The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

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Primary biliary cirrhosis

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1 Introduction

Primary biliary cirrhosis is a chronic, cholestatic liver disease which affects mainly middle-aged women. It starts with an inflammatory process of the small and middle-sized interlobular bile ducts leading first to a proliferation and then to a loss of bile ducts, to portal inflammation and in late stages to liver cirrhosis [1, 2]. It belongs to the autoimmune disorders because of the presence of antimitochondrial antibodies (AMA) in a high proportion (about 95 %) of patients, although the pathogenetic relevance of these antibodies is not entirely clear.

PBC occurs all over the world but with varying incidence and prevalence. The incidence of PBC ranges from 0.7–49 per million per year. In most recent studies, the point prevalence was estimated to range from 6.7 to 402 per million [2]. The frequency with which PBC is diagnosed increased considerably between 1980 and the present time, the reasons for this change may be complex. Assuming a life expectancy of 20 years after diagnosis, the point prevalence was estimated to be 207 per million, and for women above 45 years, 860 per million.

2 Diagnostic criteria

Typical clinical features of PBC are fatigue, pruritus and Sicca-syndrome (Table 1). However, nowadays at diagnosis, the majority of patients are asymptomatic and present for other reasons, e. g. for workup of elevated serum levels of AP or cholesterol. Increased awareness of the condition and the increasing availability of diagnostic tools, in particular serological testing, have led to more frequent and earlier diagnosis of PBC. A diagnosis of PBC is made "with confidence" when biochemical markers of cholestasis, particularly alkaline phosphatase, are elevated persistently for more than 6 months in the presence of serum AMA and in the absence of an alternative explanation (Table 2).

Table 1. Signs and symptoms of disease [1, 2].

Symptoms	Frequency (%)
Fatigue	80
Pruritus	20–70
Sicca-syndrome	20–30
Osteoporosis	35
Xanthoma	10–20
Urinary tract infection	19
Discomfort in the right upper quadrant of the abdomen	10
Fat-soluble vitamin malabsorption	Rare
Association with other autoimmune disorders	30–40

Table 2. Diagnostic criteria.

Clinical criteria

- fatigue
- pruritus
- upper abdominal pain
- Sicca syndrome

Laboratory criteria

- elevation of alkaline phosphatase (AP) and gamma-glutamyltranspeptidase (γ-GT)
- presence of antimitochondrial antibodies (AMA)
- in AMA-negative cases presence of defined ANA-specificities (antibodies to nuclear dots, nuclear membrane, centromeres)
- elevation of IgM-globulins
- hypercholesterolemia
- eosinophilia

3 Diagnostic measurements for experts

The major hallmark of PBC is the presence of AMA in serum labelled anti-M2 (Fig. 1). These react with subunits of the 2-oxoacid-dehydrogenase complex (2-OADC) and, in most cases, recognise the E2-subunit of pyruvate dehydrogenase (PDH-E2) (Fig. 2). AMA/anti-M2 positive individuals, even if they have no signs of cholestasis and/or liver inflammation, are very likely to develop PBC. AMA are present in about 95 % of PBC-patients. Of the remaining 5 %, about 2.5 % have PBC-specific antinuclear antibodies (antibodies to nuclear dots

