CASE REPORT

Tubulointerstitial Nephritis and Primary Biliary Cirrhosis with a T Cell-dominant Profile of Infiltrating Cells and Granulomas in Both Organs

Takamasa Iwakura¹, Yoshihide Fujigaki¹, Takashi Matsuyama¹, Tomoyuki Fujikura¹, Naro Ohashi¹, Hideo Yasuda¹, Akihiko Kato² and Satoshi Baba³

Abstract

A 46-year-old woman was admitted to our hospital for an evaluation of progressive renal insufficiency and elevated liver enzymes. A renal biopsy revealed chronic granulomatous interstitial nephritis. Her laboratory findings indicated primary biliary cirrhosis (PBC), which was confirmed with a liver biopsy. CD4⁺ T cells and CD8⁺ T cells with granuloma formation were the predominant cells infiltrating into the interstitium of the kidneys and liver. The etiology of tubulointerstitial nephritis in the present patient was not clear; however, it might have shared the same pathogenesis as PBC due to the relatively close onset, the similar profiles of infiltrating cells and the presence of granulomas.

Key words: interstitial nephritis, granuloma, primary biliary cirrhosis

(Intern Med 52: 467-471, 2013)
(DOI: 10.2169/internalmedicine.52.9003)

Introduction

Primary biliary cirrhosis (PBC) is a liver disease that is characterized by the progressive destruction of the bile ducts, most likely due to an autoimmune mechanism. A T cell-dependent immune reaction has been incriminated as the major mechanism of bile duct destruction (1). PBC is often associated with extrahepatic autoimmune disorders such as rheumatoid arthritis, systemic sclerosis, thyroiditis and Sjögren’s syndrome (2-4). Renal involvement in patients with PBC is not rare, as distal tubular acidosis is found in up to 33% of cases, usually without any clinical consequences (5). Additionally, some cases of PBC and Fanconi syndrome have been reported (6-9). The primary renal manifestation of Sjögren’s syndrome is tubulointerstitial nephritis; thus, it is likely that patients with PBC associated with Sjögren’s syndrome will exhibit tubulointerstitial nephritis. However, there are few reports of patients with PBC with apparent tubulointerstitial nephritis without Sjögren’s syndrome (6-10). A case of granulomatous interstitial nephritis associated with PBC is herein described. Regarding histology, the similar profiles of infiltrating cells and granuloma formation in the kidneys and liver suggested a shared pathogenesis.

Case Report

A 46-year-old woman was admitted to our hospital for an evaluation of renal insufficiency and elevated liver enzymes in September 2011. She was diagnosed with an ovarian cyst and prescribed dienogest in July 2009. She was first found to have elevated liver enzymes, including an aspartate aminotransferase (AST) level of 54 IU/L, an alanine aminotransferase (ALT) level of 103 IU/L and a γ-GTP level of 312 IU/L. Treatment with dienogest was discontinued in May 2010 because drug-induced liver damage was suspected. The patient’s health check-up indicated an increased serum creatinine (Cr) level, from 0.86 mg/dL in May 2010 to 1.2 mg/dL in May 2011. She was referred to our hospital in August 2011, where further examinations showed slightly positive urinary protein (0.15 g/gCr) without hematuria, a

¹Internal Medicine I, Division of Nephrology, Hamamatsu University School of Medicine, Japan, ²Blood Purification Unit, Hamamatsu University School of Medicine, Japan and ³Department of Pathology, Hamamatsu University School of Medicine, Japan

Received for publication September 21, 2012; Accepted for publication November 14, 2012

Correspondence to Dr. Yoshihide Fujigaki, yf0516@hama-med.ac.jp
high level of urinary β2 microglobulin and persistently elevated levels of liver enzymes.

