Primary biliary cholangitis

George Mells

Abstract

Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease characterized by lymphocytic destruction of the small, intrahepatic bile ducts, causing chronic cholestasis and progressive fibrosis that eventually leads to biliary cirrhosis. It is a complex disorder resulting from the interaction of genetic and environmental factors and is strongly predominant in female patients (female:male 9:1). Typical symptoms include cholestatic pruritus and the PBC fatigue symptom complex. Features of end-stage liver disease (ESLD) from PBC are the same as those of ESLD from other causes, i.e. variceal haemorrhage, ascites, jaundice and hepatic encephalopathy. First-line disease-modifying treatment for PBC is with ursodeoxycholic acid (UDCA). Patients with an inadequate biochemical response to UDCA (e.g. defined as serum alkaline phosphatase >1.67 times the upper limit of normal measured after 12 months of treatment) are prioritized for addition of second-line treatment with obeticholic acid or a fibrate, i.e. bezafibrate or fenofibrate. First-line treatment for PBC-related pruritus is with colestyramine. If colestyramine is unpalatable or ineffective, second-line treatment of pruritus is with rifampicin. Patients with the fatigue symptom complex and prominent somnolence can benefit from modafinil. Liver transplantation is indicated for PBC patients with chronic liver failure or intractable pruritus.

Keywords Autoimmune liver disease; cholestatic liver disease; cholestatic pruritus; colestyramine; liver transplantation; modafinil; obeticholic acid; PBC fatigue symptom complex; rifampicin; ursodeoxycholic acid

Key points

- Primary biliary cholangitis (PBC) is a rare, chronic liver disease characterised by autoimmune destruction of the small, intrahepatic bile ducts, eventually leading to cirrhosis;
- Typical symptoms of PBC include itch and fatigue; either may be debilitating;
- First-line treatment of PBC is with ursodeoxycholic acid (UDCA). Those with inadequate biochemical response to treatment with UDCA after 12 months should be considered for treatment with obeticholic acid (OCA).

Primary biliary cholangitis (PBC)

PBC is a chronic autoimmune liver disease characterized by lymphocytic destruction of the small, intrahepatic bile ducts.[1] It occurs worldwide, with the highest rates in Northern Europe and North America. It is more common in female patients (female: male 9:1). It is a disease of adult life, the peak age at diagnosis being around 55 years of age. A younger age at diagnosis is associated with more aggressive disease.

Pathogenesis

PBC is a complex disorder triggered by environmental risk factors acting in a genetically predisposed individual. Genes putatively involved in causing PBC have been identified by genome-wide association studies and related study designs.[2] These genes imply that the immune system in PBC is genetically primed for hyperresponsiveness and loss of tolerance to self-antigens, such as pyruvate dehydrogenase complex (PDC; see below). Environmental risk factors identified in large epidemiological studies include smoking, industrial pollutants (e.g. living in proximity to hazardous waste sites) and cosmetics.[3]

Histologically, PBC is characterized by chronic, non-suppurative destructive cholangitis affecting the interlobular bile ducts.[1] Portal tracts are expanded by a dense infiltrate of lymphocytes, macrophages, plasma cells and occasional eosinophils, and can contain epithelioid granulomas centred on bile ducts (granulomatous cholangitis) or lymphoid follicles (Figure 1). Interface hepatitis is common but does not invariably signify overlap with autoimmune hepatitis (AIH). There is bile duct injury with inflammatory and degenerative atypia of biliary epithelial cells. Duct destruction leads to ductopenia, ductular reactions and features of chronic cholestasis, such as periportal intermediate hepatocytes (with features of cholangiocytes as well as hepatocytes) and periportal deposition of copper-associated protein. Chronic inflammation and cholestasis results in biliary fibrosis that progresses slowly to biliary cirrhosis.

Variant syndromes are recognized:

- In **PBC/AIH overlap syndrome**, there is an abundance of plasma cells and interface hepatitis is more prominent. There is lobular hepatitis and can be rosetting of hepatocytes by lymphocytes or emperipolesis of lymphocytes within hepatocyte cytoplasm.
- In the **premature ductopenic variant**, ductopenia and features of chronic cholestasis, for example intermediate hepatocytes and deposition of copper-associated protein, are marked and disproportionate to the extent of fibrosis.
- A **portal hypertensive variant** in which features of portal hypertension, such as splenomegaly and shunt vessels are prominent and disproportionate to the degree of fibrosis. Anti-centromere antibodies are frequently detectable in serum.

