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PRIMARY BILIARY CIRRHOSIS

Primary biliary cirrhosis (PBC) is a chronic liver disease that causes slow, progressive destruction of bile ducts in the liver. This destruction interferes with the excretion of bile. Continued liver inflammation causes scarring and eventually leads to cirrhosis. Cirrhosis is present only in the later stage of the disease. In the early stages of the illness, the main problem is the build up of substances (like bile acids, cholesterol) in the blood, which are normally excreted into the bile. Ursodeoxycholic acid is a life-saving, safe, and approved therapy.

What are the symptoms?

Women are affected ten times more frequently than men. The disease usually is first diagnosed in people 30 to 60 years old. Many patients have no symptoms of disease and are diagnosed by finding an abnormality on routine liver blood tests. Itching and fatigue are common symptoms. Other signs include jaundice, cholesterol deposits in the skin, fluid accumulation in the ankles and abdomen, and darkening of the skin. Several other disorders are often associated with PBC. The most common is impaired functioning of the tear and salivary glands, causing dry eyes or mouth. Arthritis and thyroid problems may also be present. Renal stones and gallstones may develop. Bone softening and fragility leading to fractures can occur in late stages of the disease.

How is PBC diagnosed?

PBC diagnosis is based on several pieces of information. The patient may have symptoms (itching) suggesting bile duct damage. Laboratory tests, such as the alkaline phosphatase activity test, may confirm this. The test for mitochondrial antibodies is particularly useful as it is positive in nearly all patients. Infrequently, the bile ducts are X-rayed to rule out possibilities of other causes of biliary tract disease, such as obstruction. A liver biopsy is useful in confirming the diagnosis and in giving information on the severity and extent of liver damage.

Lab Studies:

- An elevation of the aminotransferases alanine aminotransferase (ALT) and aspartate aminotransferase (AST) may be identified in most patients with PBC, but significant elevations of the alkaline phosphatase (ALP), g-glutamyl transpeptidase (GGTP), and immunoglobulin (mainly IgM) levels are usually the most prominent findings.

- Lipid levels and cholesterol levels may be increased, with an increased high-density lipoprotein (HDL) fraction. The latter finding explains why these patients do not have an increased risk for atherosclerosis.
- An increased erythrocyte sedimentation rate is another finding.
- As the disease progresses to cirrhosis, an elevated bilirubin level, a prolonged prothrombin time, and a decreased albumin level can be found. The increased bilirubin level is an ominous sign of disease progression, and liver transplantation must be considered.
- Thrombocytopenia is indicative of portal hypertension. Additionally, but not as commonly, abnormalities include elevated levels of ceruloplasmin, bile acids, and serum hyaluronate.
- The hallmark of this disease is the presence of antimitochondrial antibodies (AMAs) in the sera.
 - AMAs can be found in 90-95% of patients with PBC, and they have a specificity of 98% for this disease.
 - These antibodies target different components, mainly enzymes, in the mitochondria.
 - The presence of anti-M2, anti-M4, anti-M8, and anti-M9 has been associated with the severity of the disease. Patients with profile A (ie, only anti-M9) or profile B (ie, anti-M9 and/or anti-M2–positive by enzyme-linked immunosorbent assay [ELISA]) have a better disease course than patients with profile C (ie, anti-M2, anti-M4, and/or anti-M8–positive by ELISA) and profile D (ie, anti-M2, anti-M4, and/or anti-M8–positive by ELISA and complement-fixation test).
 - Antinuclear antibodies (ANAs) can be identified in 20-50% of patients with PBC.
 - Some patients have clinical, biochemical, and histological features of PBC, but their sera are negative for AMA. The diagnosis of autoimmune cholangitis has been used for these patients, but whether these patients represent the AMA-negative PBC group is a matter of debate. In terms of autoimmune markers, their profile is compatible with this type of autoimmune hepatitis (ie, high-titer ANA and/or SMA).
 - The natural history and associated autoimmune conditions in AMA-positive and AMA-negative PBC appear to be identical. A careful review of the liver biochemical pattern reveals cholestasis (ie, ALP and GGTP are

elevated), and the liver biopsy findings are compatible with bile duct injury, ductopenia, cholestasis, and granulomas.

