Clinical manifestations, diagnosis, and prognosis of primary biliary cholangitis

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INTRODUCTION

Primary biliary cholangitis (PBC; previously referred to as primary biliary cirrhosis) is characterized by a T-lymphocyte-mediated attack on small intralobular bile ducts. A continuous assault on the bile duct epithelial cells leads to their gradual destruction and eventual disappearance (picture 1). The sustained loss of intralobular bile ducts causes the signs and symptoms of cholestasis and eventually may result in cirrhosis and liver failure [1-3]. The terminology was changed from primary biliary cirrhosis to primary biliary cholangitis to more accurately describe the disorder and its natural history [4]. With the advent of treatment with ursodeoxycholic acid, the majority of patients now have normal life expectancies and only a minority of patients develops cirrhosis. (See "Pathogenesis of primary biliary cholangitis (primary biliary cirrhosis)".)

This topic will review the clinical manifestations and diagnosis of PBC. It will also review factors associated with prognosis. The pathogenesis of PBC, the treatment of PBC, and the treatment of pruritus due to cholestasis are discussed separately. (See "Pathogenesis of primary biliary cholangitis (primary biliary cirrhosis)" and "Overview of the management of primary biliary cholangitis" and "Liver transplantation in primary biliary cholangitis" and "Pruritus associated with cholestasis".)

The American Association for the Study of Liver Diseases issued a practice guideline for PBC in 2018 [5]. The discussion that follows is generally consistent with that guideline.

EPIDEMIOLOGY

Primary biliary cholangitis (PBC) is rare, with a reported prevalence of 19 to 402 cases per million persons [6,7]. The vast majority of patients (90 to 95 percent) are women, and most patients are diagnosed between the ages of 30 and 65 years (often in their 40s or 50s), though the disease has been reported in women as young as 15 years and as old as 93 years [8-10].

The incidence of PBC developing in a well-defined population from Rochester, Minnesota was estimated to be 2.7 per 100,000 person-years (4.5 per 100,000 person-years for women and 0.7 per 100,000 person-years for men) [6]. The age and sex-adjusted prevalences per 100,000 persons were 65.4 for women and 12.1 for men.

PBC prevalence appears to vary geographically and is most common in northern Europe and North America (particularly in Scandinavia, Great Britain, and the northern midwest regions of the United States) [11]. However, one study found that disease severity was higher in Black and Hispanic Americans for reasons that were unclear [12]. (See "Pathogenesis of primary biliary cholangitis (primary biliary cirrhosis)", section on 'Clues about etiology based on the epidemiology of PBC'.)

Studies suggest that the disease burden from PBC is increasing over time:

- In a population-based study from the United Kingdom, the incidence rose from 23 cases per million in 1987 to 32 cases per million in 1994 [13].
- A 2004 study from Victoria, Australia found that the prevalence was 51 cases per million-population, compared with 10 cases per million-population in 1991 [7].
- A 2009 study from Canada estimated that the overall age and sex-adjusted annual incidence was 30.3 cases per million (48.4 per million women and 10.4 per million men) [14]. While the incidence had not changed between 1996 and 2002, the prevalence increased from 100 to 227 per million.

One possible explanation for the increase in disease burden is better detection and increased awareness of PBC, rather than a true change in disease incidence.

Familial clustering of PBC has also been noted, suggesting genetic susceptibility in some patients. The prevalence of PBC is 100 times higher in first-degree relatives of a patient with PBC compared with the general population. Allelic variations in MHC class II (DR, DQ) and in components of the innate and adaptive immune systems have been associated with

susceptibility to PBC [15]. (See "Pathogenesis of primary biliary cholangitis (primary biliary cirrhosis)", section on 'Genetic susceptibility'.)

CLINICAL MANIFESTATIONS

Patients with primary biliary cholangitis (PBC) may be asymptomatic, or they may present with symptoms such as fatigue and pruritus. Other clinical manifestations include jaundice, cholestatic liver enzymes, antimitochondrial antibodies, and signs and symptoms of cirrhosis.

Signs and symptoms — Approximately 50 to 60 percent of patients with PBC are asymptomatic at diagnosis and are detected because of abnormalities in liver biochemical tests obtained for other reasons [16-18]. Among patients with symptoms, fatigue and pruritus are most commonly seen (table 1). In newly diagnosed patients, approximately one-half complain of fatigue and one-third pruritus [8]. In addition, patients may have signs and symptoms due to associated autoimmune disorders or from complications of PBC, such as cirrhosis. (See 'Associated autoimmune conditions' below and 'Complications' below.)

- **Fatigue** – In patients with PBC, fatigue is associated with excessive daytime somnolence and can be a major factor that impairs quality of life [19-22]. It may have several contributing causes, although it does not appear to be explained by depression [23,24]. One report suggested that fatigue remains fairly constant over time in individual patients and that it may be associated with decreased survival [25]. Another report found that fatigue correlated with muscle mitochondrial dysfunction manifested as excessive acidosis after exercise [26]. An association with autonomic dysfunction has also been reported [27].

- **Pruritus** – Pruritus has been reported by 20 to 70 percent of patients and often precedes the development of jaundice [11]. It may initially develop during pregnancy and be mistaken for intrahepatic cholestasis of pregnancy. However, the latter disorder resolves in the postpartum period, whereas that due to PBC typically persists. Itching is worse at night, under constricting or coarse garments, in association with dry skin, and in hot, humid weather. (See "Pruritus associated with cholestasis".)

- **Other signs and symptoms** – Patients with PBC may report right upper quadrant discomfort, which was noted by 8 percent of patients in one study [28]. Impairment in memory and concentration has also been reported in patients with PBC. In one study, these features were present in 53 percent of 198 patients with PBC [29]. They correlated with the presence of structural brain lesions and autonomic dysfunction, but did not correlate with the severity of liver disease. Patients with advanced PBC may develop

malabsorption and steatorrhea and may have with findings associated with fat-soluble vitamin deficiencies (table 2).

Physical examination — The findings on physical examination in patients with PBC vary widely and depend on the stage of the disease at time of presentation. The physical examination is often normal in patients who are asymptomatic. Skin findings are common, such as hyperpigmentation, excoriations, xanthelasmas, and jaundice. Patients may also have hepatosplenomegaly or examination findings suggestive of cirrhosis (table 3).

- **Skin** – Skin findings in patients with PBC may include hyperpigmentation, jaundice, xanthomas (picture 2A-B), xanthelasmas (picture 3), xerosis (dry skin), dermatographism, and fungal infections of the feet or nails. The skin may initially be normal, but excoriations from scratching due to pruritus may be severe enough to cause bleeding and may occur as the disease progresses. In one study, 40 percent of patients with PBC presented with a dermatologic complaint [30].

  Approximately 25 to 50 percent of newly diagnosed patients have hyperpigmentation of skin [30]. This change is due to melanin deposition, not jaundice [31,32]. The cause is unknown, but similar findings occur in other types of chronic liver disease, such as hemochromatosis.

  Jaundice is typically a later manifestation of the disease, but may be seen at presentation in some patients. Xanthomas from hyperlipidemia are also late manifestations that occur in less than 5 percent of patients. Xanthelasmas are more common and occur in approximately 10 percent of patients. (See "Hypercholesterolemia in primary biliary cholangitis (primary biliary cirrhosis)".)

- **Hepatosplenomegaly** – Striking hepatic enlargement is often found in patients with PBC and may be detected in asymptomatic patients. Hepatomegaly becomes more common as the disease progresses [33]. The frequency with which splenomegaly is present on initial presentation has not been well described. However, it appears to be decreasing, probably because PBC is being diagnosed in earlier stages than in the past. Splenomegaly becomes more common as PBC progresses and usually is a sign of portal hypertension. (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Splenomegaly'.)

- **Other findings –** Spider nevi, temporal and proximal limb muscle wasting, ascites, and edema are all late manifestations of disease and suggest cirrhosis (table 3). Kayser-Fleischer rings are a very rare manifestation and result from copper retention [34]. (See

"Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Physical examination'.)

