PRIMARY BILIARY CIRRHOSIS - AN UNCOMMON DISEASE IN SINGAPORE

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ABSTRACT

Primary biliary cirrhosis (PBC) is uncommon in Singapore. Twelve consecutive patients with PBC were seen between 1987 and 1994 at the National University Hospital. Eleven were women and the mean age at presentation was 53 years. Three patients presented with pruritus and jaundice whilst three had decompensated cirrhosis. The remaining six patients had no symptoms attributed to their liver disease when first detected, three of them presented with associated conditions including sicca syndrome and interstitial lung fibrosis, lichen planus, and carcinoma of breast. All patients had elevated serum alkaline phosphatase and positive anti-mitochondrial antibodies. Liver histology (10/12) showed Stage II disease (2), Stage III (5) and Stage IV (3). Three patients also had co-existing gall bladder stones but their endoscopic retrograde cholangiograms were normal. The mean follow-up period was 32.6 months and four patients died during follow-up. The only male patient had liver transplantation, two patients had symptomatic treatment while the rest were treated with ursodeoxycholic acid. In conclusion, local patients tended to presented relatively early in the course of the disease with 50% being asymptomatic and in the precirrhotic Stages.

Keywords: *asymptomatic, anti-mitochondrial antibodies, serum alkaline phosphatase, pruritus, histologic stage*

SINGAPORE MED J 1996; Vol 37: 48-50

INTRODUCTION

Primary biliary cirrhosis (PBC) has been documented in all races and it accounts for 0.6% to 2% of deaths from cirrhosis worldwide[1]. However, PBC is uncommon in Singapore where hepatitis B virus is the major cause of chronic hepatitis and cirrhosis. There are only case reports published to date concerning local PBC[2,3]. In recent years PBC has been diagnosed more commonly before onset of jaundice or even during the asymptomatic phase when elevated serum alkaline phosphatase (SAP) was detected during routine examination. We describe twelve patients with PBC.

METHODS

From 1987 to 1994, twelve consecutive cases of PBC were detected in NUH. The diagnosis was based on compatible clinical features, liver histology and positive anti-mitochondrial antibodies (AMA) and exclusion of other causes of cholestasis. Extrahepatic cholestasis was excluded by either ultrasonography, computerised tomography and/or endoscopic retrograde cholangio-pancreatography (ERCP).

Patients were classified as asymptomatic if no symptoms could be attributed to their liver disease when first detected. Signs and symptoms attributed to PBC included pruritus, jaundice, variceal bleeding, ascites or edema. Known associated autoimmune disorders were not considered manifestations of the liver disease.

Liver biopsies (eight percutaneous and two wedge specimens) were performed at the time of initial evaluation and the histologic diagnosis of PBC was based on criteria described[4] previously.

RESULTS (TABLE I)

Of the twelve patients, 92% were women and the mean age at presentation was 53 years (range: 42 to 70). All of them were ethnic Chinese. Only three patients (25%) presented with pruritus and jaundice. Three (25%) had decompensated cirrhosis; two actually presented with variceal bleeding. The other six patients (50%) were detected incidentally with elevated serum alkaline phosphatase. They were asymptomatic; three of them presented with associated conditions including sicca syndrome with interstitial lung fibrosis, lichen planus and carcinoma of breast. Of the six asymptomatic patients, two had hepatomegaly which led to liver function tests.

LABORATORY TESTS

There were six patients who were jaundiced at presentation with a mean initial serum bilirubin (SB) level of 78 mmol/L (normal < 33 mmol/L). Four of these patients were cirrhotic clinically. Their mean serum albumin level was 29 gm/L (normal > 35 gm/L). The other six patients had normal initial serum bilirubin and albumin levels. All patients had elevated alkaline phosphatase (SAP) and gamma-glutamyl transpeptidase with a mean level of 503 U/L (normal < 126 U/L) and 616 U/L (normal < 80 U/L) at presentation respectively. Serum alanine transaminase (ALT) were only mildly elevated with a mean level of 108 U/L (normal < 56 U/L). Serum IgM concentrations were above the upper limit of normal in 6 out of 8 (75%) patients who had the test done. Serum anti-mitochondrial antibody (AMA) was positive in all patients, anti-nuclear factor and anti-smooth muscle antibodies were positive in 6 out of 10 (60%) and 5 out of 10 (50%) of patients respectively. None of them were HBsAg carriers. S. cholesterol was elevated in 8 out of 12 (67%) patients with a

