Primary biliary cirrhosis associated with pernicious anemia

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Primary biliary cirrhosis (PBC) is an autoimmune disease of progressive intrahepatic cholestasia, characterized by chronic nonsuppurative destructive granulomatous cholangitis leading to bile duct loss, fibrosis, and eventually cirrhosis of the liver. Diagnosis is based on a combination of clinical features, a cholestatic pattern indicating abnormal liver function, and the presence of antimitochondrial antibodies in the serum. The incidence and prevalence rates are higher in countries in the northern hemisphere, such as the United Kingdom, Scandinavia, Canada, and the United States, but the disease does affect different races. One of the clinical characteristics of PBC is its association with various autoimmune disorders. However, the association of PBC with pernicious anemia (PA) has seldom been reported; therefore, the diagnosis of PA in PBC patients might be overlooked.

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Table 1. Clinical characteristics of 9 cases of PBC associated with PA reported in the literature: All patients were female.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>AGE, Y</th>
<th>PRIMARY SYMPTOM</th>
<th>TIME LAPSED BETWEEN ONSET OF EACH CONDITION</th>
<th>AST/ALT, IU/L</th>
<th>ALP/GGT, IU/L</th>
<th>T/DBIL, mg/dL</th>
<th>HB, g/dL</th>
<th>MCV, fL</th>
<th>VITAMIN B12, pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renoux et al,2</td>
<td>68</td>
<td>Pruritus</td>
<td>Simultaneous</td>
<td>NR/22</td>
<td>Elevated/NR</td>
<td>2.6/NR</td>
<td>8.1</td>
<td>NR</td>
<td>70</td>
</tr>
<tr>
<td>Renoux et al,3</td>
<td>46</td>
<td>Pruritus</td>
<td>10 y</td>
<td>NR/26</td>
<td>Elevated/NR</td>
<td>2.4/NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Renoux et al,2</td>
<td>66</td>
<td>Pruritus</td>
<td>13 y</td>
<td>NR/32</td>
<td>Elevated/NR</td>
<td>3.5/NR</td>
<td>11.0</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Renoux et al,2</td>
<td>72</td>
<td>Pruritus</td>
<td>Simultaneous</td>
<td>NR/12</td>
<td>Elevated/NR</td>
<td>1.8/NR</td>
<td>9.6</td>
<td>NR</td>
<td>134</td>
</tr>
<tr>
<td>Arikan et al,3</td>
<td>54</td>
<td>Pruritus</td>
<td>5 mo</td>
<td>141/84</td>
<td>850/88</td>
<td>5.0/2.8</td>
<td>11.8</td>
<td>98.0</td>
<td>100</td>
</tr>
<tr>
<td>Dohmen et al,4</td>
<td>72</td>
<td>Dyspnea</td>
<td>Simultaneous</td>
<td>26/13</td>
<td>711/317</td>
<td>1.4/0.3</td>
<td>7.3</td>
<td>132.5</td>
<td>130</td>
</tr>
<tr>
<td>Takahashi et al,5</td>
<td>52</td>
<td>Asymptomatic</td>
<td>16 y</td>
<td>51/57</td>
<td>737/434</td>
<td>1.1/1.0</td>
<td>7.1</td>
<td>NR</td>
<td>99</td>
</tr>
<tr>
<td>Aoyama et al,6</td>
<td>59</td>
<td>Asymptomatic</td>
<td>5 y</td>
<td>Abnormal value/NR</td>
<td></td>
<td>4.0/2.0</td>
<td>6.4</td>
<td>136.0</td>
<td>85</td>
</tr>
<tr>
<td>Chung et al,7</td>
<td>46</td>
<td>Fatigue</td>
<td>Simultaneous</td>
<td>157/169</td>
<td>2063/169</td>
<td>12.4/7.9</td>
<td>10.5</td>
<td>114.8</td>
<td>119</td>
</tr>
</tbody>
</table>