Laboratory tests — Common laboratory test abnormalities in patients with PBC included an elevated alkaline phosphatase, antimitochondrial antibodies (AMA), antinuclear antibodies (ANA), and hyperlipidemia. Other findings may include mild elevations in the aminotransferases and an elevated bilirubin level.

- **Liver biochemical and function tests** – The serum alkaline phosphatase concentration is almost always elevated in PBC, often to striking levels, and is of hepatic origin. Serum aminotransferases may be normal or slightly elevated. The serum bilirubin concentration is usually normal early in the course of the disease, but becomes elevated in most patients as the disease progresses [35]. Both the direct and indirect fractions are increased. An elevated serum bilirubin is a poor prognostic sign [35]. (See 'Prognostic factors' below.)

  The alkaline phosphatase value tends to reach a plateau early in the course of the disease and then usually fluctuates within 20 percent of this value [36]. Serum levels of 5'-nucleotidase and gamma-glutamyl transpeptidase parallel those of alkaline phosphatase. (See "Enzymatic measures of cholestasis (eg, alkaline phosphatase, 5'-nucleotidase, gamma-glutamyl transpeptidase)".)

  If elevated, the serum levels of aminotransferases are rarely increased more than fivefold above normal. They tend to fluctuate within a relatively narrow range. When they are five times normal or higher, the overlap syndrome (PBC plus autoimmune hepatitis) should be considered. (See "Autoimmune hepatitis variants: Definitions and treatment", section on 'Autoimmune hepatitis-PBC overlaps'.)

  Additional abnormalities that may be seen in patients who have developed cirrhosis include a low serum albumin and an elevated international normalized ratio (INR).

- **Hematologic abnormalities** – Patients with PBC may have iron deficiency anemia due to gastrointestinal blood loss related to portal hypertension. Patients with cirrhosis may also have thrombocytopenia and leukopenia (table 3). (See "Portal hypertension in adults", section on 'Clinical manifestations'.)

  Increased numbers of eosinophils have been demonstrated in the blood and liver of patients with PBC, particularly in its early stages, suggesting that they may have a pathogenic role [37,38].

- **Serologic markers:** AMA are present in almost all patients with PBC. ANA are also common and found in up to 70 percent of patients with PBC

  - **Antimitochondrial antibodies** – AMA are the serologic hallmark of PBC. They are present in approximately 95 percent of patients with PBC. (See "Pathogenesis of primary biliary cholangitis (primary biliary cirrhosis)", section on 'Antimitochondrial antibodies'.)

    Occasionally, AMA are detected in patients with no other features suggestive of PBC. Many of these patients will eventually go on to develop features of PBC. (See 'Positive AMA' below.)

  - **Antinuclear antibodies** – ANA are found in up to 70 percent of patients with PBC [39-44]. A variety of staining patterns may be present. Two immunofluorescence patterns are considered "PBC-specific": the multiple nuclear dots pattern (target antigen, Sp100) and the rim-like/membranous pattern (target antigens, gp210, nucleoporin p62, and the lamin B receptor). Other antibodies such as anticentromere, anti-SSA/Ro, and anti-dsDNA antibodies can be also found in PBC.

    ANA have clinical significance in PBC for two reasons. First, their presence can cause confusion with autoimmune hepatitis or autoimmune hepatitis/PBC overlap. Second, some suggest that ANA may be associated with more rapid progression of disease and a poorer prognosis [42,45-47]. However, the strength of this association and the implications for management are uncertain. For example, patients with PBC who are AMA-negative and have a positive ANA, a disease often called autoimmune cholangitis but more appropriately AMA-negative PBC, have the same outcomes as those who are AMA-positive and ANA-negative. (See "Autoimmune hepatitis variants: Definitions and treatment".)

- **Serum lipids** – Serum lipids may be strikingly elevated in PBC. Serum cholesterol levels are elevated in at least 50 percent of patients, and may exceed 1000 mg/dL (26 mmol/L) in patients with xanthomas [48]. Patients with early PBC often have mild elevations of low-density and very-low-density lipoproteins (LDL and VLDL) and striking elevations of high-density lipoproteins (HDL) [49]. This may explain why patients with PBC, despite striking hypercholesterolemia, do not appear to be at increased risk of death from atherosclerosis. (See "Hypercholesterolemia in primary biliary cholangitis (primary biliary cirrhosis)".)

- **Other abnormalities** – Other biochemical abnormalities in PBC include:

- Increased serum concentrations of immunoglobulin M (IgM), ceruloplasmin, bile acids (which are strikingly elevated) [50], and hyaluronate [51]. Rising hyaluronate levels correlate with the serum bilirubin and histologic worsening of the disease [51].

- Antithyroid antibodies are often seen in patients with PBC, though they are not always associated with clinically apparent thyroid disease [52]. (See 'Associated autoimmune conditions' below.)

- Patients with PBC who develop cirrhosis may have hyponatremia or elevated serum creatine levels (table 3).

Associated autoimmune conditions — Patients with PBC are often diagnosed with other autoimmune disorders, including Sjögren's disease and autoimmune thyroid disease (table 1). Musculoskeletal complaints, frequently due to an inflammatory arthropathy, occur in approximately 40 percent of patients with PBC (with some estimates as high as 70 percent) [53].

- Approximately 40 to 65 percent of patients have symptoms of Sjögren's disease, including keratoconjunctivitis (dry eyes) and/or xerostomia (dry mouth) [54,55]. These clinical features usually precede those directly associated with PBC. On the other hand, PBC is an uncommon development in patients with primary Sjögren's disease [56]. (See "Clinical manifestations of Sjögren's disease: Extraglandular disease" and "Clinical manifestations of Sjögren's disease: Exocrine gland disease".)

- Thyroid disease occurs in 10 to 15 percent of patients with PBC [57,58]. The most common form is Hashimoto's thyroiditis. Clinical manifestations of Hashimoto's thyroiditis include development of a goiter and symptoms of hypothyroidism (table 4). (See "Pathogenesis of Hashimoto's thyroiditis (chronic autoimmune thyroiditis)", section on 'Clinical phenotypes'.)

- Approximately 5 to 15 percent of patients with PBC have limited cutaneous scleroderma, which is frequently associated with anticentromere antibodies and may include the CREST syndrome (Calcinosis cutis, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia) [53,59]. In approximately one-half of these individuals, the symptoms of scleroderma occur prior to those of PBC. Clonal expansion of T-cells bearing a specific beta chain variable region (TCRBV3) has been demonstrated in some of these patients, suggesting that patients with PBC and CREST syndrome may have a distinct disorder [59]. (See "Clinical manifestations and diagnosis of systemic sclerosis (scleroderma) in adults".)

- Classic rheumatoid arthritis develops in 5 to 10 percent of patients with PBC, while the "arthritis of PBC" is observed in another 10 percent [60,61]. The latter disorder is characterized by a transient nondeforming rheumatoid-factor negative synovitis involving one or more peripheral joints [60]. These manifestations are similar to those of hypercholesterolemic arthropathy [62]. (See "Clinical manifestations of rheumatoid arthritis".)

Complications

Cirrhosis — Patients with PBC that has progressed to cirrhosis have clinical manifestations similar to those seen with other forms or cirrhosis, including nonspecific symptoms (eg, anorexia, weight loss, weakness, fatigue) or signs and symptoms of hepatic decompensation (jaundice, pruritus, signs of upper gastrointestinal bleeding, abdominal distension from ascites, confusion due to hepatic encephalopathy) (table 3). (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Clinical manifestations'.)

In patients with PBC, esophageal varices may develop prior to the development of other signs of cirrhosis, possibly because of presinusoidal inflammation and subsequent fibrosis induced by granulomas [11]. The other complications of portal hypertension (eg, ascites, hepatic encephalopathy) are typically seen with end-stage cirrhosis. (See "Cirrhosis in adults: Overview of complications, general management, and prognosis", section on 'Major complications'.)

