Update on primary biliary cirrhosis

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J Heathcote. Update on primary biliary cirrhosis. Can J Gastroenterol 2000;14(1):43-48. The diagnosis of primary biliary cirrhosis (PBC) is most often made in the asymptomatic phase, sometimes before the development of abnormal liver biochemistry. The antimitochondrial antibody remains the predominant hallmark, although not all patients test positive, even when the most sensitive techniques are used. The etiology of PBC remains elusive; studies suggest that the interlobular bile duct destruction is immune based, and associated autoimmune diseases are common.

There are no surrogate markers that predict outcome in asymptomatic patients, whose chance of survival is less than that of age- and sex-matched populations but much better than the median survival of eight years in patients with symptomatic PBC. Symptoms common in this disease are fatigue, pruritus and xanthelasma, as well as complications of portal hypertension and osteoporosis. Treatment includes symptomatic and preventive measures, as well as specific therapeutic measures. Immunosuppressive therapy has yielded disappointing results in the long term management of PBC, and the only therapy shown to improve survival is the hydrophobic dihydroxy bile acid ursodeoxycholic acid. Treatment at a dose of 13 to 15 mg/kg/day is optimal, given in separate doses or as a single dose at least 4 h from giving the oral anion exchange resin cholestyramine, which may be used to control pruritus. However, liver transplantation remains the only cure for this disease, and the best postoperative survival is seen in patients whose serum bilirubin does not exceed 180 µmol/L at the time of liver transplantation. Recurrence takes place but is rarely symptomatic and does not deter from the benefits of transplantation.

Key Words: *Antimitochondrial antibody; Liver transplantation; Primary biliary cirrhosis; Ursodeoxycholic acid*

Mise à jour sur la cirrhose biliaire primitive

RÉSUMÉ : Le diagnostic de cirrhose biliaire primaire (CBP) est le plus souvent posé dans la phase asymptomatique, quelquefois avant que les examens biochimiques du foie ne deviennent anormaux. Les anticorps antimitochondries reste le signe d'appel prédominant, bien que tous les tests ne se révèlent pas positifs chez les patients malgré les techniques les plus sensibles qui sont utilisées. L'étiologie de la CBP reste inconnue ; cependant, des études laissent à penser que la destruction des canaux biliaires interlobulaires a une origine immunologique, et que des maladies autoimmunes associées sont courantes.

Il n'y a pas de marqueurs substituts qui prédisent l'évolution clinique des patients asymptomatiques, dont les chances de survie sont inférieures à celles de populations appariées pour l'âge et le sexe, mais supérieures à la survie moyenne de huit ans observée chez les patients atteints d'une CBP symptomatique. Les symptômes courants de cette maladie sont la fatigue, le prurit et des xanthélasmas, ainsi que des complications de l'hypertension portale et de l'ostéoporose. Le traitement comprend des mesures pour soulager les symptômes et des mesures préventives, de même que des mesures thérapeutiques spécifiques. Les traitements immunosuppresseurs sont décevants dans la prise en charge au long cours de la CBP, et le seul traitement qui prolonge la survie est l'acide biliaire hydrophobe dihydroxyursodésoxycholique. La dose optimale est de 13 à 15 mg/kg/jour, administrée en doses séparées ou à une dose unique au moins quatre heures avant l'administration par voie orale d'une résine échangeuse d'anions, la cholestyramine, qui peut être utilisée pour contrôler le prurit. Cependant, la transplantation du foie reste le seul moyen de guérir cette maladie, et une meilleure survie postopératoire s'observe chez les patients dont la bilirubine sérique n'excède pas 180 µmol/L au moment de la transplantation du foie. La maladie peut récidiver, mais elle est rarement symptomatique, et n'écarte pas les avantages d'une transplantation.

