Primary biliary cirrhosis

A retrospective survey at Groote Schuur Hospital, Cape Town

S. C. ROBSON, R. J. HIFT, R. E. KIRSCH

Summary

Primary biliary cirrhosis (PBC) or chronic non-suppurative destructive cholangiohepatitis is rare in southern Africa. Eight patients with this diagnosis were identified and fully investigated at Groote Schuur Hospital between 1980 and 1988. Seven patients were female, all were white or coloured, and their ages ranged from 49 years to 80 years. All patients presented with a history of malaise, fatigue, night sweats and pruritus, which had been present for 3 months - 12 years before diagnosis of PBC. Initial misdiagnosis had resulted in unnecessary invasive investigations including laparotomies. Signs of chronic liver disease, such as xantholasmas, evidence of pruritus, the sicca syndrome or hepatomegaly, were invariably present. Marked elevation of serum alkaline phosphatase level and IgM were present in all cases. Antimitochondrial antibodies were positive in significant titre in 7 of the 8 patients. Liver biopsies demonstrated stage II-III disease in all patients. Therapy was chiefly supportive and symptomatic although most patients received immunosuppressive agents. Despite the late presentation, the subsequent course was similar to that seen elsewhere where patients are recognised earlier.

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Primary biliary cirrhosis (PBC), more accurately termed chronic non-suppurative destructive cholangiohepatitis, is a chronic, progressive, cholestatic form of liver disease, which characteristically has a long duration of symptoms and ultimately evolves into cirrhosis and liver failure.[1] The condition has been found in all races, with estimates of its prevalence ranging from 3,7 cases/100 000 to 14,4 cases/100 000.[2] Our perception is that this condition is uncommon in southern Africa. This is in contrast to the higher incidence than elsewhere of sclerosing cholangitis, sarcoidosis and drug-induced cholestasis, which cause a similar derangement of liver function.

The diagnosis of PBC is usually made in a middle-aged woman complaining of fatigue and pruritus, or following investigation for unexplained hepatomegaly or raised serum alkaline phosphatase levels. Laboratory testing reveals immunological abnormalities, including impaired *in vitro* suppressor T-cell function, high levels of serum IgM and the presence of antimitochondrial antibodies.[3] The condition is characterised on histological examination of tissue specimens by the destruction of intrahepatic bile ducts, portal infiltration and parenchymal scarring.[4]

Eight patients with PBC were seen at Groote Schuur Hospital between 1980 and 1988. This group is described in the hope that our experience may lead others to make an earlier diagnosis in patients with this syndrome, thus preventing unnecessary invasive investigations, such as diagnostic laparotomy.

UCT/MRC Liver Research Centre and Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town
S. C. ROBSON, M.B. CH.B., D.C.H., F.C.P. (S.A.), M.R.C.P., PH.D.
R. J. HIFT, M.B. CH.B., F.C.P. (S.A.)
R. E. KIRSCH, M.D., F.C.P (S.A.)

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Patients and methods

All patients seen for the first time or followed up at the Groote Schuur Hospital liver clinic from 1980 to 1988 were reviewed. These patients were referred by general practitioners and specialists and therefore represented a mixture of secondary and tertiary referrals. Although the majority of our patients are referred from the Cape Town area, about 10 - 15% of referrals are from elsewhere in South Africa. Approximately 100 new and 500 'follow-up' patients are seen at the clinic each year.

The diagnosis of PBC was suspected on the basis of compatible clinical and biochemical findings and was confirmed by the detection of antimitochondrial antibodies (in most cases), exclusion of bile duct obstruction by ultrasonography and endoscopic retrograde cholangiopancreatography, and by liver biopsy. PBC was staged on the basis of histological examination only. Patients have been followed up for 1 - 8 years.

Results

During the period 1980 - 1988, 8 patients met the criteria for the diagnosis of PBC; 7 were women, 5 white and 3 coloured (mixed race). Their ages, at diagnosis, ranged from 49 years to 80 years.

Clinical manifestations

Symptoms had been present for up to 12 years in the 8 patients before they were referred to our clinic and primary biliary cirrhosis was diagnosed. These symptoms included fever, fatigue, malaise, night sweats, pruritus, arthritis and myalgias. The clinical presentations were highly variable. Two patients were initially seen by dermatologists for pruritus (Fig. 1). One patient was referred to an orthopaedic surgeon with multiple vertebral wedge fractures (Fig. 2). Two patients presented with a systemic illness marked by intermittent pyrexia and arthralgia.

