Features and Management of Primary Biliary Cirrhosis

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Primary biliary cirrhosis (PBC) is a disease of unknown origin that causes chronic liver injury. It has an insidious onset, is associated with slow progression and ultimately leads to liver failure and either death or liver transplantation. It is presumed to be of autoimmune origin, is frequently associated with other autoimmune disorders and typically affects middle-aged and elderly women. Patients may be asymptomatic at diagnosis or present with typical symptoms of fatigue, pruritus and jaundice. Although current therapy may slow the progression of disease, no therapy has yet been proven to arrest or reverse the disease process.

Key words: cirrhosis, fatigue, autoimmune, cholestasis, antimitochondrial antibodies.

Etiology
Increased frequency in family members of patients with primary biliary cirrhosis (PBC) suggests that there are genetically determined susceptibility factors. Several etiological factors, including infectious agents, environmental toxins or drugs, and abnormal or toxic bile acids, have been suggested as having putative roles in the development of PBC. Similar to other presumed autoimmune diseases, PBC has been reported to occur more frequently in women compared to men.

Clinical Features
In a 1990 review, Witt-Sullivan et al. reviewed 225 patients from Ontario with PBC.1 Among this group, the mean age at diagnosis was 59.3 years, with a range of 29–85 years. At diagnosis, 71.3% of the patients were symptomatic, with the remainder asymptomatic. The most common symptom was fatigue, which was observed in 80.6% of the symptomatic patients, while pruritus was noted in 65%, abdominal pain in 33% and jaundice in 23%. The ratio of female to male patients was 13.4 to 1.

Over time, symptoms tend to become more pronounced (Table 1). Patients may complain of diarrhea, which usually is secondary to steatorrhea caused by insufficient biliary secretion of bile acids. Fatigue, often associated with sleep disturbances and depression, can become disabling. Xanthelasma may develop with xanthomata found on the palms of the hands and soles of the feet as well as over the extensor surfaces of the elbows and knees. Eventually, symptoms of liver failure, including ascites, jaundice, encephalopathy, muscle wasting and bruising secondary to coagulopathy, develop. Esophageal variceal hemorrhage may occur prior to the development of cirrhosis secondary to the development of nodular regenerative hyperplasia. The frequency of hepatocellular carcinoma is greater among patients with PBC, with a projected frequency of 11.1% in patients with advanced disease.2

PBC is commonly diagnosed in the asymptomatic patient presenting with elevated alkaline phosphatase (ALP), hyperlipidemia, unexplained hepatosplenomegaly or a family history. Not uncommonly, PBC is diagnosed following investigation of a pre-existing autoimmune disorder, such as autoimmune thyroiditis, scleroderma, sicca syndrome or rheumatoid arthritis.

Laboratory Tests
Typically, patients present with elevated levels of ALP and gamma-glutamyl transpeptidase (GGT) with mild elevations of the serum transaminases. Serum cholesterol levels (especially of the high density lipoproteins) and serum immunoglobulins, especially immunoglobulin M, also are commonly elevated. The serum bilirubin typically reflects the extent of liver disease in PBC with higher levels reflecting more advanced disease. However, elevations in serum bilirubin may be found in PBC due to extrahepatic biliary tract obstruction, drug-induced liver injury, sepsis, hemolysis or thyroid dysfunction. Decreased albumin levels typically are seen with advanced disease.

Antimitochondrial antibodies (AMA) are found in over 90% of patients with PBC and, when found in high titer, are considered diagnostic of the condition. The AMA most commonly found in PBC is directed against a specific antigen on the inner mitochondrial membrane (M2) and is part of the pyruvate dehydrogenase complex of the mitochondrion.