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Table I - Patients' characteristics

	Patient	Age	Sex	Presentation	Associated conditions	AMA	ANF	ASM	IgM	SB	SAP	Histo Stage	Outcome
1.	NSK	43	F	Asymptomatic	Nil	+	0	0	Normal	9	206	Stage III	On UDCA
2.	CPS	50	F	Asymptomatic	Ca breast	+	0	0	Elevated	5	370	Stage III	On UDCA
3.	LYK	50	F	Asymptomatic	Nil gallstone + ERCP normal	+	0	0	Elevated	11	187	Stage III	On UDCA
4.	YLS	42	F	Pruritus + Jaundice	Nil ERCP normal	+	+	+	Elevated	38	234	Stage II	On UDCA
5.	TKE	53	F	Asymptomtic	Nil gallstone + ERCP normal	+	0	+	Elevated	10	496	Stage III	Symptomatic treatment
6.	CFS	52	F	Asymptomatic	Lichen planus ERCP normal	+	+	+	ND	34	329	Stage IV	On UDCA
7.	SKS	50	F	Asymptomatic	Sicca syndrome Interstitial lung fibrosis gallstone + ERCP normal	+	+	0	ND	16	700	Stage III	Symptomatic treatment
8.	TKM	58	M	Decompensated cirrhosis	Nil ERCP normal	+	+	ND	ND	103	455	Stage IV	Transplantation, died 2 yrs later of sepsis
9.	LAP	70	F	Variceal bleeding	Nil	+	ND	ND	Elevated	105	510	Stage IV	Died of Liver failure
10.	TBC	61	F	Variceal bleeding	Nil	+	ND	+	ND	71	599	Inconclusive, refused repeat biopsy	Died of Liver failure
11.	GY	52	F	Pruritus Jaundice	Nil	+	+	0	Elevated	57	866	No Bx	Died of liver failure
12.	SAM	54	F	Pruritus Jaundice	Nil ERCP normal	+	+	+	Normal	95	1075	Stage II	On UDCA

ND: not done

mean level of 8.3 mmol/L (normal < 5.2 mmol/L).

Histological findings

All ten biopsies showed diagnostic or compatible pathological findings: three were in Stage IV, five in Stage III and two in Stage II of the disease. One patient refused repeat liver biopsy as the initial biopsy was non-conclusive but had clinical manifestation compatible with PBC. One other had ascites and no biopsy was done but had clinically Stage IV PBC. Diagnostic histology revealed that the portal tracts showed varying degree of chronic inflammation. There was evidence of destructive granulomatous cholangitis (the so-called 'florid duct lesion') in the early stages followed by loss of interlobular bile ducts in the later stages (Fig 1). This was accompanied by increasing fibrosis in the portal areas with portal to portal linkage and progression to biliary cirrhosis. Increasing amount of stainable copper and copper-protein granules were demonstrated in the periportal hepatocytes with the rhodanine and shikata orcein stains respectively with progression of the disease.

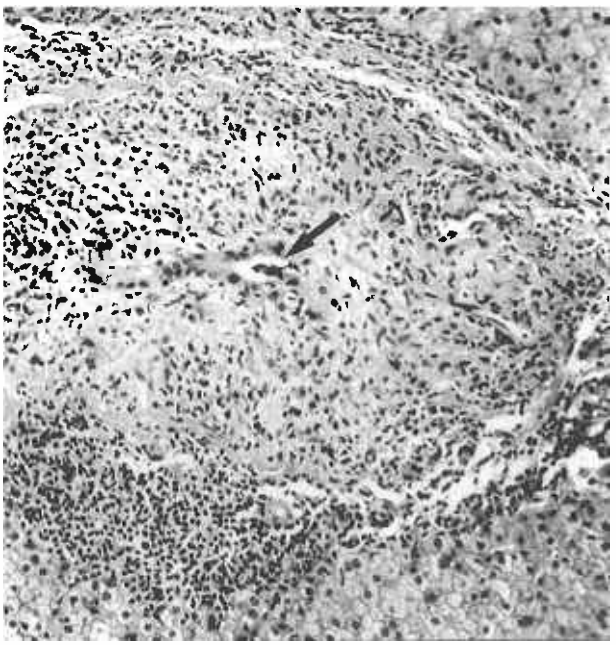
Other associated diseases

Three patients also had co-existence gall bladder stones. Their ERCP were normal with no evidence of ductal obstruction.