Hepatomegaly and abnormal liver tests were present in all patients when first seen. Hepatic enlargement was usually moderate, but was massive in 2 patients, extending to the right iliac fossa in 1. Splenomegaly and ascites were present in 3 patients. Examination usually revealed florid stigmata of chronic liver disease, including numerous spider naevi and palmar erythema, as well as peripheral oedema. All 8 patients demonstrated xantholasmas.

Associated diseases in the 8 patients included the sicca syndrome (3 cases), hypothyroidism (2 cases), renal tubular acidosis (1 case), seropositive rheumatoid arthritis (1 case) and seronegative symmetrical arthropathy (1 case). Three patients have hepatic osteodystrophy. Leg ulceration with panniculitis was noted in 2 cases.

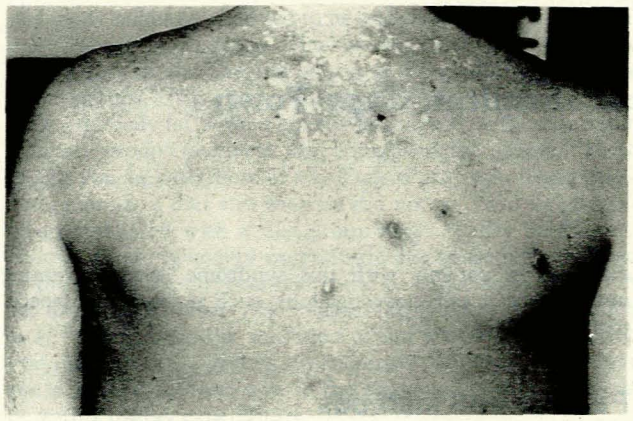

Fig. 1. Skin excoriation, scarring and cholesterol deposition in patient with severe pruritus secondary to PBC.

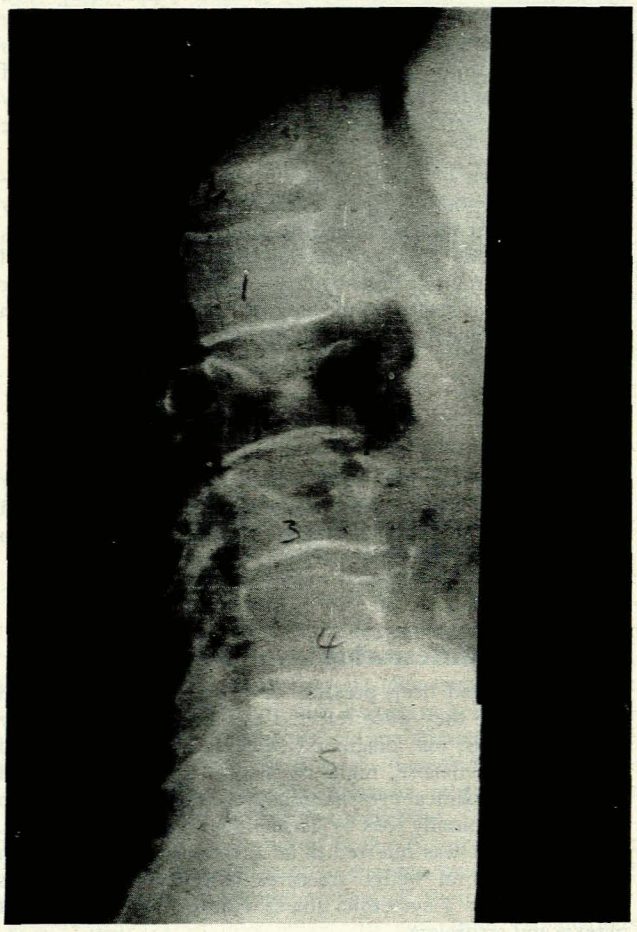

Fig. 2. Lateral radiograph of lumbar spine revealing osteoporosis and wedge compression fractures of T12 and L2, 3 in a patient with hepatic osteodystrophy and PBC.

Variceal haemorrhage has occurred in only 1 patient to date. Two others have chronic portasystemic encephalopathy. Thus 3 of the 8 cases had evidence of portal hypertension.

Initial misdiagnosis of this condition has been the rule. Hepatic tumours, lymphoma, myeloma and extrahepatic biliary obstruction had all been considered likely diagnoses before patients presented at our clinic. This had led to 2 patients undergoing laparotomy, while others were subjected to peritoneoscopy and coeliac angiography.

Laboratory tests

Liver function tests usually demonstrated cholestasis with normal or slightly elevated transaminases (Table I). One patient developed a sudden rise in serum bilirubin levels, deteriorated rapidly and died within 1 year (Fig. 3).

