

PRIMARY BILIARY CIRRHOSIS: A DESCRIPTION OF FOUR CASES

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SYNOPSIS

Four cases of Primary Biliary Cirrhosis seen over 1979–1986 are described. The diagnosis was confirmed with a liver biopsy. All our patients were middle aged women. They were symptomatic at presentation. Two of them were also jaundiced. The anti-mitochondrial antibody was present in three patients. Three of these patients gradually deteriorated over the years and one died of hepatic failure. Only one patient has remained anicteric and liver function has not deteriorated.

SING MED J. 1988; 29:68–71

INTRODUCTION

Viral hepatitis and extra-hepatic biliary obstruction from stones or malignancies are the common causes of cholestasis. Primary Biliary Cirrhosis is a rare but well recognised cause of intra-hepatic cholestasis. It has a wide clinical spectrum and the presentation ranges from that of an otherwise well anicteric patient to the classical picture of a person with jaundice and xanthalesmata. It's early diagnosis is therefore difficult and most patients seen are usually symptomatic with abnormal liver function tests. We describe four cases seen in the Dept of Medicine SGH in the period 1979–1986.

CASE 1

A 52 year old woman presented with jaundice, pruritus, dark coloured urine and pale coloured stools over three months. There was a previous history of thyroidectomy for a nodule. Clinical examination revealed hepatosplenomegaly with jaundice. No xanthalesmata were seen. Initial liver function tests revealed a raised serum alkaline phosphatase of 990iu, SGPT of 210iu and a serum bilirubin of 6.7mg/dl. Liver biopsy revealed portal tract inflammation with necrosis of the bile duct epithelium. Two non-caseating granulomas were seen. The liver parenchyma was not involved. This was consistent with a diagnosis of Primary Biliary Cirrhosis. Patient developed rashes to penicillamine. Over the last two years, she has become more jaundiced and hyperpigmented. Ascites is now present. The bilirubin level in July'86 was 9.8mg/dl. The anti-mitochondrial antibody was not present in this patient.

CASE 2

The second patient is a 58 year old women who presented at 51 years of age with pruritus, malaise and loss

of weight of three months duration. She was pale, jaundiced and there was hepatosplenomegaly. Both parotid glands were also enlarged. Liver function tests revealed a serum alkaline phosphatase of 600iu, SGPT of only 70iu and a serum bilirubin of 1.7mg/dl. The haemoglobin was only 4.8mg/dl. A gastroscopic examination showed gastric erosions and cimetidine was prescribed. She subsequently had a massive bout of haemetemesis and malaena. An emergency operation was done. The liver was found to be grossly cirrhotic and the spleen markedly enlarged. A splenectomy and wedge biopsy of the liver were done. Histology was consistent with a diagnosis of end stage Primary Biliary Cirrhosis. There were marked changes around the portal triads and heavy lymphocytic infiltration around the bile ducts with multiple epithelioid granulomata but no caseation necrosis. There were also bands of septal fibrosis (fig1,2) Cholestyramine, vitamin A & D and calcium supplements were prescribed. The patient later had intractable pruritis. The jaundice has since deepened and there is ascites and dependent oedema. The anti-mitochondrial antibody was present in this patient.

CASE 3

The third patient described was a 46 year old women who presented with a one year history of pruritis, a dry mouth and a sandy feeling in the eyes. There was however no jaundice or hyperpigmentation. Hepatosplenomegaly was present. Serum alkaline phosphatase was raised to 760 iu and the SGPT, SGOT were mildly elevated. The serum bilirubin was 1.4mg/dl and anti-mitochondrial antibody was present. Liver biopsy showed ductal inflammation and infiltration. No granulomas were seen. A diagnosis of Primary Biliary Cirrhosis was made. Patient also developed rashes to penicillamine. Her disease has remained stable and except for the pruritus, no other signs of advanced chronic liver disease were detected. A positive Schirmer's test and Rose Bengal staining suggested an associated Sjogrens Syndrome.

CASE 4

The last patient (fig 1) a 57 year old woman who presented with pruritus and jaundice. Hyperpigmentation and eyelid xanthalesmata were present. There was hepatomegaly. Initial serum bilirubin was 5.3mg/dl and serum alkaline phosphatase was 800 iu. SGPT was mildly elevated (70iu) and anti-mitochondrial antibody was positive. Percutaneous Transhepatic Cholangiography showed no obstruction or dilated ducts. Liver

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Fig. 1 Case No. 4 demonstrating hepatosplenomegaly. She died of hepatic failure.