Hepatocellular carcinoma — Patients with PBC and cirrhosis are at increased risk for hepatocellular carcinoma (HCC) [63-67]. A meta-analysis of 17 studies found that patients with PBC had a higher risk of HCC compared with the general population (relative risk 19; 95% CI 11-27) [68]. In a large cohort study including more than 4500 patients with PBC, the incidence of HCC was 0.34 per 100-patient-years [67]. In a multivariable analysis including only patients who were treated with UDCA for at least 12 months, risk factors for HCC were biochemical nonresponse (adjusted HR 3.44, 95% CI 1.65-7.14) and thrombocytopenia (adjusted HR 1.42, 95% CI 1.10-1.74).

The approach to surveillance for HCC in high-risk patients is discussed separately. (See "Surveillance for hepatocellular carcinoma in adults".)

Metabolic bone disease — Patients with PBC are at risk for metabolic bone disease, including osteopenia and osteoporosis, which are the characteristic bone disorders in PBC and may reflect the inhibitory effect of a retained toxin on the osteoblast. Rarely, patients develop osteomalacia, which is characterized by decreased bone mineralization, bone pain, and fractures. Metabolic bone disease in patients with primary biliary cholangitis is discussed in

detail elsewhere. (See "Evaluation and treatment of low bone mass in primary biliary cholangitis (primary biliary cirrhosis)".)

Other complications — Patients with advanced PBC may develop malabsorption and steatorrhea, which in turn can lead to deficiencies of fat-soluble vitamins (table 2) [11].

DIAGNOSIS

When to consider PBC — Primary biliary cholangitis (PBC) should be considered in patients with an elevated alkaline phosphatase without extrahepatic biliary obstruction, and in women with unexplained itching, fatigue, jaundice, or unexplained weight loss with right upper quadrant discomfort. PBC is more likely if the patient has signs and symptoms suggestive of associated disorders. Patients should be questioned about symptoms of diseases such as Sjögren's disease (dry eyes and mouth), arthritis, and Raynaud phenomenon. (See "Diagnosis and classification of Sjögren's disease".)

Diagnostic criteria — A diagnosis of PBC is established if there is no extrahepatic biliary obstruction, no comorbidity affecting the liver, and at least two of the following are present [5]:

- An alkaline phosphatase at least 1.5 times the upper limit of normal
- Presence of antimitochondrial antibodies (AMA) at a titer of 1:40 or higher (or other PBC specific autoantibodies [sp100 or gp210], if AMA is negative) (see 'Laboratory tests' above)
- Histologic evidence of PBC (nonsuppurative destructive cholangitis and destruction of interlobular bile ducts)

While a liver biopsy is often not required to make the diagnosis, it provides useful information with regard to staging and prognosis. (See 'Liver biopsy' below.)

Diagnostic approach — Patients suspected of having PBC based on the presence of an elevated alkaline phosphatase with or without suggestive symptoms should undergo the following evaluation (algorithm 1):

- Imaging to exclude extrahepatic biliary obstruction (typically a right upper quadrant ultrasound or magnetic resonance cholangiopancreatography, or if the suspicion for obstruction is high, endoscopic retrograde cholangiopancreatography). (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Extrahepatic cholestasis'.)

- Assay for AMA if extrahepatic biliary obstruction is excluded. Most assays are 95 percent sensitive and 98 percent specific for PBC [69]. An exception is tests using indirect immunofluorescence, which are operator dependent and have been associated with false-positive and false-negative results. (See "Pathogenesis of primary biliary cholangitis (primary biliary cirrhosis)", section on 'Antimitochondrial antibodies'.)

Additional testing depends on the results of the initial evaluation:

- **Elevated alkaline phosphatase, positive AMA, clinical picture suggestive of PBC** – If the alkaline phosphatase is at least 1.5 times the upper limit of normal, the AMA is positive with a titer of at least 1:40, and the clinical picture is suggestive of PBC (eg, the patient is female and does not have any comorbidities that might affect the liver), additional diagnostic testing is not needed. However, a liver biopsy may help stage the disease and provide useful prognostic information. (See 'Liver biopsy' below.)

- **Elevated alkaline phosphatase, positive AMA, clinical picture inconsistent with PBC** – If the alkaline phosphatase is elevated and the AMA is positive, but elements of the clinical picture are not suggestive of PBC (eg, the patient is male or has comorbidities such as overweight, diabetes, or systemic disease that might affect the liver), we confirm the diagnosis with a liver biopsy.

- **Elevated alkaline phosphatase, negative AMA** – If the alkaline phosphatase is elevated but the AMA is negative, alternative diagnoses should be considered. A liver biopsy should be obtained if additional noninvasive testing does not yield an alternative diagnosis. (See 'Differential diagnosis' below and "Approach to the patient with abnormal liver biochemical and function tests", section on 'Intrahepatic cholestasis'.)

- **Normal alkaline phosphatase, positive AMA** – If the AMA is positive but the alkaline phosphatase is normal, a liver biopsy is not required if the suspicion for PBC is high. However, if the diagnosis is in doubt or if a definitive diagnosis is required, a liver biopsy should be obtained. (See 'Liver biopsy' below and 'Positive AMA' below.)

- **Normal alkaline phosphatase, negative AMA** – If the alkaline phosphatase is normal and the AMA is negative, a diagnosis of PBC is excluded and additional causes for the patient's symptoms should be sought. (See "Approach to the adult patient with fatigue" and "Pruritus: Etiology and patient evaluation".)

Liver biopsy — While a liver biopsy is often not required to make the diagnosis of PBC, it may provide useful information with regard to staging and prognosis [70]. However, not all centers perform routine liver biopsies, reserving them for cases of diagnostic uncertainty or when

determining the stage of disease will change management decisions. Our practice is to obtain a liver biopsy if the diagnosis is in doubt, the patient also has evidence of autoimmune hepatitis (eg, a high serum ALT, anti-smooth muscle antibodies), or if the patient does not respond optimally to therapy with ursodeoxycholic acid. (See 'Prognostic factors' below and "Transjugular liver biopsy", section on 'Indications and contraindications' and "Overview of autoimmune hepatitis", section on 'Patterns of clinical presentation' and "Approach to liver biopsy" and "Overview of the management of primary biliary cholangitis", section on 'Initial therapy'.)

The pathognomonic florid bile duct lesion is uncommonly seen in percutaneous needle biopsies of the liver (picture 4A-C). However, the greater the number of portal triads in the specimen, the more likely it is that these lesions and granulomas will be present. The continuous assault on the bile duct epithelial cells leads to their gradual destruction and eventual disappearance. The hepatocyte injury is associated with foamy degeneration, which is thought to be due to the toxic effect of retained bile acids (picture 5).

Histologic findings in PBC are often staged on a scale of zero to four (see "Interpretation of nontargeted liver biopsy findings in adults", section on 'Biliary tree injury' and "Histologic scoring systems for chronic liver disease", section on 'Primary biliary cholangitis') [71]:

- Stage 0: Normal liver
- Stage 1: Inflammation and/or abnormal connective tissue confined to the portal areas
- Stage 2: Inflammation and/or fibrosis confined to portal and periportal areas
- Stage 3: Bridging fibrosis
- Stage 4: Cirrhosis

DIFFERENTIAL DIAGNOSIS

Cholestasis — The differential diagnosis of primary biliary cholangitis (PBC) includes other causes of cholestasis. Findings that suggest a diagnosis of PBC include skin hyperpigmentation, pruritus, a positive antimitochondrial antibody (AMA), and hypercholesterolemia. Other diagnoses are more likely in patients who are male and in patients who are <30 years old or >65 years old.

