

# Primary Biliary Cirrhosis – Experience in University Hospital, Kuala Lumpur

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## Summary

Primary biliary cirrhosis is an uncommon disease amongst Malaysians. Over a 12-year period, between 1979 and 1991, only seven patients with clinical, biochemical and histologic evidence of primary biliary cirrhosis were identified in University Hospital Kuala Lumpur. All were Chinese females between the ages of 30 to 55 years. The presenting complaint was pruritus in 5 patients. All except one patient was jaundiced when the diagnosis was made. These patients were followed up from 1 to 11 years. Three deaths were reported, one from massive hematemesis and two from liver failure.

**Key Words:** Primary biliary cirrhosis, Presenting features, Death

## Introduction

Primary biliary cirrhosis or more accurately termed 'chronic non suppurative destructive cholangitis'<sup>1</sup> is a slow but not invariably progressive form of cholestatic liver disease. Although the aetiology remains unknown, there is much evidence for an autoimmune process marked by presence of antimitochondrial antibody, frequent association with other autoimmune diseases and most of all, the immunological disturbance related to the bile duct destruction.

Primary biliary cirrhosis mainly affects middle aged females and has been found in all the races<sup>2</sup>. In England, epidemiological studies have estimated the prevalence of the disease range from 3.7 to 14.4 cases per 100,000 population<sup>3</sup>. We report our experience of primary biliary cirrhosis in University Hospital, Kuala Lumpur and describe the clinical features and course of disease in these patients.

## Patients and Methods

A retrospective study was undertaken of 7 patients with primary biliary cirrhosis who were treated in our institution between 1979 and 1991. The diagnosis

of primary biliary cirrhosis was established using a combination of characteristic clinical finding of chronic cholestasis, presence of antimitochondrial antibodies, compatible histology on liver biopsy and exclusion of extrahepatic biliary obstruction by ultrasonography and, or endoscopic retrograde cholangio-pancreatographic examination.

## Results

The clinical data of these patients are summarized in Table I. All patients were female of Chinese origin. Their age at presentation was between 30 to 55 years with a mean of 44.6 years. The duration from onset of symptoms to the time of diagnosis varies from 4 to 24 months, with an average of 11.6 months. Pruritus was the initial complaint in 5 patients and fatigue was also present in 3 patients. One patient presented with features of scleroderma (sclerodactyly, Raynaud's phenomenon, thickening of the skin) and another with rheumatoid arthritis. The presence of raised alkaline phosphatase in these two patients alerted to the diagnosis of primary biliary cirrhosis which was subsequently confirmed by serological testing and histology. Only one patient had xanthomas at presentation. Jaundice was present at

diagnosis in six patients. Four patients were noted to be pigmented as well. All patients had hepatomegaly and in five patients the spleen was also enlarged. Thyrotoxicosis was diagnosed in one patient. Schirmer's test was positive in three of five patients tested.

Presence of antimitochondrial antibody via indirect immunofluorescence testing was detected in all patients. In all patients the alkaline phosphatase was elevated to more than three times normal with a mean of 500  $\mu$ /L. Serum cholesterol were elevated in all patients with a range of 8 – 10 mmol/L. The histological findings were portal tract inflammation, ductular proliferation and portal-portal bridging fibrosis in three patients. These findings were characteristic of primary biliary cirrhosis although there were no granulomas. Two patients showed features of severe cholestasis, portal tract inflammation and bridging fibrosis compatible but not diagnostic of primary biliary cirrhosis. Two patients who died showed established cirrhosis.

The period of follow-up ranged from 1 to 11 years. There were three deaths, one from massive hematemesis (due to esophageal varices), another from liver failure, and the third from septicaemia and liver failure. The shortest survival was in a patient who died two years after diagnosis. The longest survival is still alive 11 years after diagnosis. Three patients who are still alive have mild to moderate pruritus and only one patient has jaundice.

### Discussion

Primary biliary cirrhosis appears to be an uncommon disease amongst Asians<sup>3,4,5</sup>. It is interesting to note that all the patients in this study are Chinese despite the multiracial population of this country. The reason for the preponderance in Chinese is unknown. All our patients are women. This is hardly surprising as 90-95% of patients with primary biliary cirrhosis are women. The age of onset in our patients are similar to Western figures – it affects those between the ages 32 and 72 years<sup>6</sup>.

The clinical presentation of our patients was similar to that described in the West in whom pruritus and fatigue

being the usual presenting symptoms. All except one of our patients were jaundiced at the time of diagnosis. This is not the usual presentation amongst western patients where pruritus occurs simultaneously with jaundice in less than a quarter of their cases<sup>6</sup>. The reason for this difference is uncertain. Our patients might have presented late in the course of their illness. A major review which spanned almost 20 years found that the patients who presented in the first 10 years had a higher incidence of jaundice and more advanced histological lesions<sup>6</sup>. In our patients who were all Chinese there is also the possibility that the jaundice might have been caused by drugs or Chinese medication used by the patients for relief of their symptoms. In fact two patients who are still alive became anicteric although they were jaundice at presentation.

