Tubulointerstitial nephritis and renal tubular acidosis of different types are rare but important complications of primary biliary cirrhosis

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Abstract
Background. A very few cases of biopsy-proven tubulointerstitial nephritis (TIN) in patients with primary biliary cirrhosis (PBC) have been reported. Although the clinical importance of this association has been suggested, information on its clinicopathological features and prognosis is limited.

Methods. We reviewed 5955 renal biopsies processed at our department, and identified four patients with TIN associated with asymptomatic PBC. We evaluated clinicopathological features and outcomes in these patients, and reviewed the previously reported cases of TIN associated with PBC.

Results. Our four patients were female. The patients’ age at the time of renal biopsy ranged from 36 to 77. Three patients had been treated with ursodeoxycholic acid. All patients had urinary abnormalities such as proteinuria and elevated levels of urinary β2-microglobulin, and three patients had renal insufficiency. All patients had distal renal...
tubular acidosis (RTA), and two patients also had Fanconi syndrome. Renal biopsy showed severe lymphocyte infiltration in the tubules and interstitium with mild-to-moderate tubular atrophy and fibrosis. All patients responded well to steroid therapy. On review of the previously reported five cases, all patients were female. The patients’ age ranged from 42 to 68. Apparent symptoms linked to PBC were not described. All patients had renal insufficiency. Three patients suffering from bone pains or bone fractures also had Fanconi syndrome. Marked or transient improvements were observed after steroid therapy in three patients.

Conclusions. TIN and RTA of different types are extremely rare but one of the important extrahepatic complications of PBC. Steroid therapy can be beneficial in treating PBC patients with these renal complications.

Keywords: distal renal tubular acidosis; Fanconi syndrome; primary biliary cirrhosis; tubulointerstitial nephritis

Introduction

Primary biliary cirrhosis (PBC) is an immune-mediated chronic cholestatic liver disease. This disorder is characterized by non-suppurative destruction of interlobular bile ducts, accompanied by increased concentrations of serum immunoglobulin M (IgM) and the presence of circulating anti-mitochondrial antibodies [1]. Extrahepatic associated disorders arise in 70% of patients with PBC. Distal renal tubular acidosis (RTA) is the main feature of renal involvement. It occurs in one-third of patients, but usually is without clinical significance [2].

Tubulointerstitial nephritis (TIN) is an inflammatory disease characterized by lymphocyte infiltration in tubules and interstitium. Chronic TIN is occasionally associated with various immunological disorders such as Sjögren syndrome [3]. Macdougall et al. [4] first reported a case of TIN with PBC in 1987. Thereafter, five similar cases, including our case, have been described in the English literature [5–8]. Although the clinical importance of this association has been suggested, information on its clinicopathological features and prognosis is limited.

In the present study, we reviewed 5955 renal biopsies processed at our department, and identified four patients with TIN associated with PBC. We evaluated clinicopathological features and outcomes in these patients.

Materials and methods

Patients

This study was based on the renal histological records (1979–2009) of 5955 patients studied at Akita University Hospital and its affiliated hospitals. PBC diagnosis was defined based on the presence of at least three of the following criteria [1,7]: (i) serum alkaline phosphatase or γ-glutamyl transpeptidase level greater than the upper limit of normal; (ii) positive anti-mitochondrial antibodies at titres of >40 or greater on immunofluorescence study or positive anti-M2 antibodies by enzyme immunoassay; (iii) increased serum IgM level; (iv) absence of biliary obstruction by means of ultrasonography, computed tomography or cholangiography; or (v) compatible liver biopsy. There were four patients with TIN associated with asymptomatic PBC. Clinical and laboratory information was obtained on each patient at the time of renal biopsy. Follow-up information was obtained in all patients. Distal RTA was defined as a normal anion gap metabolic acidosis with urinary pH persistently >6.0 [2]. Fanconi syndrome was defined by the co-existence of hypokalaemia, hypophosphataemia, metabolic acidosis, normoglycaemic glycosuria and pan-aminociduria [7]. Renal insufficiency was defined as serum creatinine of >1.2 mg/dL or an estimated glomerular filtration rate (eGFR) [9] of <60 mL/min/1.73 m².