Clinical features

PBC can be asymptomatic, identified after an incidental finding of elevated serum alkaline phosphatase (ALP) tested for some other reason. Typical symptoms, however, are pruritus and fatigue. Both are unrelated to the stage of disease but are worse in patients with more severe disease activity. Classically, pruritus is worse in the evenings and mainly affects the palms and soles

George Mells *MB BS PhD MRCP is a Consultant Hepatologist, Department of Hepatology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.*
Competing interests: none declared.

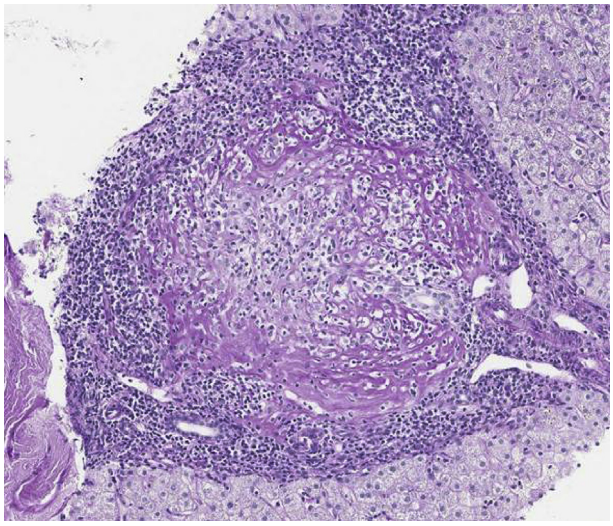

Figure 1 The pathology of PBC. Photomicrograph showing a portal tract expanded by a dense lymphocytic infiltrate and containing an epithelioid granuloma centred on an injured bile duct (*courtesy of Dr Adam Duckworth, Consultant Histopathologist, Addenbrooke's Hospital, Cambridge, UK*).

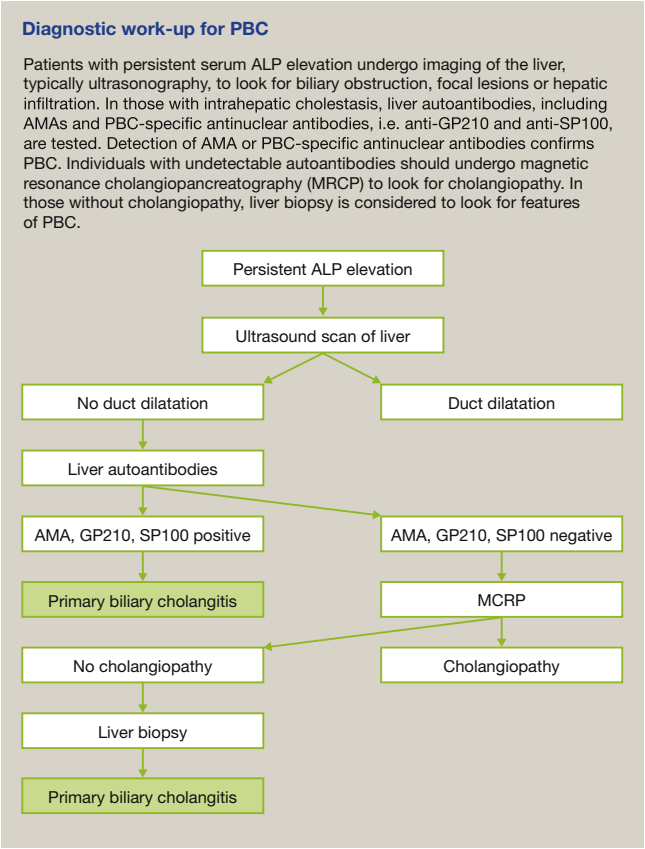

Figure 2

(palmar–plantar pruritus). It can, however, occur at any time of day and affect any area of skin. The fatigue symptom complex encompasses anergia; 'brain fog', characterized by difficulty concentrating and mild memory disturbance; and autonomic disturbance, characterized by flushing, sweating and orthostatic symptoms. Somnolence can occur but is not a universal feature of the fatigue symptom complex.

