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PRIMARY BILIARY CHOLANGITIS

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Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is an organ-specific autoimmune disease predominantly affecting middle-aged women. It does not occur in children. PBC prevalence varies depending on the geographic location of the country. Over the past 30 years, there has been an increased incidence of PBC, while significant progress has been made in understanding the pathogenesis of PBC due to the development of innovative technologies in molecular biology, immunology and genetics. The presence of antimitochondrial antibodies and cholestasis on biochemical analysis is sufficient to make a diagnosis, without the need for liver biopsy. Small- and medium-sized bile ducts are the targets of PBC. In the first stage of the disease, granulomatous destruction of the bile ducts occurs; in the second stage, loss of bile ducts, their proliferation, increased size of the portal tracts with chronic inflammation; in the third stage – fibrosis with septal formation, loss of bile ducts and cholestasis; in the fourth stage – liver cirrhosis. Previously, the survival rate of PBC patients ranged from 7.5 to 16 years. However, it has improved significantly with ursodeoxycholic acid and obeticholic acid treatment. If there is no effect from treatment and end-stage liver failure sets in, liver transplantation is performed.

Keywords: primary biliary cholangitis, PBC, pathogenesis, risk factors, ursodeoxycholic acid, obeticholic acid.

INTRODUCTION

Primary biliary cholangitis (PBC), previously known as primary biliary cirrhosis, still remains a recurring issue among hepatologists, transplantologists and physicians of other specialties. Over the past 30 years, significant progress has been made in the study of the epidemiology and pathogenesis of PBC, as well as its diagnosis. Administration of ursodeoxycholic acid (UDCA) in patients with PBC has become a revolutionary milestone in the treatment of this condition, slowing its progression to cirrhosis and end-stage liver failure, as well as reducing the need for liver transplantation. The purpose of this paper is to review the literature on the evolution of ideas about PBC.

BRIEF INFORMATION ON THE EMERGENCE OF THE TERM "PRIMARY BILIARY CHOLANGITIS"

Progressive liver disease with histological signs of cirrhosis, starting from the first description in 1949 [1] and up to 2015, received the stable name "primary biliary cirrhosis", adopted by all hepatologists and gastroenterologists of the world. However, in 2014 and 2015, the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) approved a name change from "primary biliary cirrhosis" to "primary biliary cholangitis" [2]. In 2014, 18 experts in Japan agreed to revise the nomenclature of primary biliary cirrhosis, but there was no unanimous agreement. Seven experts felt that "biliary" and "cholangitis" sounded redundant, and that "cholangitis" does not accurately reflect the pathological changes in the liver of patients with primary biliary cirrhosis. The experts concluded that an alternative nomenclature for primary biliary cholangitis should be created in the future, a name that would more accurately reflect the nature of the disease [3].

The change in the name from primary biliary cirrhosis to primary biliary cholangitis was justified by the following facts: introduction of antimitochondrial antibodies as a tool allowed physicians to diagnose primary biliary cirrhosis at earlier stages before the development of liver cirrhosis; widespread use of UDCA as a first-line drug suppressed progression of the liver disease to a cirrhotic stage among a significant part of patients [4]; in Japan, about 70–80% of patients are asymptomatic [3]. One of the arguments for the name change was that in the English transcription, the abbreviation of both names is the same – PBC. S. Shimoda and A. Tanaka (2016) [5] in accordance with the general agreement called on all members of the Japanese society of hepatologists to use the name "primary biliary cholangitis" for the disease known by the abbreviation PBC.

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EPIDEMIOLOGY OF PRIMARY BILIARY CHOLANGITIS

PBC is an organ-specific autoimmune disease [6] with chronic inflammation and cholestasis [7–11]. The disease progresses to biliary cirrhosis at different rates [12]. Without treatment, the median survival time for patients with PBC is 7.5 years in symptomatic and 16 years in asymptomatic patients [13].

The disease is predominant in women [6, 10–12, 14] over 40 years old, with an incidence of 1 per 1000 [9]. In the United Kingdom, North America and Sweden, the ratio of women to men is approximately 10:1 [15], while in China it is 6.1:1 [16]. According to T. Kogiso et al. (2017) [10], female individuals compose 90% of PBC cases. Unlike other autoimmune liver diseases, PBC does not occur in children [17].

The epidemiology of PBC has been particularly intensively studied over the past 30 years. Most studies have noted a significant increase in the incidence and prevalence of this disease. M.I. Prince and O.F. James (2003) [18] cite numerous possible factors causing the increase in the incidence of PBC. They believe that this may be due to increased exposure to a currently unknown environmental etiological agent, or demographic changes with an increased elderly, at-risk population. Prevalence may have further increased due to increased survival of patients, either due to improved care or earlier diagnosis. In addition, clinicians may have also become more able to recognize PBC based on clinical presentation. The authors conclude that whatever the cause of PBC, the recognized epidemiology of PBC has dramatically changed over the past 30 years. Geographic differences in PBC incidence strongly suggest the presence of as yet unidentified risk factors [18].

