Review Article

PRIMARY BILIARY CIRRHOSIS

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ABSTRACT

Primary Biliary Cirrhosis (PBC) is the result of long-standing damage to intra-hepatic biliary channels as a result of immune mechanisms leading to cholestasis and its associated complications. It can end up in chronic liver disease or cirrhosis. It usually manifests as pruritis that then proceeds to fatigue, jaundice and other features of chronic liver disease. It is detected by raised serological markers of cholestasis and presence of anti-mitochondrial antibody (AMA) in the blood. Some cases of AMA-negative PBC have also been reported though. Biopsy is diagnostic in such cases. Overlap syndromes also occur, in which case two autoimmune conditions co-exist in the same liver. These include autoimmune hepatitis (AIH) / PBC, AIH / Chronic Hepatitis C (CHC), AIH / Cryptogenic Chronic Hepatitis, and AIH / Primary Sclerosing Cholangitis (PSC) overlaps. Treatment of PBC is primarily with ursodeoxycholic acid, though steroids and steroid sparing drugs may be used in patients who show sub-clinical or no response to initial therapy with ursodeoxycholic acid.

Key Words: Primary, Biliary, Cirrhosis, cholestasis, anti-mitochondrial antibody, AMA-negative primary biliary cirrhosis, overlap syndromes.

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INTRODUCTION

Primary Biliary Cirrhosis (PBC) results from T-cell induced damage to intra-hepatic biliary channels leading to inflammation and cholestasis[1]. PBC was introduced by Addison et al in 1851[2]. It was named PBC by Ahrens et al in 1950[3]. Walker et al explained the correlation between AMA seropositivity and PBC[4].

The disease appears to be autoimmune in nature because of the observation of immunological symptoms and phenomena occurring in patients with PBC. It is this autoimmunity that leads to destruction of microscopic biliary channels[5]. The destruction is progressive and usually permanent. PBC is diagnosed by the presence of cholestatic blood picture, antimitochondrial antibodies (AMA), and specific liver biopsy findings[6,7,8]. The current article reviews epidemiology, pathophysiology, clinical features, diagnosis and management of PBC, and also explains the relatively new term of AMA-negative PBC. The article also reviews Overlap Syndromes which are the presence of two autoimmune liver conditions in a single liver.

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MATERIAL AND METHODS

Articles published over a span of 48 years extending from 1968 to 2016 were studied for writing the present review. Keywords comprising Primary Biliary Cirrhosis, Anti-mitochondrial antibody, cholestatic liver disease, AMA-negative primary biliary cirrhosis and Overlap Syndromes were used as search words on search engines including Google Scholar, PubMed, iMediSearch, MedConnect, Medicine, Medline, MDLinx and Medscape. Data gathered from these articles was reviewed and given the shape of current article.

EPIDEMIOLOGY

PBC has a female predominance (upto 80%) between 30th and 65th years of life[9,10]. 5-10% of the patients are men[10]. It has a prevalence of 65 per 100,000 and 12 per 100,000 in female and male populations respectively. The incidence is 5 per 100,000 for females and 1 per 100,000 for males[10].

PATHOPHYSIOLOGY

An array of multiple factors comes into play considering the pathophysiology of PBC.

1. **Genetic Factors:**

PBC is prevalent in immediate relatives of patients

with PBC thereby implying that it may be inheritable[11]. Among all the autoimmune diseases, it has the maximum reported concordance rate (62.5%) in monozygotic twins[12].

2. **Environmental Factors:**

   Viruses, bacteria (Novosphingobium aromaticivorans, Chlamydophila pneumoniae; urinary tract infections (UTIs) from E.coli or Lactobacillus delbrrueckii), smoking, possible use of Hormone Replacement Therapy (HRT) and chemicals (hair dye) may induce molecular mimicry which results in production of antibodies and clinical progression of PBC[13,14,15].

3. **Immunologic Factors:**

   Though the exact mechanism is unknown, but it is postulated that unstable lymphocytic DNA may also be responsible for the causation of PBC[16].

4. **Biliary Factors:**

   Changes in the formulation of bile acid and bile fluid in PBC patients suggest that transporter proteins may be involved in the development of PBC[17]. It is believed that biliary epithelium is protected by bicarbonate rich bile[18].

ASSOCIATIONS OF PBC

Being an autoimmune condition, PBC has been found to be related to a myriad of other autoimmune diseases[19]. These include: Dry gland 'sicca' syndrome, Sjogren's syndrome, Rheumatoid arthritis (RA), Autoimmune thyroid disease, Renal tubular acidosis (RTA), Mixed connective tissue disease (MCTD), Polymyositis, Polymyalgia Rheumatica (PMR), Pulmonary fibrosis, CREST (calcinosis, Raynaud's syndrome, esophageal dysmotility, sclerodactyly, telangiectasias) syndrome, Systemic lupus erythematosus (SLE), Pernicious anemia, Ulcerative colitis (UC), Exogenous pancreatic insufficiency, and Myasthenia gravis (MG)[20,21,22,23,24].