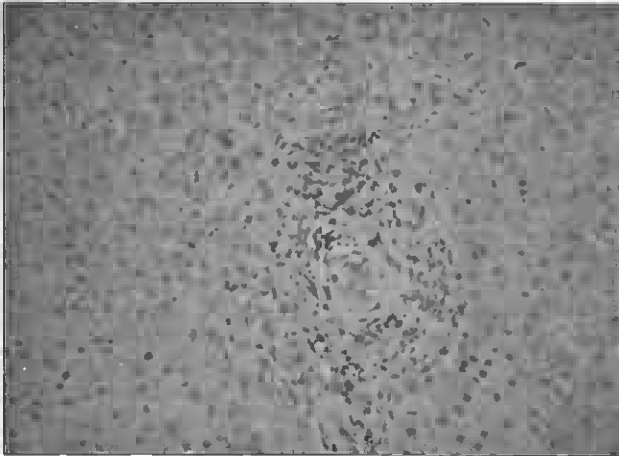


Fig. 2 Histological slide from case No. 2 showing bile duct infiltration and proliferation

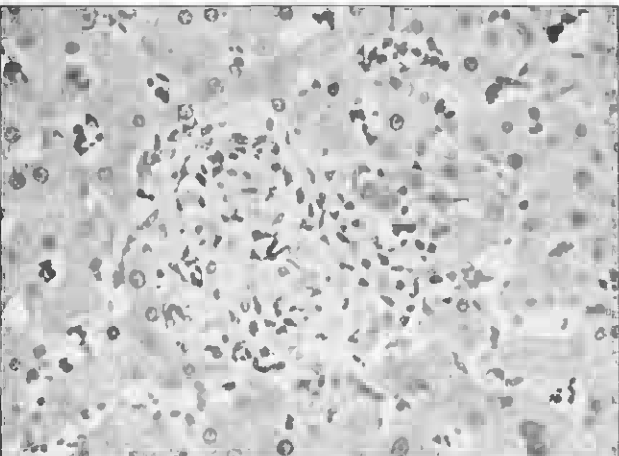


Fig. 3 Another slide from case No. 2 showing granuloma

biopsy confirmed the diagnosis. It showed bile duct proliferation, granuloma formation, cholestasis and disruption of lobular architecture. (fig 4) This patient also developed rashes to penicillamine. Her condition gradually deteriorated and was complicated by steatorrhoea and osteomalacia. Patient died of hepatic failure 4 years later. The serum bilirubin at this terminal stage was 19.6 mg/dl and the serum alkaline phosphatase was 506 iu.

TABLE I
RELATIONSHIP OF PRESENTING BILIRUBIN LEVELS AND HEPATIC HISTOLOGY TO CLINICAL COURSE

Cases	1	2	3	4
Bilirubin mg/dl	6.7	1.7	1.4	5.3
Liver Biopsy Histological Staging	II	IV	I	IV
Clinical Course	Alive (Worse)	Alive (Worse)	Alive (Same)	Died

All values and histology are those taken on initial diagnosis

TABLE II
INITIAL SERUM ALKALINE PHOSPHATASE VALUES AND THEIR SUBSEQUENT CLINICAL COURSE

Cases	1	2	3	4
Serum Alkaline Phosphatase iu	990	600	760	800
Clinical Course	Alive (Worse)	Alive (Worse)	Alive (Same)	Died

TABLE III
PREVALANCE OF SJOGREN'S SYNDROME AND ANTI-MITOCHONDRIAL ANTIBODY (AMA) IN THE PATIENTS

Cases	1	2	3	4
Sjogren's Syndrome	absent	present	present	absent
AMA	absent	present	present	present



Fig. 4 slide from case No. 4 showing copper deposition as a result of cholestasis.

RESULTS

All our patients were middle aged females. Ages ranged from 45–57 years. All presented with pruritus. Two patients were icteric and both did not fare well. Of the two anicteric patients, one remained in the same condition while the other gradually deteriorated. It is interesting to note that the patient (Case 1) who deteriorated was frankly cirrhotic on initial liver biopsy as compared to the other, who had only stage 1 histological changes. (Table I) It appears that initial liver histological staging does have prognostic value. Two of our patients with stage IV disease have deteriorated or died while the patient (case 3) has not. An initially elevated bilirubin level does also appear to suggest a poorer prognosis (Table I). There was no correlation of worsening disease with initial levels of serum alkaline phosphatase (Table II). Three of our four patients had anti-mitochondrial antibody and two patients had an associated Sjogren's syndrome (Table III). Three of the patients developed rashes to penicillamine.