Other causes of cholestasis include [72] (see "Approach to the patient with abnormal liver biochemical and function tests", section on 'Elevated alkaline phosphatase'):

- Bile duct obstruction from gallstones or malignancy
- Primary sclerosing cholangitis (PSC), IgG4-related disease

- Drug-induced cholestasis
- Sarcoidosis
- Bacterial, fungal, and viral infections
- Hepatic amyloidosis
- Lymphoma and solid organ malignancies
- Endocrine dysfunction
- Cardiac diseases
- Intrahepatic cholestasis of pregnancy
- Total parenteral nutrition
- Viral hepatitis

Patients should be questioned about the use of medications, some of which may cause cholestasis similar to that of PBC. Among the most common drugs that cause cholestasis are phenothiazines, synthetic androgenic steroids, trimethoprim-sulfamethoxazole, and in our experience, diclofenac, oxacillin, and ampicillin. The likelihood of drug-induced cholestasis is higher if the patient is taking an offending agent and the clinical picture is inconsistent with PBC (eg, the patient is AMA-negative or male). However, differentiating between drug-induced cholestasis and PBC if the clinical features are consistent with both disorders can be difficult. Liver biopsy may not help make the diagnosis because the histologic findings of chronic cholestasis injury due to drug use are similar to those of PBC. In cases where it is unclear, we reevaluate the patient with laboratory testing and liver imaging after stopping the drug for three months. (See "Drug-induced liver injury" and 'Diagnosis' above.)

Bile duct obstruction is suggested if the patient has the acute onset of jaundice or right upper quadrant pain or if the aminotransferases are moderately elevated. It should also be considered in patients with painless jaundice and no other symptoms suggestive of PBC. It is ruled out by biliary imaging. Typically, this is done with a right upper quadrant ultrasound, magnetic resonance cholangiopancreatography (MRCP), or if suspicion for a common bile duct obstruction is high, endoscopic retrograde cholangiopancreatography (ERCP). A bile duct obstruction is likely if there is intra- or extrahepatic ductal dilation, if a mass is seen, or if an obstruction is seen on cholangiography. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Extrahepatic cholestasis'.)

PSC should be considered if the patient does not have extrahepatic biliary obstruction and is AMA-negative. PSC is typically diagnosed with cholangiography (MRCP or ERCP). In patients with small duct PSC (the form most likely to resemble PBC), cholangiography is normal and a liver biopsy is needed to make the diagnosis. (See "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis", section on 'Diagnosis'.)

Patients with viral hepatitis occasionally present with cholestasis, though they typically also have aminotransferase elevations. Testing for hepatitis A, B, C, and E virus should be performed if there is no evidence of extrahepatic biliary obstruction and if the AMA is negative. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Intrahepatic cholestasis'.)

Other causes of cholestasis are suggested by the history, physical examination, and absence of AMA. (See "Intrahepatic cholestasis of pregnancy", section on 'Clinical findings' and "Gastrointestinal, hepatic, pancreatic, and peritoneal sarcoidosis", section on 'Hepatic' and "Classification and causes of jaundice or asymptomatic hyperbilirubinemia", section on 'Parenteral nutrition'.)

Positive AMA — A positive AMA may be seen in patients with features of autoimmune hepatitis or in patients who have no other signs of PBC.

Laboratory abnormalities suggestive of autoimmune hepatitis include elevated transaminases (usually higher than are seen with PBC), increased total immunoglobulin G (IgG) or gammaglobulin levels, and serologic markers (antinuclear antibodies, antismooth muscle antibodies, anti-liver-kidney microsome-1 antibodies, or anti-liver cytosol antibody-1). On biopsy, patients with autoimmune hepatitis have interface hepatitis. (See "Overview of autoimmune hepatitis".)

A variant of autoimmune hepatitis with characteristics of both autoimmune hepatitis and PBC has also been described. These patients have histologic and biochemical features of both disorders (eg, positive AMA, interface hepatitis on biopsy). (See "Autoimmune hepatitis variants: Definitions and treatment", section on 'Autoimmune hepatitis-PBC overlaps'.)

Some patients are found to have AMA without other evidence of PBC. One study suggested that the presence of AMA alone was a predictor of the eventual development of PBC [73]. The study focused on 29 patients who had AMA, but were asymptomatic and had normal liver function. Liver biopsy revealed mild changes that were nondiagnostic, but consistent with very early PBC in 24 of 29. At 10 years, symptoms of PBC were present in 76 percent and laboratory signs of cholestasis in 83 percent. Repeat liver biopsy was performed in 10 of the patients. The disease had progressed from stage I to II in two patients and from stage I to III in two. There was no histologic progression in six patients. In a second study, the five-year incidence of PBC in AMA-positive patients with initially normal alkaline phosphatase levels was only 16 percent [74].

> Approximately 13 percent of first-degree relatives of patients with PBC have AMA, suggesting they are susceptible to developing PBC [75]. Whether the early detection of such individuals has a clinical benefit remains to be determined.

Fatigue and pruritus — There are numerous causes of fatigue and pruritus other than PBC. The approaches to patients presenting with these complaints are discussed elsewhere. (See "Approach to the adult patient with fatigue" and "Pruritus: Etiology and patient evaluation".)

PROGNOSIS

The prognosis of primary biliary cholangitis (PBC) has improved markedly with treatment with ursodeoxycholic acid (UDCA). Many patients with early-stage PBC may have a normal life expectancy. Studies of patients treated with UDCA have suggested a good prognosis in patients initially diagnosed with mild disease who achieve a biochemical response to UDCA. (See "Overview of the management of primary biliary cholangitis".)

Predictive models — Several predictive models based upon laboratory and clinical data have been proposed, and two such models (GLOBE score and UK-PBC score) that were developed in the era of UDCA therapy are based on multicenter studies including large cohorts of patients with PBC [5,76,77]:

- **GLOBE score** – The GLOBE score includes the following five variables: serum bilirubin, albumin, alkaline phosphatase, platelet count after one year of UDCA treatment, and age at start of therapy. The GLOBE score estimates the duration of transplant-free survival.

- **UK-PBC score** – The UK-PBC score includes serum alkaline phosphatase, aminotransferases, and bilirubin after 12 months of UDCA therapy, in addition to baseline albumin and platelet count. This model estimates the risk of liver transplantation or liver-related death.

Prognostic factors — Treatment with UDCA has been associated with improved outcomes in patients with PBC. Factors that have been associated with a worse prognosis include presence of symptoms at the time of diagnosis, elevated alkaline phosphatase and bilirubin levels, more advanced histologic stage, presence of antinuclear antibodies, cigarette smoking, and certain genetic polymorphisms.

- **Treatment with** ursodeoxycholic acid – Patients treated with UDCA who were initially diagnosed with mild disease and achieve a biochemical response to UDCA have a better prognosis than those with more advanced disease or those who fail to achieve a biochemical response to UDCA.

- **Symptoms and associated disorders** – Some studies have suggested that patients with PBC who are asymptomatic at diagnosis may have a better prognosis than those who have

symptoms (such as fatigue), but the strength of this association is uncertain [16,18,78-81]. Other studies have suggested that patients who have coexisting disorders related to PBC such as thyroiditis, sicca syndrome, and scleroderma also have a worse prognosis, even if they do not have symptoms more classically related to PBC [80].

It is possible that the better prognosis reported in asymptomatic patients in some studies reflects lead-time bias (ie, that such patients were detected earlier in the course of their disease). Symptoms develop in two to four years in the majority of asymptomatic patients [16], although approximately one-third may remain symptom-free for many years [79]. There is no reliable way to predict which patients will develop symptoms [80].

- **Alkaline phosphatase and bilirubin level** – Alkaline phosphatase and bilirubin levels are associated with transplant-free survival. In a meta-analysis of individual data of 15 studies with 4845 patients, increased alkaline phosphatase and bilirubin levels one year after study enrollment were associated with worse outcomes [82]. As an example, an alkaline phosphatase level >2 times the upper limit of normal was associated with decreased 10-year transplant-free survival compared with an alkaline phosphatase level ≤2 times the upper limit of normal (62 versus 84 percent). Similarly, a bilirubin level >1 times the upper limit of normal was associated with lower 10-year transplant-free survival compared with a bilirubin level ≤1 times the upper limit of normal (41 versus 86 percent). The association of alkaline phosphatase and bilirubin levels with transplant-free survival was seen with both patients who had received ursodeoxycholic acid and those who had not.