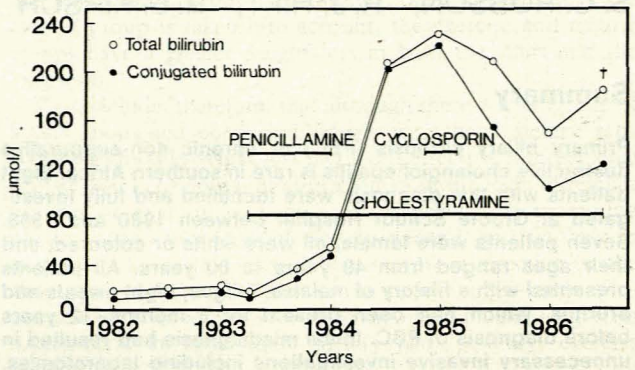

Fig. 3. Serial serum bilirubin estimations in a patient with PBC. Note accelerated increase from 1984 to 1985 before death.

All patients demonstrated hypergammaglobulinaemia with the classic elevation of IgM. Three patients had elevated IgG levels (Table I) and this appeared to correlate with the presence of piecemeal necrosis on liver biopsy. Seven patients had significant and consistent elevation of antimitochondrial antibodies. Antinuclear factor was detected in 2 patients, smooth muscle antibodies in 7 patients and rheumatoid factor (sheep cell agglutination test and latex test) in 2 patients.

Pathology

PBC may be staged histologically as follows:[5,6] stage I represents the initial lesion with bile duct injury, portal triaditis and, at times, hepatic granulomata; stage II is defined by periportal inflammation, which progresses to scarring with fibrous septa in stage III; stage IV represents cirrhosis. Although useful, this staging process is subject to sampling bias and indeed one biopsy sample may contain areas showing different stages of evolution.

Liver biopsies in the 8 patients revealed predominantly stage III and IV disease accompanied by florid ductal lesions (Figs 4 and 5).

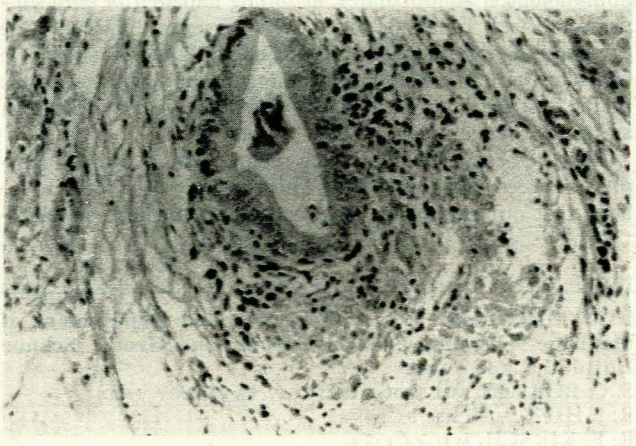

Fig. 4. Medium-sized bile duct with intra-epithelial lymphocytes and periductal inflammatory mononuclear cells with early fibrosis.

TABLE I. RESULTS OF LIVER FUNCTION TESTS AND IMMUNOGLOBULIN VALUES IN PATIENTS WITH PBC (MEANS ± SD)

	Patients	Normal range
Bilirubin		
Total (μmol/l)	30,0 ± 15,0	1 - 17
Conjugated (μmol/l)	22,6 ± 14,0	1 - 17
Alkaline phosphatase (μU)	798 ± 420	30 - 115
Gamma-glutamyl transferase (μU/l)	370 ± 217	0 - 50
Aspartate aminotransferase (μU/l)	49 ± 4	0 - 40
Alanine aminotransferase (μU/l)	56 ± 36	0 - 53
Total protein (g/l)	71 ± 14	60 - 80
Albumin (g/l)	36 ± 3	35 - 50
Cholesterol (μmol/l)	7,0 ± 0,3	3,1 - 7,1
Immunoglobulins (g/l)		
IgG	18,30 ± 5,10	6,39 - 13,49
IgA	4,06 ± 1,10	0,72 - 3,12
IgM	5,19 ± 2,20	0,56 - 3,52

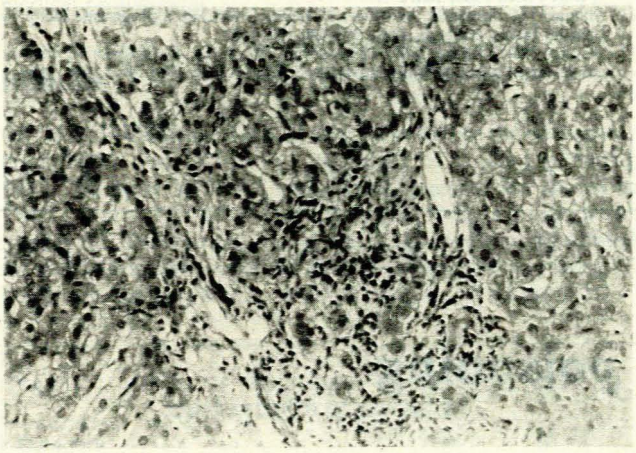

Fig. 5. Scarring with periportal inflammation, ductular proliferation and associated hepatocyte piecemeal necrosis.