The textbook description of patients with PBC (PBC) is of a middle aged woman who complains of pruritus, is found to have elevated serum alkaline phosphatase levels, tests positive for antimitochondrial antibodies (AMA) and has a liver biopsy showing granulomatous destruction of the bile ducts. Over the past decade, the spectrum of PBC has broadened considerably. First, a group in Newcastle, United Kingdom described subjects who were found to be AMA-

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positive when an immunological screening profile was performed. The subjects' liver biochemistries were entirely normal, but the liver biopsy revealed some of the histological features typical of PBC (1). A 10-year follow-up of these patients showed that, of those who survived, all developed abnormalities in serum biochemistry that reflected anicteric cholestasis, some became symptomatic and those who underwent rebiopsy showed progression of disease (2). It has also been identified that some patients may have the clinical, biochemical and histological features of PBC but remain consistently negative for AMA, even when the most sensitive immunoblotting techniques are used (3). Pathologists have described all the classical histological hallmarks of PBC in patients who have no nonorgan-specific antibodies present in serum (4). Hence, diagnosis of PBC may be expanded to include the above. The etiological factor initiating this chronic progressive destruction of bile ducts remains unknown, so it is unclear whether a single etiological agent results in this spectrum of disease or whether several agents may cause similar but not identical clinical, biochemical, serological and histological disease patterns.

DIFFERENTIAL DIAGNOSIS

As the spectrum of disease that encompasses the one diagnosis of PBC broadens, so does the differential diagnosis. The hardest to distinguish is sarcoidosis, though the skin lesions seen in this disease are never seen in PBC. Granulomatous bile duct destruction may also be seen in primary sclerosing cholangitis; however, the endoscopic retrograde cholangiopancreatography findings should be diagnostic. The other many causes of the vanishing bile duct syndrome can generally be easily distinguished from PBC. The new term 'overlap syndrome' has added great confusion, and not much benefit has been gained from its various interpretations (5-7).

PATHOGENESIS

The histological hallmark of PBC is granulomatous destruction of the interlobular and septal bile ducts, but granuloma may be absent, particularly in stage III and stage IV disease. It is presumed that the bile duct destruction is immune-mediated, first, because, in addition to granuloma, chronic inflammatory cells typically invade the interlobular ducts. In addition, in early PBC, biliary epithelial cells express cluster of differentiation 1 locus, which is known to be involved in the antigen presentation of microbial lipid antigens to T cells (8). Second, PBC is associated with many other nonhepatic autoimmune diseases (9). Some epidemiological data suggest that exogenous agents are important (10), and human leukocyte antigen studies have shown an association, albeit weak, with the class II antigen DR8 in linkage disequilibrium with DQ4 (11). It remains unclear whether AMA are an epiphenomenon or are part of the pathogenesis of this disease. It has been suggested that even in patients who test AMA-negative in serum but are thought to have PBC, careful examination of all immunoglobulin fractions may allow identification of AMA when more sophisticated techniques are used (12). In addition, both cytoplasmic and biliary epithelial cell membrane staining for the major substrate for mitochondrial antibodies (the E_2 components of the pyruvate dehydrogenase complex) have been reported to be present in both AMA-positive and AMA-negative PBC patients (13). Apoptosis of bile duct epithelium has been reported; however, it is unclear whether this is a primary or secondary event (14).

Clearly, factors in addition to autoimmunity play a role in the progression of PBC. Diminution in the number of bile ducts leads to cholestasis and early retention of endogenous hydrophobic bile acids, which themselves are hepatotoxic (15). Thrombi in the hepatic and portal venous radicals are found in the explants from PBC patients going for transplantation. The thrombi are noted to be both old and new and are associated with areas of hepatic extinction and fibrosis (16). In addition, the cytokines released from invading chronic inflammatory cells may stimulate fibrogenesis (17). Hence, in most patients with PBC, early bile duct destruction is followed by progressive fibrosis and eventual cirrhosis at a varying rate.

EPIDEMIOLOGY AND NATURAL HISTORY

PBC affects all racial groups worldwide and predominately affects women (18). It has never been described in children. The age (in years) at diagnosis varies from the low 20s to the high 80s. Approximately 60% of patients diagnosed with PBC are asymptomatic. The clinical course of asymptomatic disease cannot be predicted except to say that long term survival of asymptomatic PBC is less than that of an age- and sex-matched population, but considerably better than that of patients with PBC who are symptomatic. Approximately one-third of asymptomatic patients become symptomatic within five years; 50% survival is seen at 12 years, whereas it is seen at only eight years in symptomatic patients (19,20). Curiously, asymptomatic patients tend to be older at the time of diagnosis than those with symptoms. This may be because the most common symptom is pruritus, and this is more likely to be present in those with high circulating estrogen levels (pruritus is less common in males with PBC). It is likely that the course of disease is similar regardless of the age at diagnosis. Primary liver cell cancer may complicate PBC, particularly in men, as it does all cirrhotics (21). The prevalence of PBC varies quite considerably from country to country (19 in 1,000,000 to 250 in 1,000,000) (22); this variation is in part caused by different methods of screening and diagnosis. The highest prevalence (one of 250) reported so far is in Newcastle, United Kingdom, but these patients were not only recruited from physician offices and hospital records but were also identified through serological testing in regional immunology laboratories.