Outcome of the disease

The mean follow-up period was 32.6 months (range: 6 to 60 months). During this period, four patients died. Three of them died of liver failure three years after presentation. The other

Fig 1 - A portal tract showing destructive granulomatous cholangitis (the so-called 'florid duct lesion') involving an interlobular bile duct (arrow). There is associated chronic inflammation. (Haematoxylin & eosin, X 150)



patient, the only male patient, was transplanted 6 months after presentation with increasing jaundice but died of sepsis two years post transplantation when he defaulted and developed acute rejection. Two patients had symptomatic treatment while the rest were treated with ursodeoxycholic acid (UDCA) with decreasing SAP levels during treatment and remained clinically well and anicteric.

DISCUSSION

The prevalence of PBC in the Western world varies from 2.2 to 14.4 per 100,000 population. No information regarding prevalence of PBC in Singapore is available as yet. So far, there were only 5 cases reported in two papers published in 1979 and 1988[2,3]. The increased health screening programme in recent years does not seem to increase the number of PBC cases diagnosed by gastroenterologists or hepatologists locally. It is likely that the small number of PBC diagnosed reflects a true low prevalence of the disease locally rather than under diagnosis.

In recent years, the disease spectrum of PBC has extended to include a symptomless phase[5,6]. Increased awareness of the disease, more objective laboratory tests and increasing use of routine screening tests have allowed earlier diagnosis. Fewer patients are jaundiced at the time of diagnosis and hepatic histology shows earlier stages of the disease. James et al reported that nearly half of their patients detected with PBC were symptom-free[7]. Fifty percent of our patients were asymptomatic and were in preicteric stage at presentation. The diagnosis was first suspected because of an unexplained high serum alkaline phosphatase.

Gradual onset of pruritus followed later by jaundice is the classic presentation of PBC. However, only three of our patients had such presentation and three others who were jaundiced at diagnosis presented with decompensated cirrhosis. Two of the three who had cirrhosis admitted presence of pruritus only on direct questioning. Bleeding from oesophageal varices has been reported as a frequent initial complaint[8] but only two of our cirrhotic patients had oesophageal variceal bleeding when first seen.

Associated autoimmune diseases are not uncommon among PBC patients. The frequency of autoimmune associations was reported to be as high as 84% and the frequency of positive ANA was 22%[9]. Two (17%) of our patients had sicca syndrome, interstitial lung fibrosis and lichen planus when first presented. Six out of 10 (60%) of our patients had positive ANA but showed low titre of 1:40. The relation between PBC and breast cancer is less certain. Reports[10-12] have been conflicting. Interestingly, one of our patients was diagnosed eight years after mastectomy for breast cancer.

PBC has been divided into four histologic stages[4]. The liver is not affected uniformly in PBC and it is not uncommon to see a spectrum of severity in a single biopsy specimen. Staging is best based on the most advanced lesion. However, a small percutaneous needle biopsy specimen may miss an advanced lesion while a small subcapsular specimen may exaggerate the histologic stage. Sampling variation may partly explain the poor correlation between histologic stage and symptoms[13]. Five of our patients with Stage III and one with Stage IV disease are asymptomatic at presentation, and two of the patients who presented with pruritus and mild jaundice have only Stage II disease on biopsy. The majority of these asymptomatic patients had early histological stage but contrary to an earlier report[5], it was found that these patients do progress clinically and histologically. Their risk of death is similar to that of symptomatic PBC patients once asymptomatic patients progress to develop symptoms[13,14]. The course of the disease is however variable, ranging from a median survival of 5-7 years from the onset of symptoms to an asymptomatic period of 30 years or more.