CLINICAL FEATURES

PBC initially presents with fatigue, and this may be the only complaint of the patient for quite a long time before the other symptoms set in[25]. Patients may also complain of pruritis. Jaundice is usually evident later. Other complaints include right hypochondrium pain from hepatomegaly, splenomegaly, and steatorrhea due to fat malabsorption. Excoriations may be visible on skin from continuous itching. Xanthelasmas, xanthomas and skin hyper-pigmentation also occur[26]. Low bone density, osteoporosis and fractures occur due to vitamin D malabsorption[27]. Patients may also develop features of decompensated liver disease manifested as ascites, bleeding from esophageal varices, and encephalopathy[25]. Xerophthalmia and xerostomia may be seen if other autoimmune conditions co-exist with PBC[28].

DIAGNOSTIC PRINCIPLES

PBC is suspected when both cholestasis and cirrhosis (which occurs over a course of years or decades) are present in middle-aged women[29]. Alkaline phosphatase, gamma glutamyl transferase and serum bilirubin are elevated[30]. Levels of immunoglobulin M and high density lipoprotein (HDL) are also raised[31]. Abdominal ultrasound scan needs to be done to rule out mechanical obstruction either intra-hepatic or extra-hepatic as the cause of cholestatic picture evident on biochemistry.

Anti-mitochondrial antibodies (AMA) are present in 95% of the patients with PBC. They are formed against the E2 subunit of pyruvate dehydrogenase (PDH-E2) which in itself is a member of the inner mitochondrial membrane-expressed oxoacid dehydrogenase complex[32]. PBC-specific AMA can be detected by immunofluorescence testing, ELISA and Western Blot Analyses; this excludes drug-induced and infectious causes of AMA-positivity[33,34,35,36]. Antinuclear autoantibodies (ANA) are commonly present in PBC patients in nuclear rim or nuclear dot pattern[37].

ANTI-MITOCHONDRIAL ANTIBODIES (AMA) NEGATIVE PBC

A small sub-set of patients with PBC is AMA-negative[38,39,40]. These patients share similar clinical, biochemical, and histologic features of PBC with those who are AMA-positive[41]. This AMA-negative PBC is also known as Autoimmune cholangitis (AIC)[15]. In these patients, a biopsy is indicated for confirmation of PBC; in the presence of AMA, biopsy is done to stage cirrhosis and is usually not mandatory for diagnosis[29,32]. Prior to the introduction of the sensitive ELISA testing and immunoblotting, 10-15% of patients with PBC were AMA-negative; at present only 5-10% are AMA-negative[41,42].

There is some debate as to whether autoimmune cholangitis (AIC), AMA-negative PBC, and classic PBC are one and the same thing. AIC cannot be incorporated into a single diagnostic category. It may represent variant shapes of different autoimmune liver diseases, an evolution stage between two autoimmune disorders, or a separate entity with varying manifestations[43].

Lacerda MA and colleagues[44] reported 20 patients who had AMA negative PBC compared with 20 AMA-positive controls. There was no remarkable difference with respect to clinical features, and associated autoimmune phenomena at the time of diagnosis. The immunoglobulin levels and liver profile were also not

significantly different. Similar results were reported by Invernizzi P and colleagues[45] in 35 patients who had AMA-negative PBC compared with 180 patients who had classic PBC and later on by Galambos JT and colleagues[46], who compared 24 patients who were AMA-negative to 273 patients who were AMA-positive seen over a span of 2 decades. No major differences were observed with respect to gender, age, incidence of complications, and development of liver failure leading to death or referral for liver transplantation between the two populations.

Though serological markers other than AMA are similar for AMA negative and positive PBC, but ANA and anti-smooth muscle antibodies are present in higher proportions in AMA-negative PBC, as compared to classic PBC[44,45,46].

HISTOLOGIC STAGES OF PBC

Histologically, the features of PBC and AIC correspond to each other[43].

Stage I (Portal Stage): Presence of florid bile duct lesions comprising of a bile duct at the center of a dense lymphocytic infiltrate. In PBC, initially the inflammation does not extend beyond the portal tracts.

Stage II (Peri-portal Stage): Loss of normal bile ducts, development of bile duct reduplication, and extension of the inflammation into the hepatic parenchyma.

Stage III (Septal Stage): Bridging fibrosis of the portal triads and progressive loss of bile ducts.

Stage IV (Cirrhotic Stage): Frank cirrhosis and end-stage liver disease.

The liver is not uniformly involved in PBC, therefore taking biopsy is a tricky procedure[44,45,46].

DIAGNOSTIC CRITERIA FOR PBC[47]

1. Biochemical evidence of cholestasis
2. Detection of AMA
3. Biopsy-proven non-suppurative cholangitis and damage to small- or medium-sized bile ducts.

DIFFERENTIAL DIAGNOSES[48]

- Chronic biliary tract obstruction (stone, stricture)
- Carcinoma of bile duct
- Primary sclerosing cholangitis
- Sarcoidosis
- Cholestatic drug toxicity (chlorpromazine)
- Chronic hepatitis.