Pathological studies

Renal biopsy specimens were processed using standard techniques for light and immunofluorescence microscopy.

Results

Clinical features

Clinical features in our four patients with TIN associated with PBC are summarized in Table 1. All patients were females. The median age at the time of renal biopsy was 58 years (range 36–77). Three patients (Patient 2–4) had been given a diagnosis of PBC 7–27 years before their referral to the nephrologists, and treated with ursodeoxycholic acid. They had no symptoms linked to PBC, but were found to have urinary abnormalities during the follow-up period. The remaining one (Patient 1) was found to have urinary abnormalities by a medical check-up. Proteinuria, glycosuria, and elevated levels of urinary β2-microglobulin and N-acetyl-β-D-glucosaminidase were common abnormal findings. Three patients had renal insufficiency. All patients had distal RTA, and two patients (Patient 2 and 4) had Fanconi syndrome. Different functional tests performed in Patient 1 showed a pattern of distal RTA with bicarbonate wasting [10]: urine pH was persistently >6.0 after ammonium chloride loading, and fractional excretion of bicarbonate was 8.0% after sodium bicarbonate loading. Increased serum levels of alkaline phosphatase and IgM were found in three patients. All patients had positive anti-mitochondrial antibodies or positive anti-M2 antibodies in the serum. Liver biopsy findings performed in three patients (Patient 1–3) were consistent with those of PBC. All patients had no symptoms linked to PBC.

All patients were treated with middle-dose steroid (25–30 mg/day of prednisolone for 4–8 weeks). Thereafter, prednisolone was tapered gradually. All patients responded well to steroid therapy: they had improved or stable renal function (for 0.5–16 years) with decreased urinary β2-microglobulin levels at the last follow-up.

Pathological features

Renal biopsy findings in our four patients with TIN associated with PBC are summarized in Table 2. Similar pathological findings were observed in all cases: renal biopsy findings in Patient 4 are shown in Figure 1. Light microscopy showed minor glomerular abnormalities or mild mesangial proliferation. On the contrary, severe lymphocyte infiltration in the tubules (with tubulitis) and interstitium was observed. Tubular atrophy and fibrosis were mild-to-
Vascular disease was absent or mild. Immunofluorescence studies revealed glomerular staining for IgM in the mesangium and/or along the capillary walls in three patients.

**Discussion**

PBC is a chronic progressive cholestatic liver disease of unknown cause. Accumulated evidence suggests that cellular and humoral immunological abnormalities might cause the disease [1]. Several extrahepatic disorders closely associated with PBC are known. As renal involvement with clinical significance, TIN has rarely been described [4–8]. Table 3 summarizes previously reported cases and our cases of biopsy-proven TIN in nine patients with PBC. The median age was 56 years (range 36–68). All patients had been treated with ursodeoxycholic acid.

![Image](https://academic.oup.com/ndt/article-abstract/25/11/3575/1900025)
and suggested a distal localization of the acidification defect. All our patients had distal RTA. The results of functional tests in Patient 1 suggested distal dominant tubular dysfunction [10]. In addition, Lino et al. [7] reported the first two cases with TIN and Fanconi syndrome (non-selective proximal tubular defects [10]), and proposed that these complications should be added to the spectrum of renal diseases associated with PBC. A review of the literature and our cases support the clinical importance of their proposal. Bando et al. [11] recently reported a case of very severe osteomalacia with Fanconi syndrome and PBC.