There is still no effective treatment for PBC. Colchicine, methotrexate, cyclosporine, chlorambucil, penicillamine and lately UDCA have been evaluated. UDCA therapy was associated with a significant improvement in hepatic biochemistries but did not seem to halt histological progression or change the natural course of the disease[15-17]. Liver transplantation is now the ultimate treatment of choice for advanced stage PBC patients[18,19]. The only male patient in our study had progressive jaundice and was transplanted about 6 months after presentation. He did well after which but died of sepsis during acute rejection when he defaulted treatment. One other cirrhotic patient died while waiting for liver transplantation.

In conclusion, PBC patients in Singapore have similar clinical features as those in Western countries but tend to present at the pre cirrhotic stage of the disease and are asymptomatic as a result of routine screening.

References

1. Kaplan MM. Primary biliary cirrhosis. N Engl J Med 1987;316:521-48.
2. Lim KP, Ho KT, Gwee HM, Chan HL. Primary biliary cirrhosis in a Chinese female. Med J Aust 1979;2:364-5.
3. Chong R, Ng HS, Seah CS. Primary biliary cirrhosis. A description of four cases. Singapore Med J 1988;28:68-71.
4. Ludwig J, Dickson ER, McDonald GSA. Staging of chronic non-suppurative destructive cholangitis (sydnrome of PBC). Virchows Arch 1978; 379: 103-12.
5. Beswick DR, Klatskin G, Boyer JL. Asymptomatic primary biliary cirrhosis. A progress report on long term follow up and natural history. Gastroenterology 1985;89:267-71.
6. Long RG. Scheuer PJ, Sherlock S. Presentation and course of asymptomatic primary biliary cirrhosis. Gastroenterology 1977;72:1204-7.
7. James O, Macklon AF, Watson AJ. Primary biliary cirrhosis. A revised clinical spectrum. Lancet 1981;i:1278-81.
8. Zeegen R, Stansfeld AG, Dawson AM. Bleeding esophageal varices as the presenting feature in primary biliary cirrhosis. Lancet 1969;ii:9-13.
9. Culp KS, Fleming CR, Duffy J, Baldus WP, Dickson ER. Autoimmune associations in primary biliary cirrhosis. Mayo Clin Proc 1982;57:365-70.
10. Goudie BM, Burt AD, Boyle P. Breast cancer in women with PBC. Br Med J 1985;291:1597-8.
11. Wolke AM, Schaffner F, Kopelman B, Sacks HS. Malignancy in PBC: high incidence of breast cancer in affected women. Am J Med 1984;76:1075-8.
12. Witt-Sullivan H, Heathcote J, Cauch K, Blendis L. The demography of PBC in Ontario, Canada. Hepatology 1990;12:98-105.
13. Balasubramaniam K, Brambsch PN, Wiesner RN, Lindor KD, Dickson ER. Asymptomatic PBC: patients have a diminished survival. Hepatology 1987;7:1025.
14. Mitchison HC, Kelly P, Neuberger J, Bassendine M, Williams R, James O. Symptomatic development and prognosis in asymptomatic PBC. Hepatology 1988;5:1417.
15. Neuberger J, Lombard M, Galbraith R. Primary biliary cirrhosis. Gut Supplement 1991:S73-8.
16. Wiesner RH. Is continued enthusiasm for UDCA therapy for the treatment of PBC warranted? Hepatology 1992;15:971-3.
17. Heathcote E J, Cauch-Dudek K, Walker V, Bailey RJ, Blendis LM, Ghent CN, et al. The Canadian multicenter double-blind randomised controlled trial of ursodeoxycholic acid in primary billary ciirhosis 1994; 19: 1149-56.
18. Esquivel CO, Van Thiel DH, Demetris AJ. Transplantation for PBC. Gastroenterology 1988;94:1207-16.
19. Markus B, Dickson E, Grambsch T, Fleming V, Mazzaferro G, Klintmalm R, et al. Efficacy of liver transplantation in patients with PBC. N Engl J Med 1989;320:1709-13.