DISCUSSION

Primary Biliary Cirrhosis is a rare cholestatic syndrome. Studies in England have estimated the point prevalence to be approximately 40–50 per one million population (1,2,3). Thirty to fifty per cent of these patients are asymptomatic or present with symptoms unrelated to the liver. Unexplained hepatomegaly or an elevated serum alkaline phosphatase were the common abnormalities seen. More of such patients are being picked up with the advent of routine multiphasic health screening. Symptomatic patients most frequently presented with pruritus. Jaundice was only present in forty percent (5,6).

All our patients were symptomatic, Primary Biliary Cirrhosis is rare in this country and there have been no previous local reports on this condition.

The characteristic abnormality in the liver function test is a disproportionately raised serum alkaline phosphatase with only mildly raised transaminases. The serum bilirubin may or may not be elevated. The anti-mitochondrial antibody is present in eighty to ninety percent of patients (5,7). It is not specific as studies have shown that most people in the general population with this antibody do not have this condition (3).

While most of the antibody is IgG, the IgM component is most consistently present in all those affected. The three tests, serum alkaline phosphatase, IgM and anti-mitochondrial antibody when present together, is suggestive of this condition. The diagnosis is confirmed with a liver biopsy. Cholangiography is necessary when the suspicion of biliary obstruction exists. It is interesting to note that the clinical presentation does not correlate with the degree of liver damage present. This is well illustrated in our patients. Though all our patients presented with pruritus, their initial liver biopsies showed changes from the very mild early stages to the frankly cirrhotic picture. It should be noted that 3 out of 4 (75%) of our patients had anti-mitochondrial antibody. This percentage being close to other figures quoted (Table III).

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Primary Biliary Cirrhosis used to be thought of as a condition with a uniformly poor prognosis. Recent studies have suggested otherwise. Primary Biliary Cirrhosis can now be divided into three groups based on its presentation. The first group consists of patients who are asymptomatic. Regardless of their initial liver histology, they generally have a good prognosis. The other two groups of patients are symptomatic. They differ in their presentation. One group presents initially with jaundice, signs of liver cirrhosis, portal hypertension and liver failure. This group fares poorly despite treatment. The next group consisting of fifty to seventy percent of patients presents with pruritus or non specific symptoms. They have a variable course and factors affecting prognosis are still being evaluated. Such factors include advanced age, jaundice, hepatosplenomegaly, weight loss and ascites (9). The serum bilirubin is perhaps the most significant predictor of a poor prognosis (9). This is well illustrated in our patients (Table I). On initial histology, the presence of cirrhosis, bile stasis and erosion of the limiting plate is said to correlate with a poor prognosis (9). The presence of granulomas on initial biopsy was thought to be a good prognostic factor. This has not been substantiated in further studies (10). In our patients, patients with frank cirrhosis had a poor prognosis. Granulomas seen in three of our patients (cases 1, 2 and 4) did not correlate with a good prognosis.

Many drugs have been used in the treatment of this condition. These includes azathioprine, corticosteroids, cyclosporin A and penicillamine. Unfortunately, none have been found to be totally effective.

Penicillamine because of its anti-inflammatory and copper chelating properties was thought to be a very useful drug in the mid 70's. Though initial trials at the Royal Free Hospital were promising (12), later studies at Boston (15), the Mayo clinic (13) and the European Multicentre Trial (14) indicated otherwise. There is no improvement in patients with fairly advanced liver cirrhosis. Trials are still being continued with patients in the earlier stages of the disease. The immune system has been thought to play a big part in the etiology and pathogenesis of this condition. It is thought the disease is more an immune regulatory disorder with an actual depletion of T suppressor cells. This results in an alteration of the T suppressor/T helper ratio. Cyclosporin A is a drug which corrects this ratio and in a small trial at King's College, it was found to be of some benefit (16). The limiting factor in this drug is its nephrotoxicity. Trials are now going on with this drug given at a lower dosage resulting in the same efficacy but considerably less adverse effects (17). Plasmapheresis (18) and liver transplantation are other modalities that have been used.

CONCLUSION

Four patients with Primary Biliary Cirrhosis are described. All were females and presented with pruritus. Three out of four patients had antimitochondrial antibody. The subsequent clinical course appears to be related to the serum bilirubin and the initial liver histology.

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