Primary biliary cirrhosis (PBC) is believed to be rare in India. We analyzed our data pertaining to patients with PBC seen in a tertiary referral center over a 5-year period. The diagnosis of PBC was based on liver biochemistry, histology and antimitochondrial antibodies, in the absence of biliary obstruction. Five patients, all women, were diagnosed to have PBC. Pruritus, jaundice and fatigue were the most common initial symptoms. Hepatomegaly was seen in 4 out of 5 patients. Associated autoimmune diseases were present in 2 patients. All patients presented with mild hyperbilirubinemia (≤ 6 mg/dL) with disproportionately raised serum alkaline phosphatase level. AMA was positive in 4 patients. Liver biopsy showed stage III-IV disease in 3 of 4 patients. The clinical presentation and course of PBC in India are similar to the experience in the West. [Indian J Gastroenterol 2001;20:26-29]

Key words: Autoimmune liver disease, chronic cholestasis, liver cirrhosis

Primary biliary cirrhosis (PBC) is a chronic cholestatic disorder predominantly affecting middle-aged women. The prevalence of the disease shows wide geographical variation. Almost all studies on PBC are based on data from Europe and North America. No large study from South Asia is available, which has led to the misconception that PBC is a rare disease here. Indian experience with PBC is limited to anecdotal case reports. A recent report documented the occurrence of familial PBC in southern India. Two small reports suggested the existence of an Indian variant of PBC, which manifests without pruritus. Two small studies documented the occurrence of familial PBC in India. We document out experience with 5 cases of PBC, which is the largest single-center experience from India.

Case Reports

Patients suspected to have chronic cholestatic liver disease on clinical evaluation were subjected to liver biochemistry and serological testing for antimitochondrial antibody (AMA), anti-nuclear antibody (ANA), anti-smooth muscle antibody (ASMA), HBsAg and anti-HCV. Ultrasoundography was done in all cases to exclude biliary obstruction. This was supplemented by ERCP examination where ultrasound findings were equivocal. Endoscopic assessment of esophageal varices and portal hypertension gastroscopy was done in all patients.

Liver biopsy was performed if coagulation parameters were permissible. If hospitalization was required at any stage, reassessment of complications of PBC/end-stage liver disease was done during each admission. Bone densitometry was possible in only two patients due to financial constraints. Serial determination of liver biochemistry was done every 6 months on follow up. All patients were treated indefinitely with UDCA (15 mg/Kg) along with vitamin supplements. Cholestyramine (3 g/d) or rifampicin 300 mg/d were used in 3 patients in whom pruritus persisted despite UDCA therapy.

Five patients were diagnosed to have PBC over a 5-year period (1995-99). Fatigue was the initial symptom in all patients. Pruritus and jaundice were present in 5 and 4 patients, respectively. In four patients the pruritus either antedated the appearance of jaundice or occurred simultaneously with the onset of jaundice. One patient developed pruritus six months after the appearance of jaundice. Four patients reported minor fluctuation in the intensity of pruritus. Hepatomegaly and xanthelasma were present in 5 and 3 patients, respectively. Associated disease detected at initial assessment included psoriasis and Raynaud's phenomenon in one patient each.

The biochemical profile of the patients is given in the Table. All but two patients presented with mild hyperbilirubinemia (≤ 6 mg/dL) with disproportionately raised serum alkaline phosphatase. AMA was positive in a titer of ≥1:30 in 4 patients. All patients were positive for HBsAg and anti-HCV. Low titer (<1:40) of ASMA and ANA were seen in 1 and 2 patients, respectively. Esophageal varices were present in all patients. Bone density studies in two patients showed significant osteopenia and osteoporosis. Liver biopsy data were available in 4 patients. Changes suggestive of advanced disease (stage III-IV) were present in 3 patients. Histology of one patient showed portal tract widening, limiting plate destruction and bile ductular proliferation.

Median duration of follow up was one year (range 5 months - 5 years). Serial liver biochemistry showed minor fluctuation (<5 mg/dL) in serum bilirubin values without appreciable clinical improvement despite prolonged use of UDCA. Hospitalization was required in three patients during follow up for complications (spontaneous bacterial peritonitis, grade II encephalopathy, GI bleed) related to decompensated liver disease.

Table: Biochemical and histological profile of patients with PBC

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Serum bilirubin (mg/dL)</th>
<th>Serum alkaline phosphatase (U/L)</th>
<th>AST (U/L)</th>
<th>ALT (U/L)</th>
<th>AMA titer</th>
<th>Histology stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>51/4</td>
<td>3.7</td>
<td>1466</td>
<td>38</td>
<td>41</td>
<td>+</td>
<td>Not done</td>
</tr>
<tr>
<td>40/4</td>
<td>2.5</td>
<td>918</td>
<td>149</td>
<td>142</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>52/4</td>
<td>2.2</td>
<td>1138</td>
<td>117</td>
<td>106</td>
<td>+</td>
<td>III</td>
</tr>
<tr>
<td>35/4</td>
<td>1.2</td>
<td>1163</td>
<td>160</td>
<td>78</td>
<td>-</td>
<td>III with granulomas</td>
</tr>
<tr>
<td>45/4</td>
<td>1.0</td>
<td>163</td>
<td>160</td>
<td>78</td>
<td>-</td>
<td>III with granulomas</td>
</tr>
</tbody>
</table>
Discussion

Our report of five patients highlights several interesting features of PBC in the Indian subcontinent. The clinical presentation, course and complications of PBC in India are no different from those in the West, with the sole exception of advanced disease at initial presentation. Thus, 4 of 5 patients in our report presented with overt jaundice, which is in contrast to the West where only 10% of patients are jaundiced at presentation. As a corollary to this, none of our patients was detected in the pre-symptomatic stage, which comprises nearly 25% of Western patients. This observation possibly reflects the limited use of multi-battery screening tests for routine health examinations in India, rather than a rapidly progressive disease. Surprisingly, we did not come across any variant of PBC that presents without pruritus, as described in two small reports from India. Pruritus was present in both symptomatic patients reported recently from Vellore.

Our histological data support the fact that PBC in India is diagnosed at an advanced stage, as histological features of stages III-IV disease were present in most patients at initial presentation, which is similar to an earlier report from India. The median time to reach the diagnosis of PBC in our study as well as in the previous report from Lucknow was 2 years (range 6 months-5 years). Yet another factor contributing to the delayed diagnosis is the paucity of facilities for AMA testing in India, which are currently restricted to large metropolitan cities. Even in our center, recognition of PBC has coincided with the commercial availability of AMA testing since 1994-95.

Only one of our patients was diagnosed to have the AMA-negative variant of PBC. She underwent two liver biopsies over a period of six months, both of which showed non-caseating lymphohistocellular granulomas in addition to other features of PBC. Granulomas are well documented in patients with PBC in whom AMA is not demonstrated. This patient was negative for both ANA and ASMA, which excluded autoimmune cholangiopathy.

Results of prolonged UDCA therapy were disappointing in our study. No patient had significant clinical or biochemical response. This is not surprising since a recent study from Germany has shown that raised serum alkaline phosphatase >660 u/L at entry is a predictor for poor response to UDCA therapy. In our study all but one patient had serum alkaline phosphatase levels >660 u/L at initial presentation.

This study suggests that PBC is not very rare in adult patients with chronic cholestatic disorders in India. Lack of awareness coupled with the paucity of AMA testing may be responsible for the delay in diagnosis.

References


Correspondence to: Prof Kumar
Received May 22, 2000. Received in final revised form October 27, 2000. Accepted November 15, 2000.