Primary Biliary Cholangitis and Autoimmune Hepatitis

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KEYWORDS

• Primary biliary cholangitis • Primary biliary cirrhosis • Autoimmune hepatitis • Biliary disease • Chronic hepatitis • Overlap syndrome • Autoantibodies • Differential diagnosis

Key points

- Primary biliary cholangitis is an autoimmune disorder that usually presents with increased alkaline phosphatase and serum IgM, along with antimitochondrial antibodies.
- Liver biopsy in primary biliary cholangitis shows nonsuppurative cholangitis, along with mild to moderate portal inflammation. Granulomatous destruction of bile ducts may be present.
- Patients with autoimmune hepatitis have increased AST, ALT, and IgG. Serologic findings include antinuclear and anti–smooth muscle antibodies.
- Moderate chronic inflammation in portal tracts and lobules is seen in autoimmune hepatitis. Occasional features include hepatocyte rosette-like regeneration and emperipolesis. Patients may have fibrosis or cirrhosis at presentation.
- Primary biliary cholangitis and autoimmune hepatitis can occur in the same patient (overlap), and they can also mimic one another both clinically/serologically and histologically, necessitating careful judgment.

ABSTRACT

Primary biliary cholangitis and autoimmune hepatitis are common autoimmune diseases of the liver. Both have typical clinical presentations, including certain autoantibodies on serologic testing. Histologic features are also often typical: primary biliary cholangitis shows bile duct destruction (sometimes with granulomas), and autoimmune hepatitis shows prominent portal and lobular lymphoplasmacytic inflammation. Both have a wide differential diagnosis, including one another; they may also simultaneously occur within the same patient. Careful use of clinical and histologic criteria may be necessary for diagnosis. First-line therapy is immunosuppression for autoimmune hepatitis and ursodeoxycholic acid for primary biliary cholangitis. Both diseases may progress to cirrhosis.

OVERVIEW

Primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH) are the 2 most common autoimmune diseases that primarily involve the liver. They are distinct entities but have some clinicopathologic overlap, and 1 patient can be afflicted with both diseases. Although primary sclerosing cholangitis (PSC) is often placed alongside these diagnoses, its etiology remains unknown.[1]

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PRIMARY BILIARY CHOLANGITIS

OVERVIEW OF PRIMARY BILIARY CHOLANGITIS

"Primary biliary cirrhosis" has recently been renamed primary biliary cholangitis, because not all patients develop cirrhosis.[2] This autoimmune disease, which targets the canals of Hering and the interlobular bile ducts within portal tracts, is also the most common intrinsic biliary disorder of the liver.[3] Its incidence is rising and is highly variable among different countries[4] and among different regions within countries[5]; it has previously been reported as 4.5 per 100,000 people per year in the United States.[6] Patients are most often middle-aged women, and the male:female ratio is 1:9 or greater.[4] The disease rarely if ever affects children. More than a dozen risk loci have been identified by genome-wide association studies,[7] and relatives of patients with PBC have an increased risk of developing the disease.[8]

CLINICAL FEATURES OF PRIMARY BILIARY CHOLANGITIS

Patients with PBC may present with typical biliary-pattern symptoms (jaundice, pruritus, abdominal pain, and fatigue), although up to half of patients are asymptomatic.[9] Alkaline phosphatase levels are increased to 2 or more times the upper limit of normal, and this increase is sustained for 6 months or longer; similarly, γ-glutamyl transferase levels are increased to 5 or more times the upper limit of normal.[10] Bilirubin levels may vary, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels may increase slightly from PBC but not to an impressive degree. Patients may demonstrate an increase in serum IgM.

Pathologic Key Features of Primary Biliary Cholangitis

1. Bile ducts experience nonsuppurative cholangitis (infiltration by lymphocytes), surrounded by mild to moderate chronic portal inflammation.
2. Florid duct lesions (granulomatous destruction of bile ducts) effectively clinch the diagnosis when present.
3. Duct loss and lobular cholestasis are seen later in the disease process and should not be observed early.
4. Lobular necroinflammatory activity should be minimal or absent, unless another disease process (such as AIH) is simultaneously occurring.

Patients with PBC often have antimitochondrial antibodies (AMAs) by serology,[11] as do their first-degree relatives.[8] Of the various types (M1 through M9), M2 is considered the most specific for the disease. Serologic testing is currently performed by enzyme-linked immunosorbent assay. AMAs are sometimes considered pathognomonic for PBC, although their sensitivity and specificity are only approximately 90%. Patients with all the features of PBC but who are serologically negative for AMAs may be diagnosed with AMA-negative PBC, also termed, *autoimmune cholangitis*.[12] Most patients with AMAs but no other evidence of disease do not go on to develop PBC.[13] Other serologic findings in PBC patient include anti–smooth muscle antibodies (ASMAs) (up to 67%),[14] antinuclear antibodies (up to 50%),[15] and rheumatoid factor (70%).[16]

Radiology and cholangiography are of little direct value in diagnosing PBC, because the extrahepatic bile ducts are not affected and there are no specific findings. The tests serve more to exclude other possible biliary abnormalities.

Patients with PBC may develop other autoimmune diseases, including scleroderma and Sjögren syndrome.[16] They may also develop AIH, a situation known as *AIH-PBC overlap*, that requires careful clinical and pathologic examination for proper diagnosis.[17]

MICROSCOPIC FEATURES OF PRIMARY BILIARY CHOLANGITIS

The typical findings of PBC on hematoxylin-eosin stain include mild to moderate lymphoplasmacytic portal inflammation with variable interface hepatitis, distorted interlobular bile ducts involved by lymphocytes (nonsuppurative cholangitis), and bile ductular reaction along the periphery of the portal tracts in early disease stages (**Figs. 1** and **2**).[18,19] These findings may be patchy and may vary in severity from one portal area to the next; in some cases, the biopsy changes may be minimal, making a histologic diagnosis difficult. Nodular regenerative hyperplasia has also been described as a common early finding in PBC.[20] CD1a-positive Langerhans cells may be present within the biliary epithelium of PBC patients.[21]

As the disease progresses, the inflamed bile ducts are destroyed, leading to bile duct loss and eventually ductopenia. If necessary, this can be quantified by an immunohistochemical stain for CK19, which highlights biliary epithelium (**Fig. 3**).[22] Lobular cholestasis also manifests later in the disease, with visible bile appearing in canaliculi and in hepatocyte cytoplasm. Longstanding cholestasis elicits cholate stasis (feathery