Pathology
PBC is characterized by progressive destruction of the interlobular bile ducts (Figure 1). Involved ducts show epithelial swelling with infiltration by lymphocytes, eosinophils and plasma cells. Epithelioid aggregates or non-caseating granulomas develop close to or surrounding the affected bile ducts. As the disease progresses, bile ducts disappear (ductopenia)—a condition that is associated with the development of periductular fibrosis, periportal hepatocyte necrosis and cholestasis. Later, portal-portal septal fibrosis can be seen and, finally, portal-central septa will develop that are associated with nodular regeneration (cirrhosis). The liver may not be affected uniformly, and all degrees of liver injury may be seen in a single biopsy specimen.3

Diseases Associated with PBC
Strong associations have long been recognized between PBC and rheumatoid arthritis, sicca syndrome, autoimmune thyroiditis, Raynaud’s phenomenon and scleroderma (Table 1). Celiac disease, inflammatory bowel disease and autoim-
Primary Biliary Cirrhosis

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Investigation of the Newly Diagnosed Patient with PBC

The diagnosis of PBC is usually made following the discovery of elevated ALP and GGT in a middle-aged or elderly woman presenting with fatigue or pruritus. The presence of AMA in the serum in high titer can be considered confirmatory.

Following diagnosis, liver function tests in terms of PTINR, albumin and bilirubin levels should be measured for prognostication purposes. An abdominal ultrasound should be carried out to rule out extrahepatic biliary tract obstruction as a cause of cholestasis. Upper gastrointestinal tract panendoscopy is indicated to rule out esophageal varices, while bone mineral densitometry studies are needed to rule out osteoporosis. Measurement of thyroid stimulating hormone is indicated to rule out associated autoimmune thyroiditis.

In patients with an AMA titer ≥ 1:40 with typical symptoms and biochemistry profile, a liver biopsy may not be necessary. This is especially the case in elderly women with PBC. However, a liver biopsy may be of value in establishing prognosis, ruling out other diagnoses and confirming the diagnosis in patients with AMA-negative PBC.4

Natural History and Prognosis

Mean survival following diagnosis in a series of 279 patients was 8.4 years, with survival of 7.5 years in the symptomatic and 16 years in the asymptomatic group.5 In this series, 64% of the asymptomatic patients became symptomatic within an average of 5.3 years of the initial diagnosis. Within 11 years of diagnosis, mortality of these patients exceeded that of a control group without PBC.

Symptomatic Therapy

Fatigue is one of the most common symptoms of PBC and may be so disabling as to serve as an indication for liver transplantation. Clinicians should be alert for associated depression, which should be aggressively treated if present. It is believed that fatigue in PBC may be secondary to altered central serotonergic neurotransmission. The selective 5-HT3 receptor antagonist ondansetron might be effective in relieving fatigue in PBC.6

Pruritus, like fatigue, may serve as an indication for liver transplantation in the...
absence of liver failure. The etiology of pruritus in PBC is unknown. The standard therapy for pruritus remains cholestyramine. This oral anion exchange resin may be given at doses up to 16g daily. For patients refractory to this medication, rifampicin at doses up to 10mg/kg may be effective. Alternate therapies for refractory pruritus include large volume plasmapheresis, ultraviolet light exposure and opioid antagonists, such as naltrexone.

**Treatment of PBC Complications**

Prevention of bone disease in PBC includes adequate exercise and supplemental oral calcium (1500mg/d) and vitamin D (1000 IU/d), with therapy to start as soon as the diagnosis is made. Transdermal hormone replacement therapy may be of value in postmenopausal women. For patients with established osteoporosis, bisphosphonate therapy with etidronate may be helpful. Severe osteoporosis refractory to medical therapy is an indication for liver transplantation.

Fat-soluble vitamin deficiencies may develop secondary to malabsorption resulting from decreased amounts of bile acid in the intestinal lumen. In advanced disease, supplements of vitamins A, D, E and K should be provided. Patients with steatorrhea may benefit from substitution of medium-chain triglycerides for long-chain triglycerides in the diet and decreased total fat intake.

Although hypercholesterolemia and hyperlipidemia are present in as many as 85% of patients with PBC, there is no increased risk of arteriosclerosis. Therefore, antihyperlipidemic therapy is not indicated. Plasmapheresis may be helpful for patients with xanthomas associated with painful neuropathy.