The diagnosis of primary biliary cirrhosis was made during investigation of scleroderma and rheumatoid arthritis in two patients. This association have been reported previously and the incidence of articular symptoms in primary biliary cirrhosis is around five per cent<sup>6,7,8,9</sup>. Three of five patients were positive for Schirmer's test. When more specific tests were performed, abnormalities of lacrimal or salivary secretion, a component of Sjogren's syndrome, were found in 70 to 100% of patients with primary biliary cirrhosis<sup>10,11</sup>.

Anti mitochondrial antibody was detected in all seven patients. Presence of antibodies against mitochondria in primary biliary cirrhosis varies from 84 to 99%<sup>12,13,14</sup>. Antimitochondrial antibody is not diagnostic of primary biliary cirrhosis and patients with or without this autoantibody have similar clinical and laboratory findings<sup>13</sup>. Antimitochondrial antibodies against a specific antigen on the inner mitochondrial membrane, M2, is the most commonly found in primary biliary cirrhosis<sup>15</sup>, and regarded as the serological marker of the disease.

Mitochondrial antibodies have been detected in conditions other than primary biliary cirrhosis such as autoimmune chronic hepatitis, cryptogenic cirrhosis and collagen diseases<sup>15</sup>.

The clinical course is variable but is generally progressive. Two of our patients died from liver failure,

Table 1  
Clinical and laboratory features at diagnosis

Patient, Sex Race	Age at Dx (years)	Duration before Dx (months)	Present-ation	Jaundice	Pigment-ation	Xanthoma	Hepato-megaly	Spleno-megaly	Associated diseases or Complications	Serum bilirubin ( $\mu\text{mol/l}$ )	AMA	Outcome
1. F/C	40	6	Arthralgia Skin tightness	+	+	-	+	+	Scleroderma	49	+	Died of liver failure and septicemia after 2 years
2. F/C	51	7	Pruritus Fatigue	+	+	-	+	+	Osteomalacia Compression Fracture	75	+	Died of hematemesis after 6 years
3. F/C	30	18	Pruritus	+	-	-	+	-	Shirmer test -ve	56	+	Alive, had uneventful pregnancy - 5 years
4. F/C	53	12	Pruritus Fatigue Arthritis	+	-	-	+	-	Thyrotoxicosis Shirmer's test +ve	70	+	Alive for 11 years
5. F/C	48	24	Pruritus+ Fatigue	+	+	+	+	+	Shirmer's test +ve	52	+	Died of liver failure after 3 years
6. F/C	35	4	Pruritus	+	+	-	+	+	Shirmer test -ve	77	+	Alive and well after 3 years
7. F/C	55	10	Arthritis	-	-	-	+	+	Rheumatoid Arthritis Shirmer's test +ve	22	+	Alive and well after 1 year

F = Female C = Chinese Dx = Diagnosis AMA = Antimitochondrial antibody

two and three years after diagnosis. One patient died after a massive hematemesis from variceal bleeding 6 years after diagnosis. The duration of survival in symptomatic patients is about 10 years. Prognosis is better in asymptomatic patients; life expectancy in this group of patients is similar to those of an age and sex matched general population<sup>16</sup>. The difference in survival between symptomatic and asymptomatic group is because the disease in the latter progresses more slowly<sup>16,17</sup>. Various prognostic schemes or models have been proposed<sup>11,15,16,18</sup>. Of all the biochemical parameters, serum bilirubin is the most significant prognostic factor. If serum bilirubin is greater than 170  $\mu\text{mol/litre}$  on two successive occasions six months apart, survival time was 17 months<sup>19,20</sup>. We could not correlate death with serum bilirubin levels in our patients. The three patients who died became progressively more jaundice but of the four who are alive, only one patient is still jaundiced. Two patients cleared their jaundice during subsequent follow up. Pruritus in these patients is a difficult symptom to

treat. Cholestyramine, phenobarbitone, rifampicin, and ursodeoxycholic acid have all been used to control pruritus with varying success. Ursodeoxycholic acid, a hydrophilic bile acid, is used in primary biliary cirrhosis to replace the potentially toxic bile acids retained in the liver. It was shown in a multicentre controlled trial to be effective for the pruritus, with improvement in the biochemical parameters of liver function but has no effect on fibrosis<sup>(21)</sup>. Long term treatment with ursodeoxycholic acid has been shown to slow the progression of the disease and reduce the need for liver transplantation<sup>22</sup>.

There is no proven effective treatment directed at the underlying pathological process in primary biliary cirrhosis. Corticosteroids, penicillamine and cyclosporine have minimal efficacy. Azathioprine, colchicine and methotrexate although promising in initial trials, needed further confirmation and long term evaluation<sup>23,24,25</sup>. Penicillamine was used for one of our patients who is still alive but it was withdrawn

because of poor response and the development of myasthenia gravis which reversed after the drug was stopped. Currently all our patients are on long term ursodeoxycholic acid. Liver transplantation is currently

the treatment of choice for advanced primary biliary cirrhosis with a one year survival of nearly 70% and projected 5-year survival of 66%<sup>26</sup>. However, none of our patients had transplantation.

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