- **Histologic stage** – PBC is classified histologically into four stages. (See 'Liver biopsy' above.)

  As noted above, the natural history of PBC involves histologic progression along these stages, though treatment with UDCA may slow disease progression. In a study involving 916 biopsy specimens from 222 patients followed in the pre-UDCA era, cirrhosis developed within four years in 31 and 50 percent who presented initially with stage I or II disease, respectively [83].

  The presence of cirrhosis (stage IV) is associated with a worse prognosis and identifies a group of patients at risk for development of complications related to cirrhosis, including variceal bleeding and development of hepatocellular carcinoma [84,85]. In a study of 256 patients seen in the pre-UDCA era, 31 percent developed esophageal varices during a median of 5.6 years of follow-up [63]. One- and three-year survival rates were 83 and 59 percent, respectively, after the development of varices.

In another study, the presence of ductopenia on a baseline liver biopsy predicted histologic progression despite UDCA [86].

- **Serologic markers** – The presence of antinuclear antibodies (in particular, antiGp210, antiSp100, and anticentromere antibodies) may identify a subgroup of patients at increased risk for progressing to liver failure [42,45-47]. (See 'Laboratory tests' above.)

  Patients with antimitochondrial antibody (AMA)-negative PBC are thought to have a similar clinical course and response to treatment as patients with AMA-positive PBC [87,88].

- **Cigarette smoking** – An association between PBC and cigarette smoking has been suggested in epidemiologic studies [89]. At least two studies also suggested that cigarette smoking is associated with more advanced fibrosis stage [90,91]. In one of the studies, never-smokers were significantly less likely to have advanced fibrosis (METAVIR fibrosis score of 3 or 4) (table 5) than patients who had smoked in the past or were current smokers (16 versus 33 percent) [91]. For each pack-year increase in smoking, there was a 5 percent increase in the likelihood of advanced fibrosis. (See "Histologic scoring systems for chronic liver disease", section on 'Primary biliary cholangitis'.)

- **Genetic variants** – Certain polymorphisms of genes involved in immunity (SLCA2 [exchanger anion, AE2] and TNF-alpha) were associated with prognosis and response to UDCA therapy in a study of 258 patients [92]. More studies are needed to understand the relevance of these observations to natural history models or the choice of therapy. (See "Basic genetics concepts: DNA regulation and gene expression", section on 'Implications for medicine'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Primary biliary cholangitis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer

short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Primary biliary cholangitis (primary biliary cirrhosis) (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – Primary biliary cholangitis (PBC) is rare, with a reported prevalence of 19 to 402 cases per million persons. The vast majority of patients (90 to 95 percent) are female, and most patients are diagnosed between the ages of 30 and 65 years (often in their 40s or 50s), though the disease has been reported in females as young as 15 years and as old as 93 years. (See 'Epidemiology' above.)

- **Clinical manifestations** – Patients with PBC may be asymptomatic, or they may present with symptoms such as fatigue and pruritus. Other clinical manifestations include jaundice, cholestatic liver enzymes, antimitochondrial antibodies (AMA), and signs and symptoms of cirrhosis. (See 'Clinical manifestations' above.)

  - Approximately 50 to 60 percent of patients with PBC are asymptomatic at diagnosis and are detected because of abnormalities in liver biochemical tests obtained for other reasons. Among patients with symptoms, fatigue and pruritus are most commonly seen (table 1). (See 'Signs and symptoms' above.)

  - The findings on physical examination in patients with PBC vary widely and depend on the stage of the disease at time of presentation. The physical examination is often normal in patients who are asymptomatic. Skin findings are common, such as hyperpigmentation, excoriations, xanthelasmas, and jaundice. Patients may also have hepatosplenomegaly or examination findings suggestive of cirrhosis (table 3). (See 'Physical examination' above.)

  - Common laboratory test abnormalities in patients with PBC included an elevated alkaline phosphatase, AMA, antinuclear antibodies (ANA), and hyperlipidemia. Other

findings may include mild elevations in the aminotransferases and an elevated bilirubin level. (See 'Laboratory tests' above.)

- Patients with PBC are often diagnosed with other autoimmune disorders, including Sjögren's disease and autoimmune thyroid disease (table 1). Musculoskeletal complaints, frequently due to an inflammatory arthropathy, occur in approximately 40 percent of patients with PBC. (See 'Associated autoimmune conditions' above.)

- **Complications** – Complications of PBC include cirrhosis, hepatocellular carcinoma, metabolic bone disease, and malabsorption. (See 'Complications' above.)

- **Diagnosis** – PBC should be suspected in patients with an elevated alkaline phosphatase without extrahepatic biliary obstruction, and in females with unexplained itching, fatigue, jaundice, or unexplained weight loss with right upper quadrant discomfort. (See 'Diagnosis' above.)

  A diagnosis of PBC is established if there is no extrahepatic biliary obstruction and at least two of the following are present (algorithm 1):

  - An alkaline phosphatase at least 1.5 times the upper limit of normal
  - Presence of AMA at a titer of 1:40 or higher (or other PBC-specific autoantibodies [sp100 or gp210], if AMA is negative) (see 'Laboratory tests' above)
  - Histologic evidence of PBC (nonsuppurative destructive cholangitis and destruction of interlobular bile ducts)

  While a liver biopsy is often not required to make the diagnosis, it provides useful information with regard to staging and prognosis (see 'Liver biopsy' above)

- **Prognosis** – Several predictive models based upon laboratory and clinical data have been proposed, and two such models (GLOBE score and UK-PBC score) that were developed in the era of UDCA therapy are based on multicenter studies including large cohorts of patients with PBC. (See 'Predictive models' above.)

  Treatment with ursodeoxycholic acid has been associated with improved outcomes in patients with PBC. Factors that have been associated with a worse prognosis include presence of symptoms at the time of diagnosis, elevated alkaline phosphatase and bilirubin levels, more advanced histologic stage, presence of ANA, cigarette smoking, and certain genetic polymorphisms. (See 'Prognostic factors' above.)

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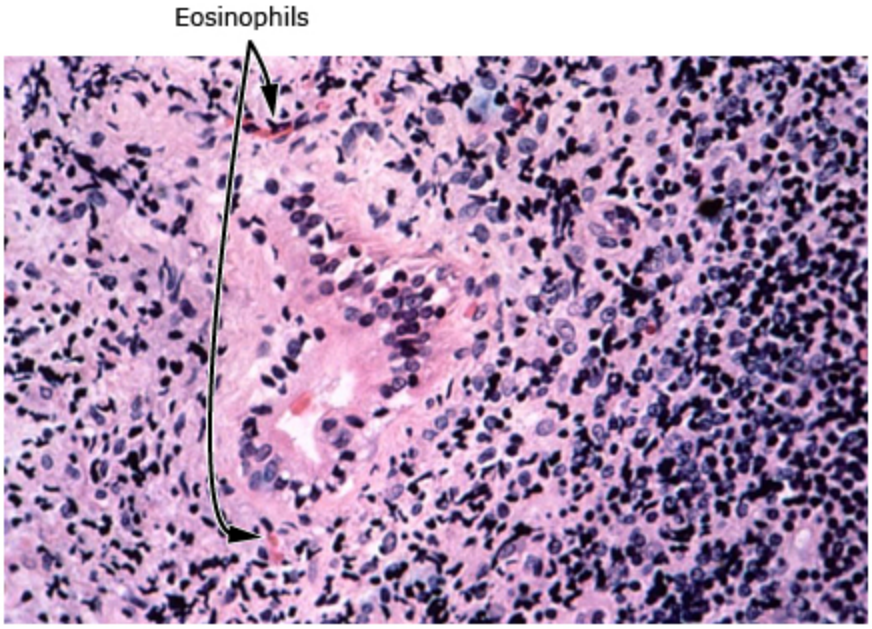
Topic 3621 Version 46.0

GRAPHICS

Liver histology of primary biliary cholangitis in a 35-year-old woman whose chief complaint was pruritus (high power, H&E)



A bile duct is surrounded by and invaded by primarily lymphocytes. There are several eosinophils. This finding is consistent with the florid bile duct lesion of primary biliary cholangitis.