Imaging Studies:

- Abdominal ultrasonography, CT scan, or MRI are important to exclude biliary obstruction.
 - Nonspecific findings include increased echogenicity of the liver parenchyma and findings compatible with portal hypertension.
 - Portal lymphadenopathy can be recognized in approximately 15% of these patients.
 - Once patients are cirrhotic, findings compatible with portal hypertension (eg, nodular appearance of the liver, splenomegaly, intraabdominal varices, and ascites) can be observed. At this stage, follow-up imaging every 6 months with abdominal ultrasound is suggested for early detection of hepatic malignancy.

Procedures:

- The diagnosis of the disease should be established or confirmed by performing a percutaneous or laparoscopic liver biopsy. This procedure also provides additional information about the stage of the disease and the patient's prognosis.
- In the late stages of the disease (ie, cirrhosis), an upper endoscopy study should be performed. If the patient has developed esophageal varices, prophylactic treatment (eg, beta-blockers, nitrates) can be initiated in an attempt to prevent variceal bleeding.

Histologic Findings: PBC is characterized by chronic, nonsuppurative, destructive cholangitis of the small interlobular bile ducts with a diameter of 40-80 μ m. Early lesions signal damage of the basement membrane of the bile ducts and reactive hyperplasia of the epithelial lining. Lymphocytic and plasma cell infiltration, with eosinophilic condensation in the portal tracts, is another feature. Epithelioid aggregates or granulomas may be found around the bile ducts. Fibrosis and cirrhosis develop later.

Staging: Various staging systems have been developed, but the most prominent are those proposed by Ludwig et al and Scheuer.

- Stage 1 (portal stage of Ludwig): Portal inflammation, bile duct abnormalities, or both are present.

- Stage 2 (periportal stage): Periportal fibrosis is present, with or without periportal inflammation or prominent enlargement of the portal tracts with seemingly intact, newly formed limiting plates.
- Stage 3 (septal stage): Septal fibrosis with active inflammatory, passive paucicellular septa or both are present.
- Stage 4 (cirrhosis): Nodules with various degrees of inflammation are present.

What causes PBC?

The exact mechanism of the liver damage is unknown, although evidence indicates that it can be of autoimmune origin. The data supporting this hypothesis are as follows: (1) abnormalities of the humoral and cellular immune systems (ie, elevated serum levels of immunoglobulins, mainly immunoglobulin M [IgM]), (2) multiple circulating autoantibodies, (3) granulomas in the liver and regional lymph nodes, (4) impaired regulation of both B and T lymphocytes, and (5) the association of this disease with a variety of autoimmune-mediated diseases (eg, autoimmune thyroiditis; keratoconjunctivitis sicca; scleroderma; calcinosis cutis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia [CREST] syndrome).

A continuous destruction of small and medium bile ducts occurs, which is mediated by activated CD4 and CD8 lymphocytes. As a result, chronic cholestasis is the prominent clinical and laboratory finding. Once destroyed, it is well established that regeneration of bile ducts is either not possible or inefficient.

Subsequent to the loss of the intrahepatic bile ducts, a disruption of the normal bile flow occurs with retention and deposition of toxic substances, which are normally excreted into bile. The retention of toxic substances, such as bile acids and copper, can cause a further secondary destruction of the bile ducts and the hepatocytes. In addition, increased expression of the HLA class II antigens in the liver occurs, rendering hepatocytes and bile duct epithelial cells more susceptible to activated T lymphocytes and perhaps exacerbating immunologically mediated cytotoxicity. An association has been suggested between PBC and haplotype HLA-DR8 and, for some populations, HLA-DPB1.

Complications:

- Osteoporosis resulting from a decreased formation of bone has been found in a third of patients.
- Fat-soluble vitamin deficiency is a rare complication that is present in patients with long-standing hyperbilirubinemia.
- Hypercholesterolemia and hyperlipidemia have been identified in 85% of patients.

- Esophageal motility problems can occasionally occur, with asymptomatic or symptomatic reflux causing esophagitis and, possibly, stricture. This is more common in patients with CREST syndrome.
- Patients with jaundice can develop steatorrhea. This complication results from the decreased excretion of bile acids. Mild pancreatic insufficiency has also been reported.
- Renal tubular acidosis can be observed in approximately half of patients with PBC. Copper deposition in the renal tubules or an autoimmune phenomenon might be the mechanism for this complication.
- Hypothyroidism has been noted in 20% of patients with PBC.
- Hepatocellular carcinoma can develop, with an overall incidence of approximately 6% (4.1% in women; 20% in men with advanced disease).
- Asymptomatic bacteriuria has been found in 35% of patients with PBC.
- Autoimmune thrombocytopenia and hypoglycemia with insulin receptor autoantibodies may occur.
- Transverse myelitis and necrotizing myelopathy caused by vasculitis may occur.
- Xanthomatous peripheral neuropathy may occur.