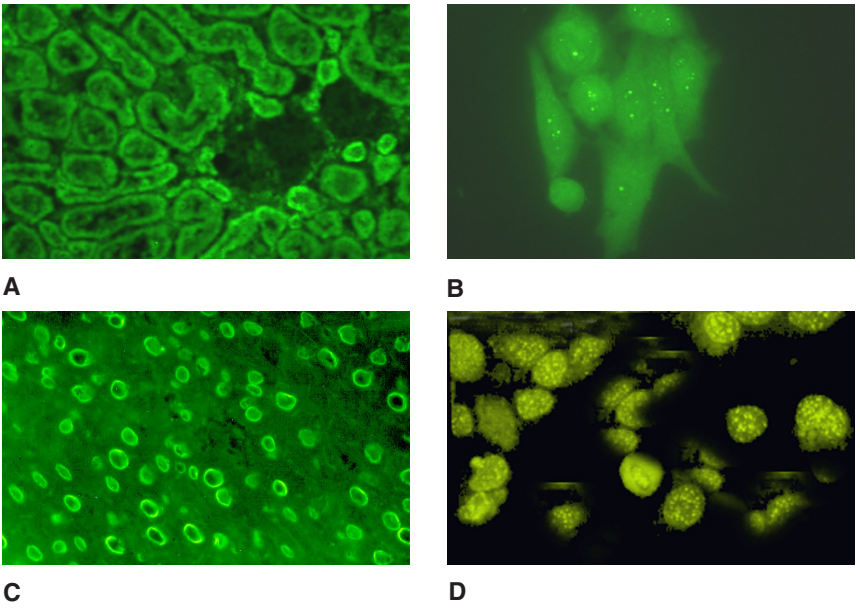

Figure 1. Demonstration of PBC-specific autoantibodies by immunofluorescence test (IFT). A) Demonstration of antimitochondrial antibodies (AMA) on rat kidney showing a coarse granular staining of proximal tubules; B) demonstration of antibodies to 'nuclear dots' (sp 100) on cell cultures; C) demonstration of antibodies to nuclear membranes (gp210) on heart muscle from rat; D) demonstration of antibodies to centromeres on cell cultures.

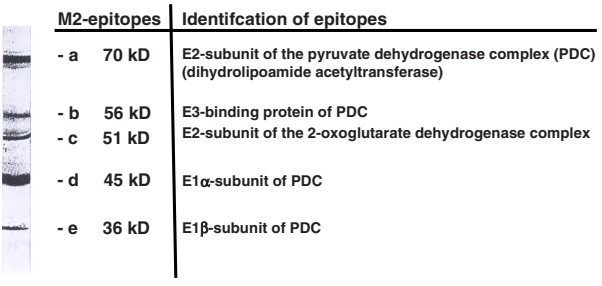

Figure 2. Identification of M2-determinants as subunits of the 2-oxoacid dehydrogenase complex.

[sp100], nuclear membrane [gp210], centromeres) (Fig. 1), but there are still about 2.5 % patients who have no relevant autoantibodies but otherwise all the features typical for PBC.

A liver biopsy is no longer regarded as mandatory for the diagnosis of PBC in patients with elevated serum markers of cholestasis and positive serum AMA, but may be helpful in excluding other potential causes of cholestatic disease and in assessing disease activity and stage. A liver biopsy may also be helpful in the presence of disproportionably elevated serum transaminases and/or serum IgG levels to identify additional or alternative processes, especially autoimmune hepatitis.

Histological staging of PBC (stage 1 to stage 4) is determined by the degree of (peri)portal inflammation, bile duct damage and proliferation, and by the presence of fibrosis/cirrhosis (Table 3).

Table 3. Histology and staging of PBC.

Stage I (portal stage)
Portal hepatitis, bile duct destruction, granuloma formation
Stage II (periportal stage)
Periportal hepatitis, interface-hepatitis extending to lobules, bile duct proliferation
Stage III (septal stage)
Presence of fibrous septa or bridging necrosis
Stage IV (cirrhotic stage)
Ductopenia, cirrhosis

4 Requirements for family practitioners

Nowadays, most patients are asymptomatic but an elevation of cholestatic enzymes, IgM- and cholesterol levels is observed during laboratory investigations. Many patients also show an eosinophilia. In symptomatic patients, fatigue, pruritus and Sicca-syndrome or symptoms of a collagen disorder such as myalgia or arthralgia are the most common complaints with which patients consult their general practitioner. When the diagnosis is suspected, the patient should be transferred to a hepatologist for further examination and laboratory testing. The presence of AMA confirms the diagnosis. Ultrasound examination of the liver and biliary tree is obligatory in all cholestatic patients in order to differentiate intrahepatic from extrahepatic cholestasis. A normal biliary system is typical for PBC. Abdominal lymphadenopathy, particularly in the hilar region of the liver, is seen in 80 % of patients with PBC.