A physical examination performed on admission showed a blood pressure of 89/58 mmHg, a regular pulse rate of 77 beats/min and no lymphadenopathy. A laboratory test showed the following results: blood urea nitrogen: 17.0 mg/dL, serum Cr: 1.13 mg/dL, total protein: 7.7 g/dL, serum albumin: 4.1 g/dL, potassium: 3.9 mEq/L, calcium: 9.2 mg/dL, inorganic phosphate: 4.0 mg/dL, uric acid: 3.0 mg/dL, AST: 38 IU/L, ALT: 50 IU/L, alkaline phosphatase (ALP): 694 IU/L, γ-GTP: 190 IU/L, total cholesterol: 218 mg/dL, glycosylated hemoglobin (HbA1c): 4.6%, fasting blood sugar: 94 mg/dL, angiotensin converting enzyme: 16.4 IU/L (normal: 8.3-21.4 IU/L), IgG: 1,341 mg/dL, IgA: 224 mg/dL, IgM: 966 mg/dL, hemoglobin: 12.2 g/dL, white blood cell count: 7,000/μL and platelet count: 21.1×10^4/μL. The fractional excretion of uric acid (normal: <10%) and % tubular reabsorption of phosphate (normal: 81-90%) were 17.0% and 85.2%, respectively. The level of urinary glucose was 400 mg/day. No panaminoaciduria was detected. A chest X-ray examination was normal. Abdominal echography showed that both kidneys were of normal size and shape. An ophthalmological examination did not reveal uveitis or sicca syndrome on Schirmer’s test or the Rose Bengal staining test, respectively. Taken together, the diagnoses of Sjögren’s syndrome, renal tubular acidosis and Fanconi syndrome were excluded.

A renal biopsy was performed in September 2011. The light microscopic findings of the renal biopsy showed only a mild increase in the mesangial matrix in some glomeruli along with the presence of foci of mononuclear interstitial infiltration with small non-necrotizing granulomas and moderate interstitial fibrosis (Fig. 1A, B). The immunofluorescence findings showed slight staining for IgM in the mesangium (not shown). Electron microscopy showed no electron-dense deposits in the examined glomeruli or tubular basement membranes. Mitochondria with normal profiles were contained in one proximal tubule (Fig. 2A), whereas various sized and shaped mitochondria with irregular cristae and some lucent matrices were found in another proximal

**Figure 1.** Photographs of interstitial fibrosis in the kidneys and granuloma formation in the kidneys and liver. (A) Masson’s trichrome staining of a renal biopsy specimen shows moderate interstitial fibrosis. Original magnification: ×100. (B) Periodic acid-Schiff staining of a renal biopsy specimen shows small granuloma formation. Original magnification: ×400. (C) Hematoxylin and Eosin staining of a liver biopsy specimen also shows epithelioid granuloma formation. Original magnification: ×400.
Figure 2. Electron micrographs of mitochondria in two proximal tubules. (A) Mitochondria with a normal profile. (B) Mitochondria showing various sizes and shapes with some mitochondria showing irregular cristae and lucent matrices or severe alterations with amorphous matrices (asterisks). Original magnification: ×20,000. Inset, mitochondrial morphology shown at a higher magnification.

Figure 3. Photographs of immunohistochemistry for CD4 (A, D), CD8 (B, E) and CD20 (C, F) in the kidneys (A-C) and liver (D-F). Mouse monoclonal anti-human CD4 antibody (Leica Biosystems Newcastle Ltd., Newcastle upon Tyne, UK), mouse monoclonal anti-human CD8 antibody (Leica Biosystems Newcastle Ltd.) and mouse monoclonal anti-human CD20 antibody (DakoCytomation, Glostrup, Denmark) were used, respectively. Original magnification: ×400.

tubule (Fig. 2B). Immunohistochemical staining of CD4⁺, CD8⁺ and CD20⁺ revealed CD4⁺ and CD8⁺ T cell-dominant infiltration in the interstitium compared with that observed for CD20⁺ B cells (Fig. 3A-C). Chronic granulomatous interstitial nephritis was diagnosed, although the patient had no obvious contributing factors, such as granulomatosis with polyangiitis or sarcoidosis.

To confirm the diagnosis of PBC, which was suggested by several laboratory findings, a liver biopsy was performed. An examination of the liver specimen revealed moderate inflammatory infiltrations primarily composed of lymphocytes in the portal area. Interface hepatitis, slight nonsuppurative cholangitis, epithelioid granuloma formation (Fig. 1C) and atypical cholangiolar hyperplasia were also found in association with partial bridging fibrosis and cellular infiltration of hepatocytes. These features were compatible with stage II to III PBC. Immunohistochemistry showed that the infiltrating cells were primarily composed of CD4⁺ T cells and CD8⁺ T cells compared with CD20⁺ B cells (Fig. 3D-F).