ALP—alkaline phosphatase, ALT—alanine aminotransferase, AST—aspartate aminotransferase, GGT—γ-glutamyl transpeptidase, Hb—hemoglobin, MCV—mean corpuscular volume, NR—not reported, PA—pernicious anemia, PBC—primary biliary cirrhosis, T/DBIL—total and direct bilirubin.
hyperbilirubinemia (Table 12-7) and revealed cholestatic hepatic injury with predominant elevation of serum alkaline phosphatase and γ-glutamyl transpeptidase relative to serum aminotransferase levels. The patient’s hemogram results revealed macrocytic anemia (hemoglobin, 105 g/L [normal range 113 to 153 g/L]; mean corpuscular volume, 114.8 fL [normal range 79 to 99 fL]). Abdominal ultrasonography and magnetic resonance cholangiopancreatography disclosed cirrhosis of the liver but ruled out biliary obstruction. Serologic test results for viral hepatitis B and C were negative, but test results for antinuclear antibodies (1:640) and antimitochondrial antibodies (1:20) were positive. Elevated levels of immunoglobulin M (1040 mg/dL [normal range, 88.37 to 232.77 mg/dL]) were noted. Liver biopsy showed portal fibrosis, marked ductular proliferation, and lymphoplasmacytic infiltration (Figure 1). The patient was diagnosed with PBC at Scheuer stage II (early stages, I and II; advanced stages, III and IV). Ursodeoxycholic acid (600 mg daily, taken orally) was prescribed. The initial dose of ursodeoxycholic acid was slightly lower (about 12.2 mg/kg). However, the patient’s body weight decreased from 49 kg to 45 kg. Therefore, there was no further adjustment past 600 mg daily.

To differentiate between macrocytic anemia and PA, a peripheral blood smear was done, which revealed anisocytosis, macro-ovalocytes with tailed red blood cells, and hypersegmented neutrophils (Figure 2). Vitamin B12 deficiency (serum level, 119 pg/mL [normal range, 239 to 931 pg/mL]) and the presence of antiparietal cell antibodies (1:20) favoured the diagnosis of PA. An upper gastrointestinal endoscopy demonstrated pale yellowish mucosa with transparent blood vessels at the gastric body, and a biopsy disclosed atrophic gastritis with intestinal metaplasia. With the diagnosis of PA, the patient received intramuscular injections of vitamin B12 (1000 µg weekly for 2 months, then 1000 µg monthly over a long-term period). Her anemia substantially improved after medical treatment; however, she still had progressive jaundice, moderate to severe ascites, and intermittent sepsis. She passed away 3 years after the diagnosis of PBC while awaiting liver transplantation.

Discussion

One of the characteristics of PBC is its association with various kinds of autoimmune disorders, such as Sjögren syndrome,8 scleroderma, CREST (calcinosis, Raynaud phenomenon, esophageal mobility disorder, sclerodactyly, and telangiectasia) syndrome, rheumatoid arthritis, systemic lupus erythematosus, chronic thyroiditis, and interstitial pneumonitis. The disease most frequently associated with PBC is Sjögren syndrome, which is reported in approximately 70% to 80% of patients with PBC.8 Pernicious anemia is often associated with other autoimmune disorders as well, such as Hashimoto thyroiditis, Addison disease, and insulin-dependent diabetes mellitus.10 However, its association with PA is infrequent.

The incidence of PBC associated with PA has not been well understood, but Culp et al observed a link between these 2 disorders in 2 of 113 (1.8%) patients with PBC.9 Case reports describing the association of PA with PBC in the literature are rare. The first case of PBC associated with PA was reported in 1980 by Renoux et al.2 Between the case described above and our literature review, we found a total of 9 patients affected with PBC and PA; they were all women whose ages ranged from 46 to 72 years (Table 1).2-7 The mean age was 59.4 years, which is
approximately the peak age of onset of PA and older than the mean age of onset of PBC. Most of the patients initially presented with pruritus, and only 2 of the 8 patients had symptoms of anemia (i.e., dyspnea and fatigue). The length of time between the first signs of PBC and PA varied widely—the 2 conditions sometimes appeared simultaneously, but often months to years passed from the onset of the first condition to the onset of the second.

Conclusion
This case illustrates the possible association between PBC and PA. As mild anemia is usually asymptomatic and easily overlooked, clinicians caring for PBC patients should keep a high index of suspicion for coexisting PA when macrocytic anemia is present. Effective therapies are available for both PBC and PA and underscore the importance of correct diagnosis. If PA is left untreated, serious nerve, heart, brain, and digestive tract complications might occur. To avoid overlooking macrocytic anemia in patients with PBC, family physicians should actively look for PA in patients with PBC.

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Competing interests
None declared

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References