In the United States, PBC is relatively rare, up to 39.2 persons per 100,000 population [19]. In the Asia-Pacific region, the overall prevalence of PBC is on average 118.75 (49.96–187.55 range) and the incidence is 8.55 (8.05–9.06 range) persons per million population per year. Prevalence is highest in Japan and China (191.18 per million population), medium in New Zealand (99.16 per million population) and low in South Korea and Australia (39.09 per million population). The 5-year accumulative incidence of decompensation, hepatocellular carcinoma and death/liver transplantation in PBC patients was 6.95% (2.07–11.83%), 1.54% (0.9–2.19%), and 4.02% (2.49–5.54%), respectively [20].

ETIOLOGY AND PATHOGENESIS

The etiology of PBC is poorly understood. Cigarette smoking, nail polish, urinary tract infections and low socioeconomic status have previously been considered as etiological factors, but none of them have been confirmed [21].

The liver is the most important organ controlling immune tolerance. Despite its exceptional ability to induce tolerance, the liver remains a target organ for autoimmune diseases, including PBC [22].

The discovery of mitochondrial autoantigens recognized by antimitochondrial antibodies in 1987 marked the beginning of a new era in PBC research. Since then, significant progress has been achieved in understanding this disease, due in part to the development of innovative technologies in molecular biology, immunology and genetics [23, 24].

PBC is a disease of immune dysregulation, including loss of tolerance to mitochondrial antigens [7]. In 95% of patients, a whole family of antibodies to various mitochondrial antigens is present in the blood serum [25]. The serologic hallmark of PBC is the presence of antibodies to mitochondria, especially to the E2 component of the pyruvate dehydrogenase complex [9].

The mechanisms by which anti-mitochondrial antibodies produce liver tissue injury are unknown. However, the presence of these antibodies has allowed detailed immunological definition of the antigenic epitopes, the nature of reactive autoantibodies and the characterization of T-cell responses. Several mechanisms may now be proposed regarding the immune-mediated bile duct damage in PBC, including the possible role of T-cell-mediated cytotoxicity and intracellular interaction between the IgA class of antimitochondrial antibodies and mitochondrial autoantigens [17]. An imbalance of circulating regulatory and helper T cells may be involved in the pathogenesis of PBC [31].

It is assumed that the pathogenesis of PBC, having an autoimmune mechanism of origin, develops in genetically susceptible subjects. In addition, not only genetic, but also environmental factors are involved in the pathogenesis of PBC [7, 27]. Numerous studies have shown that environmental factors, hereditary genetic predisposition, and loss of tolerance are involved in PBC pathogenesis [28].

Genomic association studies have revealed a strong relationship between certain HLA alleles and PBC [21]. It has been previously shown that only HLA class II loci (HLA-DRB1 *08, *11 and *13) were associated with PBC. Many other loci, including IL12A, IL12RB2, STAT4, IRF5-TNPO3, 17q12.21, MMEL1, SPIB, and CTLA-4, were later found to be associated with the disease. Taken together, this confirms the important role of innate and adaptive immune systems in the development of PBC. Identifying the risk loci associated with the disease may contribute to the development of rational, specific therapies in the future [7].

The mechanism of bile duct damage by antimitochondrial antibodies is associated with an immune attack on aberrantly expressed molecules of the pyruvate dehydrogenase complex-E2 antigens and bile-duct epitheliocytes. Some microbial proteins, through molecular

mimicry, become like pyruvate dehydrogenase complex-E2. Therefore, the immune response can also be directed against certain bacteria in the bile duct wall with damage to their epithelial cells [29].

The multilinear immune response at various stages of PBC development includes the involvement of galectin-3 in the pathogenesis of this disease. Recently, its role in specific binding to NLRP3-inflammasomes and activation of the inflammatory process in PBC models has been described. Galectin-3 is a β-galactoside-binding lectin that plays an important role in a variety of biological processes, including cell proliferation, differentiation, transformation and apoptosis, pre-mRNA splicing, inflammation, fibrosis, and host defence. The NLRP3 inflammasome is a multimeric protein complex that initiates the inflammatory process upon activation [30].

DIAGNOSIS

Anti-mitochondrial M2 antibodies and specific antinuclear antibodies (gp210 and Sp100) are typical and specific for PBC. The presence of these antibodies and cholestasis in biochemical analysis are sufficient to make the diagnosis without a need for liver biopsy [6, 11].