SYMPTOMS ATTRIBUTABLE TO PBC

Fatigue affects up to 70% of patients with PBC. The cause of this phenomenon is unknown, as is the case for fatigue in all other patients with chronic liver disease. Studies have shown that the degree of fatigue does not correlate with the severity of the disease but is associated with both depression and/or

sleep disorder (23). It is difficult to know whether fatigue antedates or postdates the onset of depression and/or sleeping problems. It is likely that the fatigue is a central phenomenon; antidepressants may be helpful on occassion.

Pruritus can be mild, moderate or extremely severe, causing patients to be awake at night and even promoting suicidal ideation. The cause of pruritus is unknown, although many hypotheses have been generated. There is no correlation of the degree of pruritus with the level of bile acids in serum, but some have suggested that skin bile acid concentrations may affect pruritus; others have suggested that the particular bile acid mileux within the hepatocyte may be associated with the symptom of pruritus (24). More recently, evidence has been put forward that suggests that endogenous opiods, levels of which are elevated in serum and possibly also in the brain, may be responsible for the symptom of pruritus in patients with chronic cholestasis (25). The cause of the increase in endogenous opioids is unknown but may be altered hepatocyte metabolism.

Xanthelasma: Xanthelasma are noted more often in patients with PBC than in those with any other cholestatic liver disease. Xanthelasma are most common around the eyes but may be found over tendons and in the palms of the hands. Occasionally, they are severe and even affect peripheral nerve function, giving rise to a painful neuropathy. Xanthelasma regress with progression of disease. They are not always associated with hypercholesterolemia (26). The lipid profile in PBC shows that the high density lipoprotein cholesterol levels are elevated, but the mechanism is unknown (27).

Complications of portal hypertension: Portal hypertension may occur very early in the course of PBC; initially it is due to presinusoidal venous damage because PBC predominately affects the portal tracts. Small portal venous thrombi are observed, and the typical histological features of nodular regenerative hyperplasia may be found (28). As the disease progresses and fibrosis and cirrhosis ensue, the portal hypertension becomes sinusoidal. Hence, patients may present de novo with a variceal hemorrhage; ascites is less common because cirrhosis needs to be present. Hepatic encephalopathy is generally only observed in preterminal patients because liver function in this disease remains preserved for a long time.

Nonhepatic complications: Osteoporosis is common in patients with chronic cholestasis, and in PBC is due to decreased osteoblast function and increased osteoclast function, as well as to impaired calcium and vitamin D malabsorption in the icteric patient (29). Osteoporosis is generally silent but is easily detected using dual-energy x-ray absorptiometry to assess bone mineral density and should be part of the baseline workup of all cholestatic patients, whether they are jaundiced or not.

Associated autoimmune disorders: The prevalence of associated autoimmune disorders varies from study to study, but almost all patients with PBC have at least one, the most common of which is thyroid dysfunction (25%). Symptoms of the sicca syndrome, when patients are directly questioned, are present in 70% of those with PBC, but much fewer actually present with symptoms (30). Various manifestations of Sjögren's and CREST (calcinosis cutis, Raynaud's phenomenon, esophagel motility disorder, sclerodactyly and telangiectasia syndrome) are not infrequent; symptoms of Raynaud's phenomenon are particularly troublesome in cold climates. Rheumatoid factor is frequently found in the sera of PBC patients, but symptomatic disease is less frequent. Celiac disease is said to affect 6%, hemolysis may be another rare cause of anemia and some patients have immune thrombocytopenia. Other less common presumed autoimmune disorders include renal tubular acidosis, systemic lupus erythematosus, glomerulonephritis and various pulmonary syndromes.