Natural history

Despite the delayed diagnosis and presence of advanced disease the 5-year survival figures are 75%. The rate of progression of the disease has been highly variable.

Discussion

In series from elsewhere published before 1960 the diagnosis was usually made late in the course of the illness, at a time when jaundice, liver failure and portal hypertension are more common. Now, in contrast, the onset of disease is typically recognised earlier, between the ages of 30 years and 65 years. This is apparently because of a greater awareness of the disease and its presenting manifestations.

It is our impression that the patients resemble those described in the earlier series, rather than more recent series. This suggests a generally late diagnosis in most instances.

Clinically, PBC progresses through five stages.[5] The presymptomatic phase is characterised by mild fatigue and menorrhagia. Hepatomegaly may be present. The serum alkaline phosphatase level is always raised. The diagnosis at this point should be confirmed by liver biopsy, which may reveal mononuclear cell infiltration confined to the portal tract. Detection of antimitochondrial antibodies strengthens the diagnosis considerably.

The oligosymptomatic phase, with 'bile regurgitation', merges into the symptomatic anicteric phase. This is characterised by a disturbance of bile secretion, and pruritus and fatigue are invariably present.

Eventually the clinical picture evolves into the icteric phase. Bile secretion is severely disturbed. Patients have jaundice (progressive or stable) with pruritus. Skin pigmentation, excoriations, xantholasmas and spider naevi are common (Fig. 1). The liver is usually enlarged but splenomegaly is only noted in about one-third of cases. Steatorrhoea and hepatic osteodystrophy are common and may cause distressing symptoms.[1] The final phase is that of hepatocellular failure. Patients develop symptoms of portal hypertension, and may have encephalopathy and ascites. A number of patients present for the first time with such advanced disease.[7]

The association of PBC with scleroderma, Sjögren's syndrome, arthropathy, hypothyroidism and renal tubular acidosis is well established.[1] That PBC is associated with both hepatocellular[8] and breast cancer[9] is less well known.

Advanced age, hepatomegaly, an elevated serum bilirubin level, a decreased serum albumin value and histologically confirmed cirrhosis are thought to correlate with shortened survival.[10] The serum bilirubin level is typically normal in the early stages of the disease but rises later in most patients. An elevation in the serum bilirubin value is associated with a poor prognosis.[11] Indeed, a rapid rise in the serum bilirubin level, as we observed in 1 patient, is associated with a marked clinical deterioration, which may preclude liver transplantation.

An awareness of the clinical features of PBC and a high index of suspicion are important in making the diagnosis. It must be stressed, however, that an obstruction of the biliary system must always be excluded before accepting the diagnosis. Ultrasonography, computer tomography and endoscopic retrograde cholangiopancreatography are important in demonstrating patency of the bile ducts. Percutaneous needle biopsy will provide confirmatory information and allow histological staging of PBC.

There is no satisfactory treatment for the condition. The pruritus usually responds to cholestyramine, an anion-binding

resin that binds bile acids in the bowel lumen. Other options for the treatment of pruritus include histamine-2 receptor blockers, large-volume plasmapheresis and the administration of rifampicin. Attention to nutrition is important and parenteral supplements of the fat-soluble vitamins A, D, E and K must be administered regularly.[1]

More specific treatments used for this condition are reviewed by Kaplan *et al.*[1] These include corticosteroids, azathioprine, penicillamine, colchicine, chlorambucil, cyclosporin and ursodeoxycholic acid. Most of our patients received immunosuppressive agents, and we have tended in recent years to treat patients with colchicine (0,5 mg twice a day), which is said to slow the progression of the disease and has minimal side-effects.[12] None of these agents is curative and liver transplantation remains the treatment of choice in patients with liver failure and in those with recurrent oesophageal variceal haemorrhage.[1]

Conclusion

PBC is rare in South Africa. The diagnosis in our patients was almost always delayed and they had often been subjected to unnecessary invasive investigations. Early referral to a liver centre is essential in order to confirm the diagnosis, to treat the symptoms, minimise complications and to ensure that liver transplantation is considered at an appropriate stage of the disease.

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