According to Japanese national guidelines, PBC can be diagnosed if there are at least two of the following three signs: elevated cholestatic enzymes, presence of antimitochondrial autoantibodies, and presence of histological signs [6].

The disease is often detected based on abnormal increase in alkaline phosphatase activity, followed by confirmation in the presence of antimitochondrial antibodies [21]. The presence of antimitochondrial antibodies or antinuclear antibodies that are highly specific for PBC in combination with cholestasis is usually sufficient to confidently diagnose PBC [8].

The severity and activity of the disease at baseline and during treatment should be assessed to identify individuals with elevated bilirubin levels, platelet counts below 150, or biochemical disease activity during treatment. Liver ultrasound should be performed to detect overt cirrhosis and splenomegaly; transient elastography to detect increased liver stiffness [8].

The commonly accepted non-invasive measure of the degree of liver fibrosis is the Fib-4 formula, which includes age, aspartate aminotransferase level and platelet count. It has been tested and validated in a variety of liver diseases, including PBC [31]. The aspartate aminotransferase to platelet ratio index (APRI) reflects the presence or absence of progressive fibrosis or cirrhosis in PBC [32].

PATHOMORPHOLOGY

The targets in PBC are small and medium bile ducts [7, 33]. This is because of the fragility of biliary epithelial cells caused by apoptosis, aging, and autophagy [6]. The disease is characterized by chronic progressive destruction of small intrahepatic bile ducts [34, 35] with portal inflammation [11] and eventually fibrosis [17] and cirrhosis [6, 11].

The study of liver biopsies showed that the development of PBC occurs in four stages. At the first stage, there is granulomatous destruction of interlobular and septal bile ducts. At the second stage, there is bile duct loss, their proliferation, increased size of the portal tracts with chronic inflammation (infiltration by mononuclear cells). The third stage is characterized by septal fibrosis, bile duct loss and cholestasis. At the fourth stage features cirrhosis of the liver. This division into stages is conditional, since in different parts of the liver of the same patient, there may be histological changes characteristic of different stages of PBC [36].

According to T. Warnes et al. (2019) [37], liver biopsy is required in the diagnosis of around 20% of patients with PBC. The Ludwig PBC staging system (sinusoidal fibrosis, orcein deposition, bile duct loss, and cholestasis) is of more prognostic value than other staging systems (Ishak and Nakanuma), but the major histological parameter providing independent prognostic value is the presence or absence of sinusoidal fibrosis.

CLINICAL PICTURE

Most patients remain asymptomatic and are diagnosed when cholestasis and elevated alkaline phosphatase levels are detected incidentally [11]. Detection of the disease at a young age (less than 45 years) and male sex are predictors of a more severe course of PBC [8]. The recipient's APRI >2 is negatively associated with patient survival ($P = 0.0018$) [38, 39].

Clinical symptoms include pruritus (itchy skin), dry complexion, fatigue, abdominal discomfort, arthralgia, and bone pain [11]. The most common symptoms in PBC are fatigue and itching, occurring in 85% and 70% of patients, respectively [40, 41]. In patients with PBC, fatigue and itching occur regardless of the severity of the disease [42]. In the work of J.A. Talwalkar et al. (2003) [43], about 55% of patients had itching. Severe pruritus significantly reduces the quality of life of patients [44]. Scratching provides little or no relief, and intense scratching can cause severe skin damage [45]. Nearly three-quarters of patients reported that itching prevented them from sleeping, and 3.6% of patients itched to blood [46]. Cholestyramine is the only FDA-approved drug for the treatment of pruritus in people with PBC. However, it can cause gastrointestinal complications, which limits its clinical use [45].

When examining 97 women with PBC, M.K Prashnova et al. (2018) [47] revealed osteoporosis in 48.9% of patients, and osteopenia in 30.0%. According to the authors, age and duration of menopause were independent predictors of osteoporosis in PBC, and postmenopausal fractures were associated with low dietary protein.

Patients with PBC may have a combination with various other autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, but most often (in about 60% of patients) with Sjogren's syndrome [48]. There is no consensus on the effect of PBC with Sjogren's syndrome on patient survival. Some authors [49] report that the overall survival of patients with this combination is significantly lower than with PBC alone, while other authors [50] found no such differences.

In the same patient, PBC can be combined with autoimmune hepatitis at the same time. Both diseases have typical clinical manifestations and typical histological features. In PBC, the bile ducts are destroyed and sometimes granulomas form, while autoimmune hepatitis shows severe portal and lobular lymphoplasmacytic inflammation. Nevertheless, a careful analysis of clinical and histological criteria is required to make a diagnosis and prescribe appropriate therapy for both diseases. The first-line therapy for PBC is UDCA, and immunosuppression for autoimmune hepatitis. Both diseases can progress to liver cirrhosis [51]. Familial cross-over between autoimmune hepatitis and primary biliary cholangitis is rare [52]. The authors presented such observations in siblings. If a combination of PBC with autoimmune hepatitis is suspected, liver biopsy is necessary [8].