Courtesy of Marshall M Kaplan, MD.

Graphic 79032 Version 5.0

Manifestations of primary biliary cholangitis

Manifestations of PBC
Fatigue
Pruritus
Portal hypertension
Metabolic bone disease
Xanthomas
Fat-soluble vitamin malabsorption

Urinary tract infection
Malignancy
Associated disorders
Thyroid dysfunction
Sicca syndrome
Limited cutaneous systemic sclerosis or scleroderma overlap syndromes
Raynaud phenomenon
Rheumatoid arthritis
Celiac disease
Inflammatory bowel disease

PBC: primary biliary cholangitis.

Adapted from: Heathcote EJ. Management of primary biliary cirrhosis. The American Association for the Study of Liver Diseases practice guidelines. Hepatology 2000; 31:1005.

Graphic 50201 Version 8.0

Signs and symptoms of intestinal malabsorption

Malabsorption of	Clinical features	Laboratory findings
Calories	Weight loss with normal appetite	
Fat	Pale and voluminous stool, diarrhea without flatulence, steatorrhea	Fractional fat excretion (% of dietary fat not absorbed) >7%
Protein	Edema, muscle atrophy, amenorrhea	Hypoalbuminemia, hypoproteinemia
Carbohydrates	Watery diarrhea, flatulence, acidic stool pH, milk intolerance, stool osmotic gap	Increased breath hydrogen
Vitamin B12	Anemia, subacute combined degeneration of the spinal cord (early symptoms are paresthesias and ataxia associated with loss of vibration and position sense)	Macrocytic anemia, vitamin B12 decreased, serum methylmalonic acid and homocysteine increased
Folate (Vitamin B9)	Anemia	Macrocytic anemia, serum and RBC folate decreased, serum homocysteine increased
Vitamin B, general	Cheilosis, painless glossitis, acrodermatitis, angular stomatitis	
Iron	Microcytic anemia, glossitis, pagophagia	Serum iron, ferritin and iron saturation decreased
Calcium and vitamin D	Paresthesia, tetany, pathologic fractures due to osteomalacia, positive Chvostek and Trousseau signs	Hypocalcemia, serum alkaline phosphatase increased, abnormal bone densitometry
Vitamin A	Follicular hyperkeratosis, night blindness	Serum retinol decreased
Vitamin K	Hematoma, bleeding disorders	Serum vitamin K, vitamin K-dependent coagulation factors decreased

RBC: red blood cell.

Graphic 76166 Version 10.0

Clinical manifestations of cirrhosis

Symptoms
Anorexia
Weight loss
Weakness
Fatigue
Muscle cramps
Easy bruising
Amenorrhea/oligomenorrhea/metrorrhagia (women)
Impotence (men)
Infertility
Decreased libido (men)
Jaundice*
Dark or "cola-colored" urine*
Pruritus*
Hematemesis/melena/hematochezia*
Abdominal distension*
Lower extremity edema*
Confusion or sleep disturbances*
Physical examination
Hepatomegaly
Splenomegaly
Spider angiomata/spider telangiectasias
Palmar erythema
Digital clubbing
Hypertrophic osteoarthropathy
Dupuytren's contracture
Muehrcke nails
Terry nails
Parotid gland enlargement (likely due to alcohol use and not cirrhosis per se)
Gynecomastia (men)

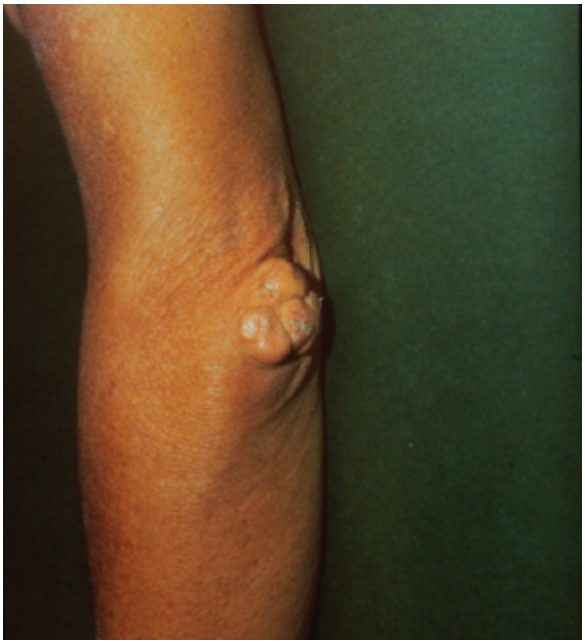
Loss of chest or axillary hair (men)
Testicular atrophy (men)
Caput medusa
Cruveilhier-Baumgarten murmur (venous hum heard best with the stethoscope over the epigastrium)
Jaundice*
Ascites (abdominal distension, shifting dullness, fluid wave)*
Asterixis*
Fetor hepaticus*
Laboratory tests
Moderately elevated aminotransferases (often with an AST:ALT ratio >1)
Elevated alkaline phosphatase (2 to 3 times the ULN)
Elevated gamma-glutamyl transpeptidase
Thrombocytopenia
Leukopenia/neutropenia
Anemia
Low serum albumin*
Prolonged prothrombin time/elevated INR*
Hyperbilirubinemia*
Hyponatremia*
Elevated serum creatinine*
Imaging tests
Surface nodularity
Increased echogenicity (ultrasound)
Atrophy of the right lobe
Hypertrophy of the caudate or left lobes
Small, nodular liver*
Ascites*
Hepatocellular carcinoma*
Portal/splenic/superior mesenteric vein thrombosis*
Portosystemic collaterals*

AST: aspartate aminotransferase; ALT: alanine aminotransferase; ULN: upper limit of normal; INR: international normalized ratio.

* Suggests advanced disease or the development of a major complication.

Graphic 90943 Version 3.0

Tuberous xanthomas

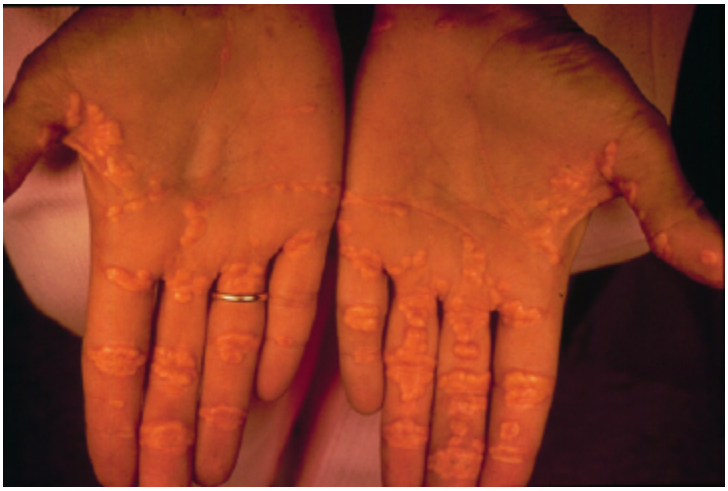


Tuberous xanthomas on the elbow of a woman with primary biliary cholangitis and a marked elevation in the serum cholesterol concentration (1400 mg/dL [36.4 mmol/L]).

Courtesy of Marshall M Kaplan, MD.