The sicca syndrome is present in most patients with PBC. These patients will benefit from artificial tears, good dental hygiene, oral saliva substitutes and vaginal creams and lubricants. Food should always be swallowed with liquid. Patients with Raynaud’s phenomenon need to be advised about limiting exposure of their extremities to cold temperature or cold water. They should be strongly advised to quit smoking. Calcium channel blockers may be of limited benefit.

**Therapy of Underlying Disease Process**

Trials of therapy in PBC have been directed along three different pathways, namely using immunosuppressive drugs to reduce immune-mediated inflammation, relieving cholestasis and reducing hepatic fibrosis. Clinical trials of the immunosuppressive agents azathioprine, chlorambucil, cyclosporine, methotrexate and adrenocorticosteroids have all failed to demonstrate that these drugs improve the course of the disease. Although the antifib-
Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid that, when given orally, accumulates in the liver mitigating the effect of other more toxic bile acids. In an analysis of three randomized, controlled trials of UDCA given in doses of 13–15mg/kg/d, Poupon et al. reported that survival free of liver transplantation was significantly improved in the patients treated with UDCA compared with patients assigned to placebo. A recent report from Jorgensen et al. reported that UDCA was particularly likely to be beneficial when instituted early in the course of the disease. Normalization of liver tests following therapy with UDCA was considered a possible marker for a clinically important response. A recent meta-analysis of five long-term clinical trials of UDCA in PBC suggested a 32% lower risk of either dying or undergoing liver transplantation compared to placebo.

Despite these favourable results, several authors have suggested that UDCA may not be of benefit in PBC. Goulis et al. reviewed 11 randomized trials encompassing 1,272 patients. They concluded that, although UDCA therapy resulted in improved laboratory results, there was no significant beneficial effect on symptoms, disease progression, mortality or frequency of liver transplantation. In a 12-year, prospective, randomized, controlled trial, Papatheodoridis et al. reported no demonstrable effect of UDCA on the long-term prognosis of PBC. A recent Cochrane Review examined 16 randomized trials, with a total of 1,422 patients, that compared UDCA to placebo. UDCA therapy did not significantly affect mortality, quality of life, liver histology, portal pressure, or frequency of liver transplantation or symptoms, such as pruritus and fatigue.

Liver Transplantation

At present, the only definitive treatment for advanced PBC is liver transplantation, with one-year survival following liver transplant of 85–90% and a five-year survival of 70–80%. Unfortunately, many patients with PBC are not candidates for liver transplantation due to advanced age and other medical conditions precluding transplantation. PBC may recur in the transplanted liver.

Conclusions and Future Directions

Presently, there is no therapy that can prevent progression of disease. At best, the available therapies, such as UDCA, may slow progression. Liver transplantation is not a cure for PBC as the disease may recur in the transplanted liver. Improved understanding of the pathogenesis of PBC may result in more effective medical therapy, thereby reducing the need for liver transplantation. New treatments are required to reduce the debilitating effects of osteoporosis, pruritus and fatigue, and, by doing so, improve patient quality of life.

Table 1

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<tr>
<th>Manifestations of Primary Biliary Cirrhosis and Associated Disorders</th>
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<tbody>
<tr>
<td><strong>Manifestations of PBC</strong></td>
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<td>Pruritus</td>
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<td>Fatigue</td>
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<td>Osteoporosis</td>
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<td>Xanthomata</td>
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<td>Diarrhea</td>
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<td>Fat soluble vitamin malabsorption</td>
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<td>Portal hypertension and features of decompensated cirrhosis:</td>
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<td>- ascites</td>
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<td>- bleeding esophageal varices</td>
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<td>- coagulopathy</td>
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<td>- jaundice</td>
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<td><strong>Manifestations of Associated Disorders</strong></td>
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<td>Hyper- or hypothyroidism (autoimmune thyroiditis)</td>
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<td>Esophageal dismotility, telangiectasia, Raynaud’s (CREST)</td>
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<td>Diarrhea, iron deficiency (celiac disease)</td>
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<td>Arthropathy (rheumatoid arthritis)</td>
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<td>Anemia (autoimmune hemolytic anemia)</td>
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<td>Diarrhea, rectal bleeding (inflammatory bowel disease)</td>
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References