Other common symptoms of PBC include Raynaud's phenomenon, bone pain, arthralgia and myalgia, and the sicca symptoms xerophthalmia and xerostomia. Features of end-stage liver disease (ESLD) caused by PBC are the same as those of ESLD from any other cause, i.e. variceal haemorrhage, ascites, jaundice and hepatic encephalopathy.

Patients with the premature ductopenic variant can develop jaundice well in advance of cirrhosis; in this context, jaundice does not indicate poor prognosis. Patients with the portal hypertensive variant can experience variceal haemorrhage well before cirrhosis (owing to non-cirrhotic portal hypertension; see above); in this context, variceal haemorrhage does not indicate poor prognosis.

PBC is associated with other autoimmune conditions, including autoimmune thyroid disease, Sjögren's syndrome, systemic sclerosis, systemic lupus erythematosus and idiopathic pulmonary fibrosis.[3] Patients with PBC can therefore exhibit symptoms of these other conditions. There is increased risk of osteoporosis in PBC, especially in individuals with uncontrolled disease.

Diagnosis

The diagnostic algorithm for PBC is shown in Figure 2.

Liver biochemistry shows cholestasis characterized by disproportionate elevation of ALP and γ-glutamyl transpeptidase, with concentrations approximately correlated with disease activity. The transaminases alanine aminotransferase and aspartate aminotransferase are mildly elevated in patients with early or active disease; marked elevation suggests PBC/AIH overlap. Total and direct bilirubin can be elevated in individuals with active disease, advanced ductopenia (e.g. premature ductopenia variant) or ESLD. Albumin concentration is low and prothrombin time (PT) and international normalized ratio are prolonged in ESLD.

Serum immunoglobulins show a disproportionate elevation of immunoglobulin (Ig) M. Marked elevation of IgG suggests PBC/AIH overlap. Elevation of IgA occurs in advanced disease or comorbid alcohol-related or non-alcoholic fatty liver disease (NAFLD).

Most patients have autoantibodies detectable in serum. More than 90% of patients have antimitochondrial antibodies (AMAs), typically specific for the self-antigen PDC, located on the inner mitochondrial membrane. Approximately 50% of individuals have antinuclear antibodies, especially anti-GP210, anti-SP100, anti-PML or anti-centromere antibodies. In patients with persistent intrahepatic cholestasis (i.e. elevated ALP without bile duct dilatation), anti-mitochondrial, anti-GP210 or anti-SP100 antibodies are diagnostic of PBC. Anticentromere antibodies also occur in systemic sclerosis and are therefore not diagnostic of PBC.

Liver biopsy features are described above. In patients with intrahepatic cholestasis and detectable antimitochondrial, anti-GP210 or anti-SP100 antibodies, liver biopsy is not required to make the diagnosis of PBC, nor is it recommended to grade or stage disease. Liver biopsy is, however, required to diagnose

seronegative PBC in patients with intrahepatic cholestasis and undetectable antimitochondrial, anti-GP210 or anti-SP100 antibodies. It is also required to diagnose PBC/AIH overlap in PBC patients with elevated transaminases, elevated IgG and positive anti-smooth muscle, liver–kidney microsomal (LKM) or soluble liver antigen (SLA) antibodies. Liver biopsy can be considered to diagnose the premature ductopenic variant in patients with PBC with elevated bilirubin but normal PT (possibly after vitamin K correction) and no clinical or radiological features of cirrhosis, as well as to evaluate the relative severity of co-morbid liver diseases, especially co-morbid NAFLD.

Treatment

Current guidelines recommend a step-up approach to disease-modifying treatment of PBC.[1] First-line treatment for all patients is the hydrophilic bile acid ursodeoxycholic acid (UDCA), at an optimal dose of 13–15 mg/kg/day. Approximately 30–40% of patients treated with UDCA monotherapy experience an inadequate biochemical response, typically evaluated after 12 months of treatment with UDCA, and are prioritized for addition of a second-line agent.