Graphic 75143 Version 2.0

Planar xanthomas

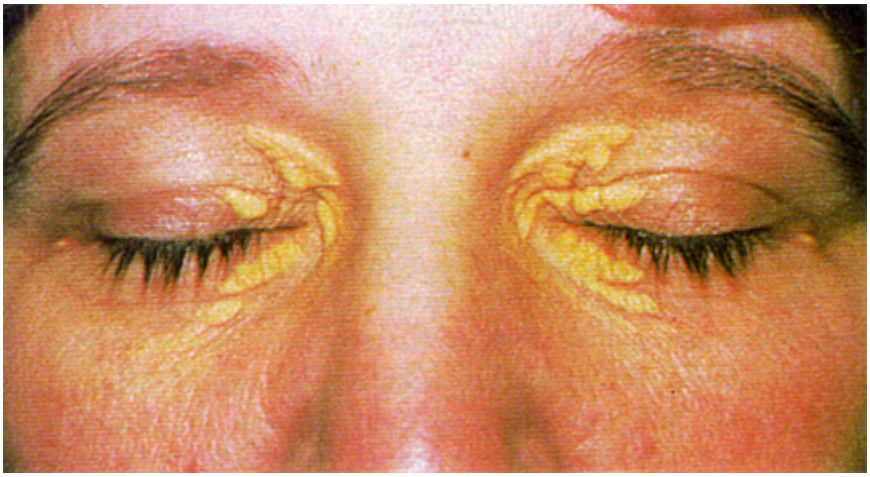


Bilateral planar xanthomas in the palms of a 35-year-old woman with primary biliary cholangitis. Xanthomas started in the creases and expanded. At the time that the xanthomas began to form, the serum bilriubin level was 18.6 mg/dL and serum cholesterol concentration was 970 mg/dL (25.2 mmol/l).

Courtesy of Marshall M Kaplan, MD.

Graphic 57793 Version 2.0

Xanthelasma



Yellow plaques are present bilaterally.

With permission from: Slomovits TL (Ed), Basic and clinical science courses section, American Academy of Ophthalmology, San Francisco 1996.

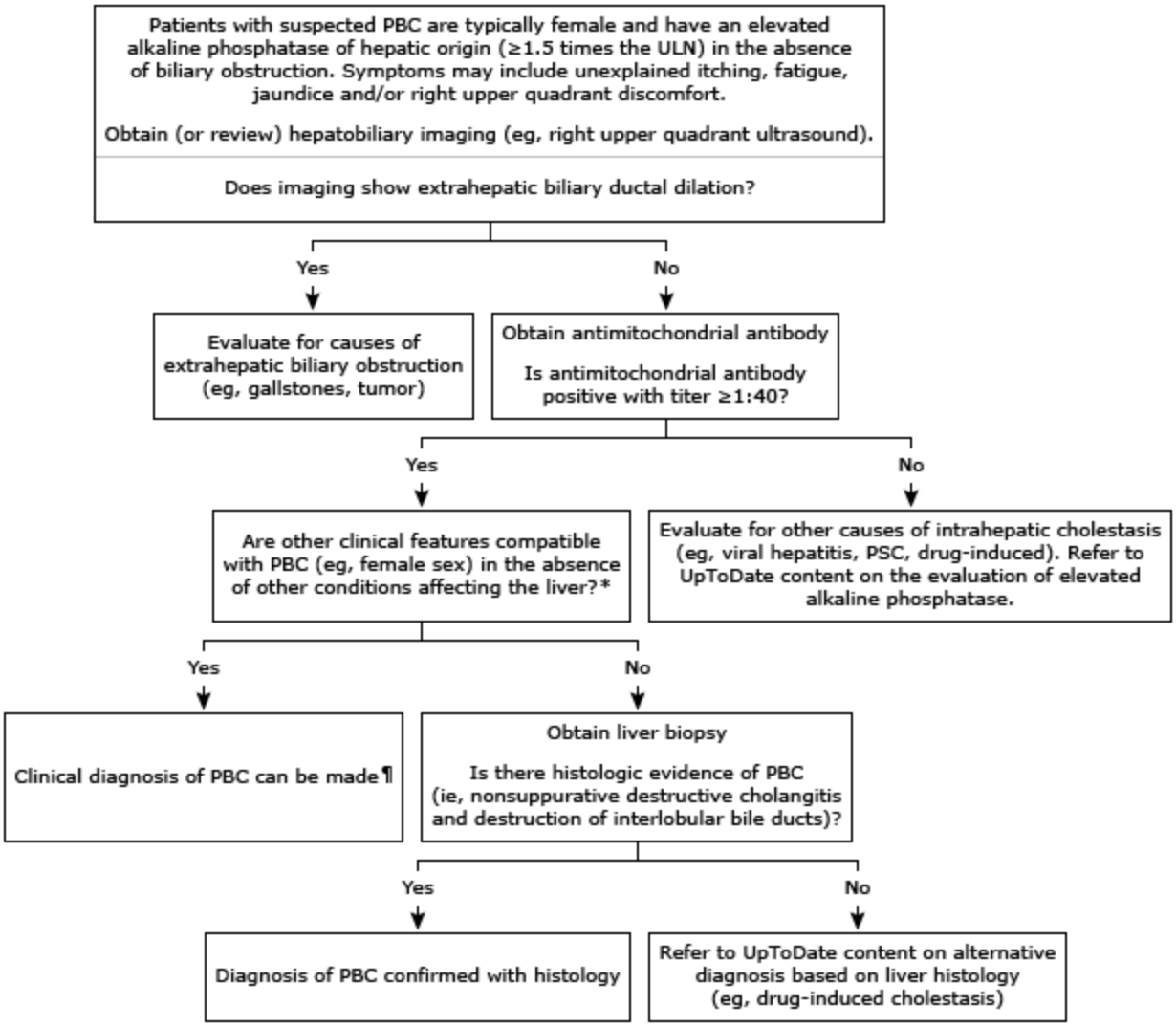
Graphic 67919 Version 2.0

Major symptoms and signs of hypothyroidism

Mechanism	Symptoms	Signs
Slowing of metabolic processes	Fatigue and weakness Cold intolerance Dyspnea on exertion Weight gain Cognitive dysfunction Intellectual disability (infantile onset) Constipation Growth failure	Slow movement and slow speech Delayed relaxation of tendon reflexes Bradycardia Carotenemia
Accumulation of matrix substances	Dry skin Hoarseness Edema	Coarse skin Puffy facies and loss of eyebrows Periorbital edema Enlargement of the tongue
Other	Decreased hearing Myalgia and paresthesia Depression Menorrhagia Arthralgia Pubertal delay	Diastolic hypertension Pleural and pericardial effusions Ascites Galactorrhea

Graphic 62676 Version 5.0

Evaluation of a patient with suspected primary biliary cholangitis (PBC)



This algorithm summarizes an approach to evaluating patients with suspected PBC. Some patients with PBC have associated conditions such as Sjögren's syndrome (dry eyes and mouth), arthritis, and Raynaud phenomenon. This algorithm is intended for use in conjunction with UpToDate content on the clinical features and diagnosis of PBC.

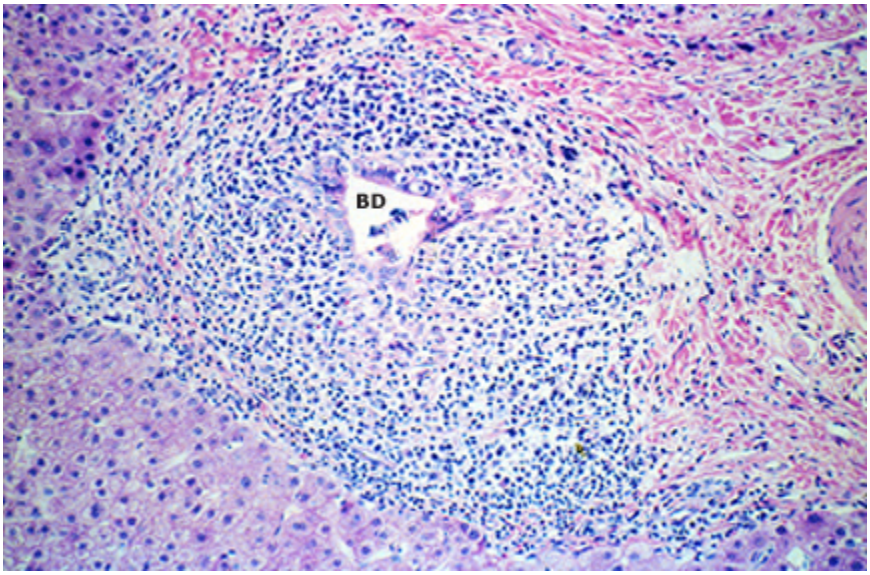
PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis; ULN: upper limit of normal.