PROGNOSTIC MARKERS

There are no markers that can predict outcome in patients with PBC who are asymptomatic with normal serum bilirubin. There is a suggestion that the pattern of serum bile acids may be helpful, but such analyses are not readily available (31). There is a correlation, albeit weak, between histology and outcome; patients found to be cirrhotic at diagnosis have a lesser chance of survival than those who are not cirrhotic (32). It is not unusual to find an asymptomatic patient with cirrhosis, but in a study of close to 100 asymptomatic patients, even baseline histology was not found to predict who would and who would not develop symptoms (20). Serum bilirubin level is a very reliable indicator of final outcome (33). The Mayo risk score is a more precise but also more complicated way to calculate this outcome than serum bilirubin levels. However, not all hyperbilirubinemia in patients with PBC is due to hepatic dysfunction. Particularly in patients whose albumin and international normalized ratio (INR) are normal, an elevated bilirubin level suggests that the patient may have Gilbert's syndrome. Fractionation of the bilirubin may also be useful to identify patients who have hemolysis, which is rarely associated with PBC (34). Other causes of hyperbilirubinemia excluding natural progression of disease include sepsis, thyrotoxicosis, common bile duct stones, drug toxicity, etc, all of which need to be considered in a patient with PBC who has a sudden change in their serum bilirubin level.

Serum bilirubin level and/or Mayo risk score have been found to be particularly useful in determining when the patient requires referral for liver transplantation. Post-transplantation outcome correlates well with the level of serum bilirubin; optimal post-transplantation survival requires the bilirubin level to be less than 180 μmol/L at the time of transplantation (35). Although treatment with ursodeoxycholic acid (UDCA) reduces the serum bilirubin level, it does not alter the validity of bilirubin level or the Mayo risk score in assessing prognosis (36).

MANAGEMENT OF PATIENTS WITH PBC

The management of patients with PBC is best covered under three headings: symptomatic management, preventive management and therapeutic management.

Symptomatic management: The most predominant symp-

tom in patients with PBC is fatigue. This symptom should not be ignored, rather the patient and their family should be counseled on the best way to manage this disabling complaint. Antidepressants are helpful in some. Amitryptylene to facilitate sleep may help others. An empathetic ear is always helpful, and it may be necessary to help the patient to reorganize their daily activities. Regular exercise is beneficial, and careful attention to sleep hygiene is important.

Pruritus: Itching of the skin in PBC is generally worse at night, worse in the winter and generalized. The severity of pruritus can range from mild to life-threatening. This symptom seems often to be ignored by physicians until the skin becomes thickened, pigmented and scarred. Most patients are helped by the oral anion exchange resin cholestyramine, which is best taken before and after breakfast in those with a gallbladder, thus facilitating maximal binding of bile. This resin appears to remove the pruritigen, the nature of which remains unknown. Cholestyramine is hence ineffective in patients with complete biliary obstruction (37). Because cholestyramine very effectively binds drugs such as thyroxin, digoxin and the oral contraceptive pill as well as UDCA, all patients should be advised to leave at least 4 h between taking cholestyramine and taking any other medication. Unfortunately, gastrointestinal disturbance is not uncommon in those using cholestyramine, and some patients find the side effects intolerable. In this situation, and when the drug is ineffective, rifampin 150 mg bid may be an extremely effective antipruritogenic agent (38). Rifampin occasionally gives rise to renal tubular problems. If both of these therapies fail, the third line of treatment is ultraviolet light therapy, in the absence of sunblock, either 'down south' or in the dermatology clinic. It has become clear from several small studies that opioid antagonists given to patients with pruritus secondary to cholestasis are extremely effective in eliminating this symptom (39,40). However, the best dose to use is difficult to ascertain, and treatment is usually associated with the symptoms of narcotic withdrawal, the worst being total inability to sleep. Naltrexone is the only drug that has been tried in a randomized control trial and was shown to be of benefit over the short term (one month). Antihistamines are not helpful for pruritus secondary to cholestasis, but they may facilitate sleep.

Xanthelasma: Many patients request surgical removal of these sometimes unsightly plaques around the eyes, but unfortunately the beneficial effect of their removal is short lived because the plaques generally return within one year. No therapy appears to be beneficial, and xanthelasma disappear as the disease progresses. Severe involvement of the palms of the hands and peripheral nerves, resulting in a painful xanthomatous neuropathy, may be acutely relieved by plasmaphoresis.