The only medication licensed for second-line treatment of PBC is the bile acid-based farnesoid X receptor (FXR) agonist obeticholic acid (OCA).[4] Unlicensed but recognized second-line agents include the peroxisome proliferator-activated receptor-α (PPARα) agonists fenofibrate and bezafibrate.[5] Budesonide, a synthetic glucocorticosteroid with 90% first pass metabolism, has been proposed as an unlicensed second-line agent but its role is less clear cut; it is probably best reserved for patients with prominent interface or lobular hepatitis on liver biopsy.

PBC/AIH overlap is treated as above but can also require immunosuppression, usually prednisolone for remission induction and azathioprine for maintenance of remission; in individuals without cirrhosis, budesonide can be used instead of prednisolone. The timing of immunosuppression is case-dependent: in those with severe AIH injury, immunosuppression is required from the outset; in those with mild AIH injury, the decision to introduce immunosuppression may be deferred until treatment with UDCA has been established because the AIH injury can settle with choleresis. There are no specific treatments for the premature ductopenic or portal hypertensive variants.

Current guidelines also recommend a stepwise approach to the treatment of PBC-related pruritis.[1] First-line treatment is with the bile acid sequestrant colestyramine. The only formulation is, however, a powder made into a suspension, which many patients find unpalatable. The other bile acid sequestrants, colesevelam and colestipol, are available as tablets but have no proven efficacy for PBC-related pruritus.

For individuals in whom colestyramine is ineffective or intolerable, second-line treatment is with rifampicin, an antituberculous antibiotic that is unlicensed but highly effective for PBC-related pruritus, probably because of potent pregnane X receptor (PXR) agonism. Other unlicensed medications for PBC-related pruritus include naltrexone, gabapentin, sertraline and ondansetron. Non-pharmacological treatments include phototherapy, plasmapheresis and nasobiliary drainage, which are generally reserved for patients in crisis as a bridge to liver transplantation. There are no medications for the PBC fatigue symptom complex, but modafinil can be effective for patients with prominent somnolence; it is worth trying if there are no contraindications.

Liver transplantation is the only treatment option for patients with liver failure.[1] It is also indicated for intractable pruritus, even in the absence of liver failure (e.g. in the premature ductopenic variant). The fatigue symptom complex is not an accepted indication for liver transplantation, mainly because transplantation appears not to bring about lasting improvement. In PBC patients with non-cirrhotic portal hypertension, variceal haemorrhage does not imply poor prognosis; in these patients, a transjugular intrahepatic portosystemic shunt can be considered.

Prognosis

Prognosis in PBC is most accurately predicted by liver biochemistry on treatment (the so-called 'treatment response').[1] Thus, patients with normal or near-normal liver biochemistry have survival comparable to that of the general population, whereas those with abnormal liver biochemistry despite treatment have a reduction in transplant-free survival.

Treatment response is therefore used to identify patients who remain at risk despite first-line treatment with UDCA, who might therefore benefit from the addition of a second-line agent. Several definitions of treatment response have been published; however, ALP <1.67 times the upper limit of normal has become the pharmaceutical industry standard and is used in the UK NHS to determine eligibility for OCA. Multivariable prediction models based on treatment response, which accurately predict long-term transplant-free survival, are available as online risk calculators to assist with clinical decision-making. ◆

KEY REFERENCES

1 European Association for the Study of the Liver. EASL Clinical practice guidelines: the diagnosis and management of patients with primary biliary cholangitis. *J Hepatol* 2017; **67:** 145–72.

2 Cordell HJ, Han Y, Mells GF, et al. International genome-wide meta-analysis identifies new primary biliary cirrhosis risk loci and targetable pathogenic pathways. *Nat Commun* 2015; **6:** 8019.

3 Gershwin ME, Selmi C, Worman HJ. Risk factors and comorbidities in primary biliary cirrhosis: a controlled interview-based study of 1032 patients. *Hepatol* 2005; **42:** 1194–202.

4 Nevens F, Andreone P, Mazzella G, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *N Engl J Med* 2016; **375:** 631–43.

5 Corpechot C, Chazouillères O, Rousseau A, et al. A placebo-controlled trial of bezafibrate in primary biliary cholangitis. *N Engl J Med* 2018; **378:** 2171–81.