About 20 % of patients exhibit other simultaneous or consecutive autoimmune diseases, the most frequent being autoimmune hepatitis, CREST syndrome and/or scleroderma, Sjögren's syndrome and thyroiditis.

First-degree relatives of patients with PBC are at high risk of PBC or other autoimmune diseases. The patients and their relatives should be informed and evaluated for these conditions.

Attention should focus on the severity or potential severity of the disease.

Because the prognosis of PBC is far better than two or three decades ago, two associated conditions deserve particular attention. Hypercholesterolemia with increased LDL cholesterol is observed in about 20 % of patients. Accordingly, the risk of cardiovascular disease should be evaluated and medical therapy possibly proposed. Osteoporosis and osteopenia might be more frequent in women with PBC so metabolic bone disease should be assessed and prevented.

5 Follow up

Clinical observations and expectations

There are three major forms of PBC. The typical or classical form is represented by the slowly progressive decline of small bile ducts and parallel increase in liver fibrosis, leading to biliary cirrhosis over a period of about 20 years. These patients may remain asymptomatic for a long time or suffer from fatigue and pruritus.

A second form, which affects 10–20 % of patients, is characterised by the fluctuating or persistent presence of the features of AIH. These patients have a more severe disease course with early development of liver fibrosis and cirrhosis. A third form, which affects 5–10 % of patients, is characterised by a rapid onset of ductopenia and severe icteric cholestasis, progressing very quickly towards cirrhosis in less than 5 years. In these patients the typical signs of portal hypertension (ascites, oesophageal bleeding, encephalopathy, jaundice, etc.) may develop.

Blood tests

During treatment, laboratory parameters should be assessed once or twice a year in asymptomatic patients, in patients with symptomatic PBC every three months. An increase of bilirubin is a strong indicator for progression of the disease and serves as marker for the indication of a liver transplantation.

Antimitochondrial antibodies are barely influenced by any therapy. Nevertheless, autoantibodies and quantitative immunoglobulins should be analysed at least once a year in order to exclude or recognise the development of an autoimmune hepatitis (or other autoimmune disorders) as early as possible.

Even after liver transplantation, AMA titres only transiently decrease about one year after the transplant but then again become positive, i. e. they cannot be taken as a marker for the recurrence of PBC in the transplanted liver.

6 Management

The cause of PBC is unknown and, therefore, no causal therapy exists. Ursodeoxycholic acid (UDCA) introduced in 1985 into the treatment of PBC, is currently considered the mainstay of therapy at a dosage of 13–15 mg/kg/day, and it is

the only FDA-approved drug for PBC. Randomised, double-blinded, placebo-controlled trials have consistently shown that UDCA improves parameters of liver biochemistry including serum bilirubin. UDCA delays the progression of fibrosis and histological stage, improves quality of life, survival free of transplant and overall survival [3, 4]. It is safe, and side effects are few but it may produce gastric discomfort, a burning sensation or diarrhoea.

The survival rate of UDCA-treated patients in the early stages is similar to that in a control population.

In a subset of patients, the daily dose of 13–15 mg/kg UDCA is not sufficient to achieve the optimal biochemical response. In those patients, a trial with daily doses up to 20 mg/kg/day may be proposed.

About 30–40 % of PBC patients have a suboptimal response to UDCA; these patients need an adjuvant therapy. Currently, glucocorticoids and methotrexate are considered for these patients. Serious side effects of long-term glucocorticoid treatment may outweigh the potential benefit. In this respect, the introduction of budesonide, a nonhalogenated corticosteroid with an extensive first-pass metabolism has been a promising innovation. The effect of methotrexate is still controversial.

Other immunosuppressive agents including azathioprine, cyclosporine, mycophenolate mofetil, and drugs with antifibrotic properties including penicillamine, colchicines, and silymarin have been evaluated and have been shown to be either ineffective or toxic.

