bilirubin (mg/dL)	0.35	0.29
Alkaline phosphatase (U/L)	107	276
γ-Glutamyltranferase (U/L)	53	51
Aspartate aminotransferase (U/L)	41	25
Alanine aminotransferase (U/L)	67	34
Proteinuria (g/d)	1.3	1.47
Hematuria (red blood cells/μL)	25	25
β_2-Microglobulinuria* (mg/24 h)	25	57
Fractional tubular reabsorption of phosphate† (%)	42	16
Hyperaminoaciduria	+	+
Urinary pH	6.5	6
Glycosuria	+	+

NOTE. To convert SCr in mg/dL to μmol/L, multiply by 88.4; CrCl in mL/min to mL/s, multiply by 0.01667; potassium and total carbon dioxide in mEq/L to mmol/L, multiply by 1; uric acid in mg/dL to μmol/L, multiply by 59.48; bilirubin in mg/dL to μmol/L, multiply by 17.1.

*Normal, less than 0.35 mg/24 h.

†Normal, greater than 0.86 mg/24 h.

Histopathologic Studies

Kidney biopsy findings. In both patients, renal biopsies showed features of severe TIN characterized by: (1) marked interstitial cellular infiltrate (Fig 1A, F, and G); cellular