ORIGINAL ARTICLE

Primary Biliary Cirrhosis at Hospital Kuala Lumpur: A Study of 17 Cases Seen Between 1992 and 1999

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Summary

A prospective descriptive study of Primary Biliary Cirrhosis at Hospital Kuala Lumpur was undertaken from January 1992 to December 1999. A total of 17 patients were seen with a female to male ratio of 3.25:1. The mean age at presentation was 45.9 years (range: 14 years to 67 years) with a mean follow-up of 33.4 months (range: 3 months to 95 months). Fatigue was the most common clinical symptom at presentation. Alanine transaminase and alkaline phosphatase levels were elevated in 93% of patients at presentation. The antimitochondrial antibody was positive in 87% of patients. Ursodeoxycholic acid therapy resulted in significant symptomatic relief and biochemical improvement in all those who were treated.

Key Words: Primary Biliary Cirrhosis, Fatigue, Ursodeoxycholic acid

Introduction

Addison and Gull *et al*[1] in 1851 first described Primary Biliary Cirrhosis (PBC) and later Rubin and Schaffner *et al*[2] in 1965 aptly described the pathological changes. PBC is a chronic cholestatic liver disease that slowly progresses to cirrhosis and subsequently liver failure. A disease that predominantly affects middle age women (ratio women to men 9:1) in the West tends to present with fatigue and pruritus. The aetiology of PBC is unclear but there is evidence to suggest an autoimmune aetiology[3] with the presence of autoantibodies and its association with other autoimmune disorders. The presence of antimitochondrial antibody (AMA) in 95% of patients with PBC makes it a specific feature in this disease[4].

Ursodeoxycholic acid (URSO) has been shown in randomized clinical trials[5] to improve biochemical parameters and also delays time to liver transplantation, which is the only means of cure. Recurrence of disease in transplanted grafts has been reported. We report our experience of 17 patients in Hospital Kuala Lumpur over a period of 8 years. This is the largest series of this disease in this country and we attempt to outline local disease features including demographic patterns, sex distribution, complications and efficacy of treatment and highlight differences from existing Western data.

Materials and Methods

An analysis of 17 patients with PBC seen at Hospital Kuala Lumpur was performed from

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January 1992 till December 1999. Analysis of age, sex, ethnic, clinical features, biochemical and histological features, treatment options and complications was prospectively done over this period. Data was entered systematically into a standard form, which formed a database of all PBC cases. The form was completed by ticking of boxes provided for each positive feature and also in a narrative form where needed. It contains details of symptoms, signs, laboratory parameters, treatment details, progression with treatment and complications that were encountered in the entire follow-up period. The data was then analysed, minus personal identification details by the team of physicians. The diagnosis of PBC was based on a constellation of clinical features, cholestatic liver parameters and positive antimitochondrial antibody. Liver histology was assessed in 13 patients. Endoscopic retrograde cholangio-pancreaticography (ERCP) was performed in all male patients in order to exclude primary sclerosing cholangitis (PSC), as PBC is far less common in males.

Results

Seventeen patients were reviewed. There was a female preponderance of 3.25 to 1. There was a slight Chinese preponderance of 47% followed by Malays (41%) and Indians (12%) in this series. The age range was 14 to 67 years with a mean of 45.9 years. The follow up duration was 3 months to 95 months with a mean of 33.4 months. The clinical features by order is listed in Table I. The associated illnesses were noted in 8 patients as summarized in Table II. Table III summarizes the baseline biochemical, immunological and histological profile in our patients.

The most consistent biochemical abnormality that was noted was elevated alkaline phosphatase levels. This feature was seen in 15 (94%) patients. Only one patient had normal alkaline phosphatase level. This patient initially presented with autoimmune hemolytic anaemia and was noted to have a positive antimitochondrial antibody. Liver biopsy confirmed the diagnosis of primary biliary cirrhosis. Antimitochondrial antibody was positive in 87% (14 out of the 16) patients tested. Total cholesterol was elevated in 80% of patients tested. IgM was elevated in 56% (5 out of the 9) patients tested.

Table I
Clinical Features

Clinical Features	Number of Patients
Fatigue	14 (82%)
Jaundice	13 (76%)
Pruritus	10 (59%)
Hepatomegaly	10 (59%)
Pigmentation	7 (41%)
Splenomegaly	5 (29%)
Xanthelasma	2 (12%)

Table II
Associated Illnesses

Patient	Illness
B	NIDDM, Post Thyroidectomy for MNG
C	NIDDM
F	NIDDM, Autoimmune Hemolytic Anaemia, Cholecytectomy and Right nephrectomy
G	Systemic Lupus Erythematosus with Ig A nephropathy
F	Autoimmune Thyroiditis
J	NIDDM with Pulmonary Fibrosis
O	NIDDM with Klatskin's tumour Stage IV
Q	NIDDM

NIDDM - Non Insulin Dependent Diabetes Mellitus
MNG - Multinodular Goitre

Thirteen patients had liver biopsies of whom 6 had Stage I disease, another 6 had Stage II disease and 1 had stage III disease based on Ludwig *et al*[6] histology classification. All patients had ultrasound examination of the hepatobiliary system. Eleven patients (64.7%) had features suggestive of cirrhosis.