Liver transplantation is the treatment of choice in patients with late-stage PBC with decompensated cirrhosis or liver failure. In highly selected patients treatment-resistant pruritus, in the absence of decompensated cirrhosis, or severe osteoporosis may be an indication for transplantation. Survival rates of 80–90 % at 5 years have been reported. The disease recurs in up to 30 % at 10 years after transplantation, but usually displays a mild course under immunosuppressive therapy.

7 Therapy of extrahepatic manifestations

UDCA also has a beneficial effect on *hypercholesterolemia*; it induces an average 15–20 % decrease in total and LDL cholesterol at 1 year of therapy. Statins can be given additionally.

The effect of UDCA on *pruritus* in PBC is variable. Cholestyramine is widely used as first-line treatment. Other therapies include glucocorticoids, sertraline, and opiate antagonists.

For *fatigue* the centrally acting modafinil, a drug approved for the treatment of narcolepsy, has been reported to provide significant benefit. The drug, used at doses up to 400 mg/day, seems well tolerated and very effective in those with excessive fatigue.

Current treatments for *osteopenia and osteoporosis*, which affect up to 30 % of PBC patients, include supplementation with calcium (1000–1200 mg/day) and vitamin D (400–800 IU/day). The use of bisphosphonates is controversial.

Management of *portal hypertension* in PBC is the same as that for other cirrhotic patients. Severe portal hypertension, even without any other signs of decompensation, is a good indication for liver transplantation.

8 Diagnostic tests

Antimitochondrial antibodies (AMA) are detected primarily by immunofluorescence testing (IFT) using cryostat sections from rat kidney, liver, heart or stomach (Fig. 1). A positive test should be verified by Elisa or Western blotting using the M2-antigen prepared from inner membranes from bovine heart mitochondria or recombinant antigens representing its five components (E2-, E1α- and E1β-subunit and E3-binding protein of pyruvate dehydrogenase complex [PDC], 2-oxoglutarate dehydrogenase complex [2-OGDC]). About 95 % of PBC patients are positive with the M2-antigen, about 85 % react with PDC-E2. In about 10 %, only antibodies to 2-OGDC are observed. However, there are still patients who are AMA positive but anti-M2 negative, i. e. further AMA-subspecificities may exist [5].

AMA can also react with antigens of the outer mitochondrial membrane (anti-M4, -M8), and these antibodies seem to correlate with comparatively active courses.

In about half of the patients with AMA/anti-M2 negative PBC, specific antinuclear antibodies can be observed (antibodies to nuclear dots [sp100], nuclear membrane [pg210] or centromeres) (Fig. 1). These cannot be detected by IFT on cryostat sections but only by IFT on cell cultures (for instance Hep2-cells) or by Elisa using the applicable recombinant antigens (Scheme 1).

Association of AMA with a homogeneous pattern ANA, antibodies to actin or to the soluble liver (liver-pancreas antigen (SLA/LP) are strongly indicative of an association of PBC with autoimmune hepatitis, especially when IgG-globulins are elevated.

9 Testing methods

The benefits of the diagnostic laboratory tests, i. e. AMA and anti-M2 and ANA-subspecificities, are the excellent performance characteristics; in particular with specificity (∼100 %) and sensitivity (∼95 %).

Limitations of the IFT are the need for experience in the interpretation of IFT-patterns. Special laboratory equipment (fluorescence microscope) and training of technicians are required. Disadvantages of Elisas are their high sensitivity which may result more frequently in false positive results due to the detection of low-titre,

naturally occurring autoantibodies. The use of recombinant antigens may result in false negative results, because AMA may be directed against conformational epitopes which are not expressed in the soluble phase required for Elisa. Furthermore, in contrast to most other autoimmune disorders, it is important in PBC to look for AMA of the IgG- and IgM-type because some patients have only anti-M2 antibodies of the IgM type.

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