THERAPEUTIC PRINCIPLES

1. URSODEOXYCHOLIC ACID (UDCA):

This is the only medical treatment approved by FDA for PBC[49]. The therapeutic dose in PBC is 15mg/kg body weight per day. It brings about an improvement in liver and immunological profile, histology and also improves chances of survival, but no effect has been seen on fatigue and osteoporosis[50,51]. It is an immunomodulator, that alters cell signal transduction and also modifies biliary hydrophilicity[52,53,54]. The drug is very effective in stages I and II of PBC, in which the survival is similar to that of healthy controls[55]. It is not indicated in severe cholestasis and first trimester of pregnancy[55]. Weight gain and loose stools are the reported side effects[56]. Currently it has no therapeutic alternative[49].

IMMUNOSUPPRESSION IN PBC

Immunosuppression has generally been disappointing in treatment of PBC[57].

1. CORTICOSTEROIDS:

Treatment with steroids can improve liver biochemistry, and raised immunoglobulin levels. No significant improvement of bilirubin, pruritis or histology has been noticed with corticosteroid therapy. Budesonide may cause improvement in liver histopathology but leads to worsening of bone density[58,59].

2. AZATHIOPRINE:

It has not been proven to be as effective in PBC, as in autoimmune hepatitis[59].

3. CYCLOSPORIN A:

Cyclosporin is a classic transplant immunosuppressant. In a study carried out in 346 patients, it did not show any significant effects on histopathological progression[59].

4. D-PENICILLAMINE:

Because copper accumulates in biliary channels in PBC, d-penicillamine can be given on a trial basis as a copper chelator. It is an immunosuppressive and anti-fibrotic drug[60].

5. COLCHICINE:

It has anti-inflammatory and anti-fibrotic properties. Though improvement occurs in liver biochemical and synthetic functions, a remarkable difference in clinical features and histopathology has not been observed with colchicine[61].

6. METHOTREXATE:

In a dose of 15mg/week it leads to improvement of biochemical parameters except bilirubin[62,63].

OTHER DRUGS UNDER TRIAL

Mycophenolate mofetil, tacrolimus and monoclonal antibodies against interleukin-2 receptor are also being investigated as possible alternative therapies for refractory cases of PBC[64,65].

THERAPY IN NON-RESPONDERS

Non-responders may be treated with a combination of ursodeoxycholic acid with steroids, sulindac, colchicine or methotrexate[66].

SYMPTOMATIC TREATMENT OF COMPLICATIONS[67]

1. Pruritis can be managed with cholestyramine, rifampicin, opioid antagonists, and serotonin antagonists. Resistant cases may be treated with plasmapheresis.
2. Ascites can be treated conservatively with diuretics, and beta blockers to control portal HTN.
3. Osteoporosis can be managed with vitamin D and calcium supplementation, and bisphosphonates.
4. Bleeding esophageal varices require endoscopic intervention in the form of band ligation or scleotherapy.
5. Fat-soluble vitamin supplementation is necessary to cover up for deficiencies of fat soluble vitamins. Deficiencies are aggravated when cholestyramine is administered.
6. Modafinil is given for daytime somnolence associated with PBC.

LIVER TRANSPLANTATION

This is the definitive treatment for PBC-induced liver failure. Fatigue may not be reversed by liver transplantation[68]. Ten-year survival rates after liver transplantation are 75-80% and recurrence of PBC occurs in 10-40% of the patients after transplantation.

RISK OF HEPATOCELLULAR CARCINOMA

PBC is associated with a risk of hepatocellular carcinoma. Risk factors include: Older age, male sex, prior blood transfusions, advanced histologic stage, signs of cirrhosis and portal hypertension[68].

PROGNOSIS

The Mayo Risk Score is widely used to predict survival in patients with PBC[69]. It takes into account age of the patient, total bilirubin, prothrombin time (PT), and presence or absence of edema[69]. Since most of the features of AMA-negative PBC are similar to those of classic PBC, the Mayo Risk Score can also be used in patients with AMA-negative PBC.

OVERLAP SYNDROMES

This term has recently been coined; it is used when two autoimmune pathologies co-exist in the same liver[69,70]. Overlap is seen between Autoimmune Hepatitis (AIH) / PBC, AIH / Chronic Hepatitis C, AIH / Cryptogenic Chronic Hepatitis, and AIH / Primary Sclerosing Cholangitis.

CONCLUSION

Primary Biliary Cirrhosis (PBC) is an important clinical entity. If AMA is negative by immunofluorescence, it needs to be repeated by ELISA or immunoblotting. If negative by any of these modalities as well, only then can it be labelled as AMA-negative PBC. Overlap syndromes need to be considered in patients diagnosed with PBC. In such cases steroids need to be added in the very start for the treatment of autoimmune hepatitis which is usually one of the autoimmune conditions in the syndrome.

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