Table III
Baseline Biochemical, Immunological Markers and Histology

PATIENT	TB umol/l	ALT mmol/l	ALP U/L	TC Mmol/l	IgM g/l	AMA +/-	Histology I/II/III/IV
A	168	171	281	NA	NA	+	NA
B	418	253	198	NA	4.6	+	II
C	29	53	496	5.9	3.7	+	I
D	498	412	173	NA	NA	-	II
E	22	41	253	NA	2.1	-	II
F	22	141	74	4.0	NA	+	I
G	37	247	612	7.2	NA	+	I
H	270	87	238	NA	NA	+	NA
I	22	290	490	6.7	NA	+	I
J	30	61	371	6.5	9.6	+	I
K	396	NA	NA	NA	NA	NA	III
L	54	118	487	9.1	3.8	+	II
M	39	246	658	9.0	4.2	+	II
N	345	184	1237	NA	NA	+	II
O	47	71	715	4.5	1.7	+	NA
P	52	195	861	6.2	1.7	Pos	I
Q	17	68	523	9.8	1.25	+	NA

NA - not applicable, TB - total bilirubin, ALT- alanine transaminase, ALP- alkaline phosphatase, TC- total cholesterol, AMA- antimitochondral antibody

Table IV
Bilirubin and Alkaline Phosphatase Level Change with Treatment with URSO

Patient	Bilirubin Level		Alkaline Phosphatase Level		Duration of Treatment
	Pre	Post	Pre	Post	
B	418	10	198	144	6 months
C	29	17	496	193	4 months
D	494	10	173	156	24 months
E	22	15	253	183	3 months
I	12	15	490	249	3 months
J	30	17	371	119	6 months
L	54	28	497	373	16 months
M	39	25	658	409	3 months
N	345	131	1237	670	15 months
P	52	20	861	280	3 months

A total of 13 patients (76.5%) underwent upper gastrointestinal endoscopy examination. Six patients (35.3%) had normal examination. Five patients (29.4%) had oesophageal varices, 2 (11.8%) of who had grade I varices and 3 (17.6%) had grade IV varices of which 2 had bled. Another 2 patients had mild portal hypertensive gastropathy.

Four patients underwent ERCP, three male patients who had normal examination done to exclude PSC and one female patient who had dilated intrahepatic ducts on ultrasound examination was found to have cholangiocarcinoma. This was a rare case where an association between cholangiocarcinoma and PBC existed. Ursodeoxycholic acid (URSO) was the mainstay of treatment in our patient population followed by management of complications of portal hypertension.

Ursodeoxycholic acid (URSO) was started in 10 patients. The doses ranged from 250mg bd. to 500mg bd. Nine out of the ten patients noted improvement in fatigue and pruritus on direct questioning. All 9 patients had noted reduction in their bilirubin and ALP's levels as shown in table IV. There were no adverse effects noted in this series.

A total of 3 patients had undergone endoscopic variceal band ligation for secondary prophylaxis of oesophageal varices and were started on propranolol 40mg b.i.d. Spironolactone was started in 2 patients who developed ascites with dosage adjustment raised on response, both clinically and biochemically.

Discussion

The above review has demonstrated that PBC is not common in our population as has been described in an earlier study[7]. It is interesting to note that this disease predominantly affects middle-aged women in our population. It's ratio of 3.25:1 however is significantly lower than in Western data. The most likely reason is that the patient numbers are not large enough to verify sexual distribution. Our series however reports a multiracial distribution with a slight preponderance to Chinese patients.

PBC was associated with a number of symptoms, mainly fatigue and pruritus in the earlier phase of illness as compared with jaundice and features of portal hypertension in the later stage[8]. Fatigue, jaundice and pruritus were the most common features in our patients. Jaundice is a late presentation but this occurred in 76% of our patients at presentation compared to 63% complaining of pruritus. The opposite holds true in the West as patients present with pruritus earlier in the disease[7]. This observation suggests that our patients present later in their disease and do not consider pruritus as a problem.

The associations noted were non-insulin dependent diabetes mellitus, thyroiditis, pulmonary fibrosis, systemic lupus erythematosus and cholangiocarcinoma. These have been reported in PBC series previously[9] confirming an autoimmune basis for this disease. Elevated alkaline phosphates level, which is the most consistent biochemical abnormality, was seen in 16 cases (94.1%).

The sensitivity and specificity of AMA for PBC is around 95% and seen in approximately 90% of PBC patients. AMA was present in 87% of our patients, which is comparable with one retrospective review of 200 patients with typical findings of PBC who were AMA negative[10] in 12% of their patients. All patients had imaging studies done of which 11 patients had evidence to suggest liver cirrhosis on ultrasound. Only 5 patients had oesophageal varices and two patients had portal hypertensive gastropathy.

The main stay of treatment in our patients was ursodeoxycholic acid (URSO). The duration of URSO usage ranged from 3 to 24 months. It is interesting to note 3 patients who had bilirubin levels more than 300μmol/l responded with two

normalizing their levels and one had a reduction by half. Many randomized controlled trials have shown that UDCA therapy leads to significant increase in survival after therapy translating to delay to liver transplantation[11] or enhanced transplant free survival. Current evidence suggest that ursodeoxycholic acid helps by facilitating the transportation of intracellular bile acid across the canaliculus[12], has a cytoprotective effect on cell membrane as reduces the intracellular bile acid level[13,14]. Finally it has an immunomodulatory effect[15].

The effectiveness of URSO therapy in PBC is underscored by the significant response seen in all those treated and this resulted in significant symptomatic relief and improvement in quality of life when analysed by direct questioning. Our patients appear to tolerate the URSO very well.

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