The patient was given only oral ursodeoxycholic acid for
PBC because no tubulitis was found, and the efficacy of corticosteroids for treating chronic granulomatous interstitial nephritis is considered questionable. Her progressive renal function decrease stopped, and other parameters, including urinary β2 microglobulin and liver enzymes, did not worsen over the 11 months following her discharge. At the last follow-up in August 2012, the levels of AST and ALT were normal, the levels of ALP and γ-GTP were 389 IU/L and 190 IU/L, respectively, and the level of urinary β2 microglobulin was 3,743 μg/L.

Discussion

PBC is often associated with extrahepatic autoimmune disorders (2, 3) such as Sjögren’s syndrome. The tubulointerstitial nephritis observed in Sjögren’s syndrome (11, 12) is sometimes found in patients with PBC (13). Tubulointerstitial nephritis caused by Sjögren’s syndrome is associated with inflammatory cell infiltration consisting of lymphocytes, plasma cells and histiocytes (12). Nine cases of biopsy-proven tubulointerstitial nephritis, which were unrelated to Sjögren’s syndrome (6-10), have been reported in association with PBC, six of which involved Fanconi syndrome (6-9). Lino et al. examined the profile of infiltrating cells in the renal interstitium and reported marked interstitial cellular infiltration composed primarily of CD3+ lymphocytes (8). Lino et al. also mentioned two possible mechanisms underlying the genesis of tubulointerstitial nephritis induced by PBC (8). First, autoreactive T lymphocytes driven by abnormal antigen expressions in both hepatocytes and renal tubular cells might be involved, leading to T lymphocyte infiltration into the renal interstitium. Second, antimitochondrial antibodies, especially antimitochondrial M2 antibodies, might thus play a role in the genesis of tubulointerstitial nephritis, which could significantly reduce the activities of three mitochondrial enzymes. This explanation suggests that PBC might contribute to Fanconi syndrome, as Fanconi syndrome and tubulointerstitial nephritis are typical renal features of mitochondrial cytopathies (14).

A T cell-dominant profile of infiltrating cells and (epithelioid) granuloma formation were found in both the interstitium of the kidneys and portal areas of the liver in the present patient. In addition to macrophages, T cells are thought to contribute to granuloma formation (15). Based on the histological features and the relatively close onset of the renal and hepatic symptoms, the present case might therefore support the first hypothesis regarding the involvement of autoreactive T lymphocytes proposed by Lino et al. In addition, electron microscopy showed altered mitochondrial morphology in the proximal tubules. The second hypothesis involving decreased mitochondrial activity caused by antimitochondrial antibodies suggested by Lino et al. might also explain the tubulointerstitial nephritis observed in this case to some extent. The phenotype of the disease might depend on the severity of dysfunction. In the present case, the mitochondrial damage in the tubules might not have been severe enough to result in the clinical appearance of Fanconi syndrome and/or renal tubular acidosis. After being treated with ursodeoxycholic acid, the patient’s levels of transaminases normalized and the serum creatinine level stabilized for the next 11 months. It is unlikely that ursodeoxycholic acid has immunological actions in both PBC and interstitial nephritis. If the pathogenesis of tubulointerstitial nephritis in this case is completely in accord with that of PBC, then tubulointerstitial nephritis is less likely to show spontaneous remission since spontaneous remission of PBC is not widely accepted. Therefore, fluctuating factors other than factors related to PBC might also contribute to the progression of tubulointerstitial nephritis.

The case of a patient who was simultaneously diagnosed as having granulomatous interstitial nephritis and PBC was herein described. The etiology of these conditions might have partly shared the same pathogenesis and developed insidiously at an early stage. Much attention should be paid to the diagnosis of related complications in patients with tubulointerstitial nephritis or PBC, and further investigations are necessary to explore the possible common pathogenesis of these diseases.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

The authors thank all of the staff at the Department of Hepatology, Internal Medicine 2 at Hamamatsu University School of Medicine for their cooperation in the diagnosis of PBC.

References


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