* Common conditions that may warrant a liver biopsy include obesity, nonalcohol-associated fatty liver disease, and heavy alcohol use.

¶ While a liver biopsy is not required to make the clinical diagnosis of PBC, it may provide useful information with regard to staging and prognosis. A clinical diagnosis of PBC can be established in a female patient with an alkaline phosphatase ≥1.5 ULN, with an antimitochondrial antibody ≥1:40, and without extrahepatic biliary obstruction or other comorbidity affecting the liver.

Graphic 140937 Version 1.0

Primary biliary cholangitis

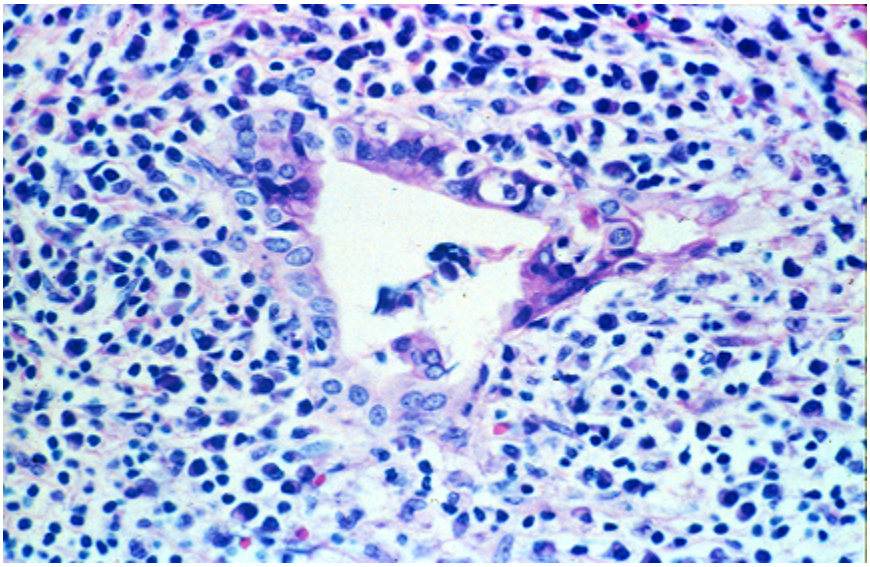


Low power view of liver biopsy in primary biliary cholangitis. A damaged bile duct (BD) is visible in the center of an intense inflammatory cell reaction in an enlarged portal triad. The bile duct appears to be the target of this inflammatory reaction.

Courtesy of Sanjiv Chopra, MD.

Graphic 54128 Version 2.0

Primary biliary cholangitis

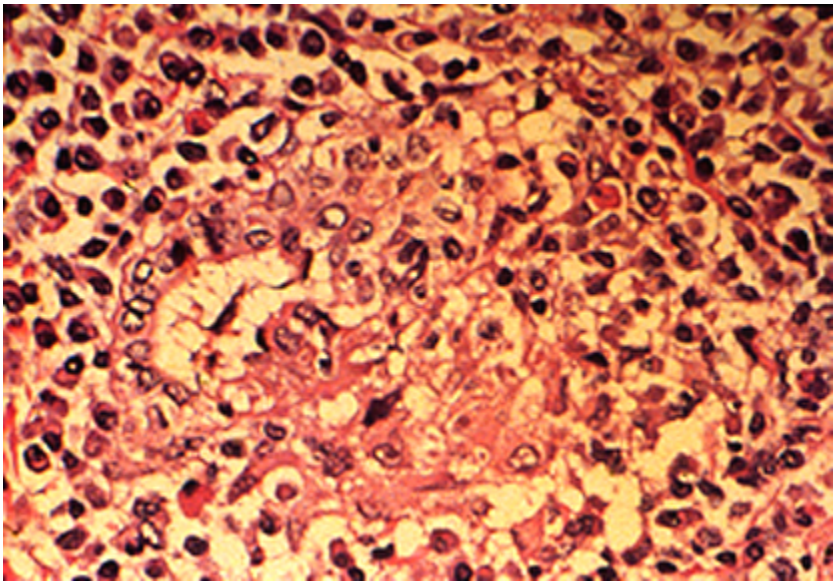


High power view of liver biopsy in primary biliary cholangitis in the same patient showing a marked mononuclear cell infiltrate surrounding and destroying a bile duct.

Courtesy of Sanjiv Chopra, MD.

Graphic 66904 Version 2.0

Florid bile duct lesion in primary biliary cholangitis

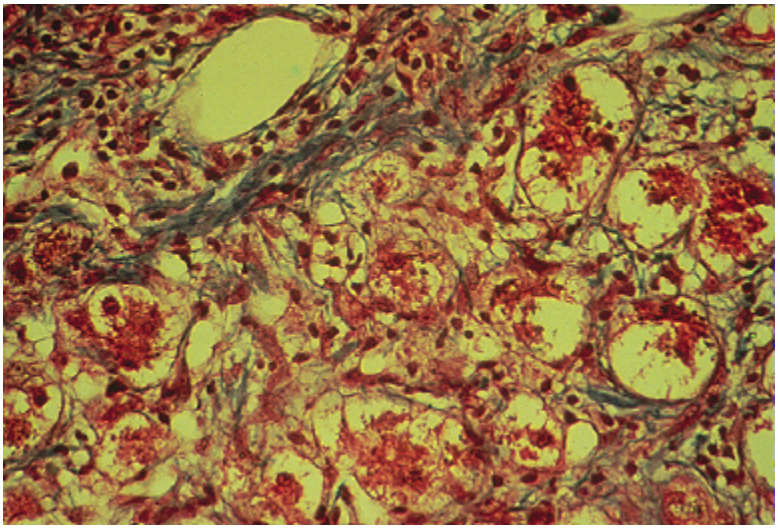


High power view of a liver biopsy from a patient with primary biliary cholangitis shows a portal bile duct with degeneration and periductular granulomatous inflammation ("florid" bile duct lesion).

Courtesy of Robert Odze, MD.

Graphic 53861 Version 3.0

Foamy degeneration in primary biliary cholangitis



Foamy degeneration of hepatocytes adjacent to portal triads in a patient with primary biliary cholangitis. There are hyaline droplets in many of these swollen hepatocytes, which are similar to those seen in alcoholic hepatitis. The lesion is thought to be due to the toxic effect of retained bile acids (Masson trichrome, x496).

Courtesy of Marshall M Kaplan, MD.

Graphic 65727 Version 2.0

METAVIR fibrosis and activity score

METAVIR fibrosis score		METAVIR activity score	
No fibrosis	F0	No activity	A0
Portal fibrosis without septa	F1	Mild activity	A1
Portal fibrosis with few septa	F2	Moderate activity	A2
Portal fibrosis with numerous septa without cirrhosis	F3	Severe activity	A3
Cirrhosis	F4		

References:

1. *The French METAVIR Cooperative Study Group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. Hepatology 1994; 29:15.*
2. *Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 1996; 24:289.*

Graphic 98097 Version 1.0

Contributor Disclosures

Raoul Poupon, MD No relevant financial relationship(s) with ineligible companies to disclose. **Keith D Lindor, MD** Consultant/Advisory Boards: Pliant [DSMB member]. All of the relevant financial relationships listed have been mitigated. **Kristen M Robson, MD, MBA, FACG** No relevant financial relationship(s) with ineligible companies to disclose.

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