Sicca syndrome: It is important to ask patients directly about xerostomia and xerophthalmia because these symptoms are not always volunteered but are frequently present. Use of artificial tears to prevent corneal ulceration is important, and the importance of regular dental hygiene, using antireflux measures and taking pills with plenty of fluid while upright needs to be explained to patients with a dry mouth. Some patients also have a dry vagina, and the use of lubricants is advised.

Raynaud's syndrome: Avoidance of the usual precipitants is important, and sometimes calcium channel blockers may be beneficial, though if the patient has esophageal scleroderma this problem may be worsened by the use of these drugs.

Preventive management – *Portal hypertension:* Examination of the esophagus for varices is necessary at diagnosis because portal hypertension is often present even in patients with early, noncirrhotic disease. If a patient is found to have grade II or larger varices, prophylaxis against hemorrhage with the use of selective beta-blockers plus or minus long acting nitrates is advisable (41). If no varices are seen, repeat endoscopy every three years is probably appropriate.

Osteoporosis: Silently progressing osteoporosis is common in patients with PBC, particularly in women who are postmenopausal, though it is often present in premenopausal patients. Hence, all patients with PBC are advised to take 1500 mg of calcium daily and 1000 U of vitamin D daily. It is probably safe for postmenopausal women to use transdermal hormone replacement therapy (42). In those who are found to be osteoporotic, specific therapy for osteoporosis with biophosphonates has been shown to be beneficial in patients with PBC (43).

Other preventive measures: Because 25% of PBC patients develop hypothyroidism, regular checks of the serum thyroid-stimulating hormone are advisable, particularly in patients with overwhelming fatigue. Screening for hepatocellular carcinoma via ultrasound in those with cirrhosis may be advisable.

Therapeutic management – *Immunosuppressive therapy:* No immunosuppressive therapy has been shown in large randomized control trials to improve the survival of patients with PBC. In addition, a high rate of side effects has been described with some therapies, eg, cyclosporine (44), chlorambucil (45) and prednisolone (46). The lack of value of immunosuppressive agents in the treatment of PBC is somewhat surprising in view of its presumed etiology, and one can only assume that immunosuppressive therapy may be of benefit if given at the start of the disease or in a more targeted fashion. The results of a large American study employing methotrexate are eagerly awaited.

Antifibrotics: There have been three small trials of colchicine therapy in PBC, all of which have shown that treatment is associated with an improvement in liver function (INR and serum albumin), but no study has been large enough to show an effect on survival (47-49). This drug has been tried in combination with UDCA and has not been shown to be particularly beneficial.

UDCA: There have been many randomized control trials employing the hydrophilic bile acid UDCA. All studies have shown that UDCA leads to a marked improvement in the serum markers of cholestasis in patients with PBC. Few studies have suggested that this therapy relieves the symptoms of PBC, and individual studies are not of sufficient size to have the power to show an effect on survival. A combined analysis

of three large, randomized control trials of UDCA has shown that patients randomly assigned to UDCA and receiving treatment for up to four years had a significantly improved survival over those randomly assigned to placebo, even though more than half of those given placebo eventually received treatment with UDCA (50). It appears that a dose of 13 to 15 mg/ kg/day is optimal, 10 mg/ kg/day is too little and 20 mg/kg/day has no additional advantage. Treatment may be given as a single daily dose or in divided doses, making sure to avoid its binding to cholestyramine. Side effects are minimal; patients whose liver biochemistries return entirely to normal with treatment do better than those who have a partial response (51).

However, UDCA only delays the progression of disease, which some argue may cause a patient to be too old or too sick to receive a transplant should this become necessary (52). However, a recent follow-up of the Canadian multicentre trial shows that this is not the case (53).

Liver transplantation: Liver transplantation remains the ultimate cure for PBC. Although there is good evidence to suggest that the disease may return in the transplanted liver, recurrent disease is only slowly progressive and this possibility should not be a contraindication to liver transplantation. Several studies have now shown that the five- to seven-year outcome following liver transplantation affords a marked survival advantage over the predicted outcome using the Mayo risk score had the patient not received a liver transplant (54,55). Five-year survival rates range from 68% to 74%.

CONCLUSIONS

There is still a long way to go with regards to knowledge about the pathogenesis and treatment of PBC. In order to target therapy more appropriately, it is essential that the specific pathogenic processes involved in the development and progression of this disabling disease be understood.

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