Prognosis:

- The most reliable determinants of patient prognosis in PBC are the height of the serum bilirubin level and the Mayo risk score.
 - Published reports indicate that, when serum bilirubin values are constantly above 2, the mean survival rate is 4.1 years.
 - When bilirubin levels are constantly above 6 mg/dL, the mean survival rate is 2.1 years.
 - When bilirubin levels are constantly above 10 mg/dL, the mean survival rate is 1.4 years.
 - The Mayo risk score is calculated as follows:

$$R = 0.871 \log_e (\text{bilirubin in mg/dL}) + (-2.53) \log_e (\text{albumin in g/dL}) + 0.039 \text{ age in years} + 2.38 \log_e (\text{prothrombin time in seconds}) + 0.859 (\text{edema score of 0, 0.5, or 1})$$
 - A recent report reassessed the Mayo risk score, taking into consideration other factors found to be important in the timing of transplantation in

patients with chronic cholestatic liver disease. Neither the height of the serum bilirubin level nor the Mayo risk score are invalidated by UDCA therapy. Treatment with UDCA before liver transplantation does not alter the posttransplantation outcome.

PBC typically advances slowly. Many patients lead active and productive lives for ten to fifteen years after diagnosis. Patients who show no symptoms at the time of diagnosis often remain symptom-free for years. Jaundice appears to be a sign of diminishing liver reserve and may be an important indication regarding the progression of the disease. The illness is chronic and may lead to life-threatening complications, especially after cirrhosis develops.

For asymptomatic patients with antimitochondrial antibody (AMA)-positive findings, a normal biochemical liver profile, and histologic features that are compatible with PBC, the progression of the disease is relatively slow; however, the patient life expectancy is not identical to that of the general population. Of these patients, 40-67% develop symptomatic disease in approximately 5-7 years. Once they develop symptoms (mainly cholestasis) and remain untreated, the median patient survival duration ranges from 5.5-12 years. Generally, the median survival duration from the time of diagnosis is 7.5 years for patients who are symptomatic and 16 years for patients who are asymptomatic.

How is PBC treated?

Treatment may be useful in several ways. Proper advice will ensure the elimination of potentially harmful drugs, foods, or toxins. If the patient is deficient in vitamin D, then this should be corrected. Patients with PBC should take calcium to help prevent osteoporosis [loss of bone], a common complication of this disease. The thyroid function should be tested and, if low, treated with a thyroid hormone. Symptoms may be successfully relieved. Itching is often reduced by using cholestyramine and rifampin. Salt restriction may be effective in reducing fluid accumulation. The diet should be well-balanced. Corticosteroids have been found ineffective in most patients. The FDA has approved only URSO 250 (manufactured by Axcan Scandipharm) for use in patients with PBC. The recommended dose is 13-15 mg/kg once a day. Physicians who treat PBC patients often prescribe other ursodiol products off-label. These products include Actigall (manufactured by Novartis) and various generic formulations.

Liver transplantation

When medical treatment no longer controls the disease and the patient has severe liver failure, transplantation is indicated. Signs of liver failure include accumulation of fluid in the abdomen, malnutrition, gastrointestinal bleeding, intractable itching, jaundice, and bone fractures. Transplantation may be recommended before all these events occur. The outcome for patients with PBC who have undergone transplantation is excellent. The survival rate for two or more years is about 80 percent. The use of new drugs to suppress rejection has made transplantation even more successful. The disease's slow progress makes it possible to plan elective transplant surgery.

The future

PBC has been known for more than 100 years. This knowledge has led doctors to make earlier diagnoses. Many clues to the cause have been supplied by careful observation of patients over the last 25 years, but the basic cause is unknown.

Research is following two paths:

- Basic investigation of the causes and development of the disease.
- Drug therapy trials, involving a large number of patients around the world, are exploring the potential use of several additional medications to lessen the symptoms and control liver damage.