In summary, TIN and RTA of different types are extremely rare but important extrahepatic complications of PBC. To find these complications at an early stage, careful patient monitoring including urinalysis and periodic measurement of routine chemistries are necessary. If patients with PBC show urine abnormalities, such as tubular proteinuria and glycosuria and hypokalaemia, arterial blood gas analysis and renal biopsy should be considered. Steroid therapy can be beneficial in treating these renal complications.

Conflict of interest statement. None declared.

References


Table 3. Previously reported cases and our cases of biopsy-proven tubulointerstitial nephritis associated with primary biliary cirrhosis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age/sex</th>
<th>Manifestations</th>
<th>RI/dRTA/FS</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macdougall</td>
<td>50/F</td>
<td>Hypokalaemia</td>
<td>(+)/(-)/(+)</td>
<td>PSL/effective</td>
</tr>
<tr>
<td>Kamouchi</td>
<td>58/F*a</td>
<td>Hypokalaemia</td>
<td>(+)/(+)/(+)</td>
<td>PSL/effective</td>
</tr>
<tr>
<td>Lino</td>
<td>51/F</td>
<td>Bone pains</td>
<td>(+)/ND/(+)</td>
<td>PSL/effective</td>
</tr>
<tr>
<td>Lino</td>
<td>68/F</td>
<td>Bone fractures</td>
<td>(+)/ND/(+)</td>
<td>PSL/effective</td>
</tr>
<tr>
<td>Terrier</td>
<td>42/F*b</td>
<td>Bone pains</td>
<td>(+)/ND/(+)</td>
<td>PSL/effective</td>
</tr>
<tr>
<td>Patient 1*</td>
<td>36/F</td>
<td>Urinary abnormalities</td>
<td>(+)/(+)/(+)</td>
<td>PSL/effective</td>
</tr>
<tr>
<td>Patient 2</td>
<td>66/F</td>
<td>Urinary abnormalities</td>
<td>(+)/(+)/(+)</td>
<td>PSL/effective</td>
</tr>
<tr>
<td>Patient 3</td>
<td>77/F</td>
<td>Urinary abnormalities</td>
<td>(+)/(+)/(+)</td>
<td>PSL/effective</td>
</tr>
<tr>
<td>Patient 4</td>
<td>52/F</td>
<td>Urinary abnormalities</td>
<td>(+)/(+)/(+)</td>
<td>PSL/effective</td>
</tr>
</tbody>
</table>

dRTA, distal renal tubular acidosis; FS, Fanconi syndrome; ND, not described; RI, renal insufficiency.
*aTransient improvement.
*bSjögren syndrome and chronic thyroiditis were also diagnosed.
*cIncomplete type.
*dSystemic sclerosis and celiac disease were also diagnosed.
*ePreviously reported by Kodama et al. [6].
Renal biopsy practice in France: results of a nationwide study

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Abstract

Background. Although several risk factors associated with complications after renal biopsy (RB) have been identified, the gold standard for RB procedures remains to be defined. Practices vary widely among nephrologists, depending on personal experience and the availability of particular techniques. The purpose of our study was to depict the main aspects of the practice of RB in adults in France.

Methods. Members of the Société de Néphrologie in France were asked to participate in a questionnaire survey on RB procedures.

Results. Eighty-eight nephrologists from 74 units (27 in teaching hospitals, 35 in public general hospitals and 12 in private centres) participated in our study. Native kidney and graft biopsies were performed in 73 and 35 units, respectively. RB activity was highly variable among units, ranging from several hundred to <10 per year. Transjugular renal biopsy was judged to be smoothly accessible in 28 out of 73 units (38.4%). Significant variations in practices were observed regarding patient information before RB, assessment of hemorrhagic risk factors, management of patients with antiplatelet agents and hemorrhagic risk factors, and radiological guidance. Early discharge (<12 h) was the rule in 3 (4.1%) units for native kidney biopsies and in 10 (28.6%) units for graft biopsies.

Conclusions. Our study is the first to provide a representative picture of ‘everyday’ RB practices in a country. Important variations in procedures were observed. Our study may