There are cases of PBC combined with autoimmune hepatitis and generalized sarcoidosis [53]. However, since granulomatous liver damage is observed in both PBC and sarcoidosis, it is necessary to carry out morphological differential diagnosis of these two diseases [54].

EXTRAHEPATIC MANIFESTATIONS OF PBC

Extrahepatic manifestations of PBC include lung damage with involvement of the parenchyma, vessels, pleura, and regional lymph nodes in the pathological process. In the lungs, fibrosis may develop, and the degree of respiratory failure depends on severity of the fibrosis. The most reliable diagnosis method is high-resolution CT scan [55]. The authors believe that due to the possibility of a prolonged asymptomatic course of the pulmonary process with the development of irreversible changes in patients with PBC, it is advisable to conduct screening to be able to timely detect and treat lung lesions.

TREATMENT

The survival rate of patients with PBC previously ranged from 7.5 to 16 years [13]. However, it has considerably improved after treatment with UDCA [56–58], which is the first-line therapy for PBC [59]. Its therapeutic effect is multifaceted: 1) it increases cholesterol saturation of bile, reduces bile viscosity and improves its outflow; 2) it has an anti-inflammatory effect, suppressing the expression of HLA class I antigens on hepatocytes and production of pro-inflammatory cytokines, regulating phagocytosis and peroxidation reactions; 3) activates hepatocyte antiapoptotic mechanisms; 4) influences lipid and glucose metabolism through interaction with nuclear farnesoid X receptors of the small intestine and liver; 5) influences the functional state of the intestine by providing a laxative effect, stimulating intestinal secretion and peristalsis [60].

The British Society of Gastroenterology recommends that oral UDCA at 13–15 mg/kg/day be used as first-line pharmacotherapy in all patients with PBC. If tolerated, treatment should usually be life-long. The use of UDCA in PBC delays histological progression of the disease and prolongs the survival of patients without liver transplantation. It is assumed that progression of the disease slows down due to reduction of cholestatic damage by acting on the target biliary epithelial cells [61]. Although treatment with UDCA shows good clinical results in most patients [62], there remain about 40% of patients with PBC who do not respond adequately to therapy, which is accompanied by a high risk of severe complications [61].

UDCA is a specific treatment with an excellent response in over 60% of patients. When there is no positive effect, treatment can be continued in combination with other drugs such as obeticholic acid (OCA) and fibrates [11]. OCA, a farnesoid X receptor (FXR) agonist, which has been evaluated as a second-line therapy for PBC, has been licensed by the U.S. Food and Drug Administration and the European Medicines Agency for use in patients who show inadequate response to UDCA or are unable to tolerate it [61].

Treatment with OCA in patients with PBC has shown promising results. For instance, initial clinical trials showed that the use of OCA (in addition to UDCA) in patients with PBC with an inadequate response to UDCA significantly reduced serum alkaline phosphatase [21]. A randomized, double-blind trial of the efficacy of OCA in the treatment of PBC showed that approximately 50% of patients also achieved significant reductions in serum alkaline phosphatase, a marker that predicts disease progression, the need for liver transplantation, or patient death [63]. Although there has been a biochemical improvement in treatment with OCA, there is no conclusive evidence that it reduces the severity of clinical outcomes or improves quality of life. In addition, OCA is not suitable for patients with pruritus, as it can worsen it [61]. This drug does not have sufficient therapeutic effect in all patients; approximately 50% of patients may require other therapies [64].

Therefore, there is an urgent need for more effective treatments for this problematic disease. Several other drugs are currently being investigated for therapy in patients with PBC who do not respond to UDCA treatment [21]. Other new drugs currently in clinical development may have fewer side effects. Fibrates have this potential, but there is presently no evidence to support their routine clinical use in PBC [61]. In Japan, bezafibrate is often used for this purpose, but clinical trials have

not been able to clearly demonstrate the effectiveness of this drug [5].

The current focus is on the study of the modulation of nuclear receptor pathways, which specifically and effectively improve bile secretion, reduce inflammation, and attenuate fibrosis. Pharmacological FXR agonists and receptors activated by peroxisome proliferators are effective. Immunotherapy remains challenging as drug targets and pleiotropic immune pathways have not been identified. Symptomatic treatment, particularly pruritus, is a significant goal achieved in the development of rational therapy with apical sodium-dependent bile acid transporter [12]. Cholestatic pruritus is treated with first-line drugs (bile acid sequestrants) or second-line drugs (rifampicin). However, these drugs are poorly tolerated by patients and have side effects [8]. Ademetionine is used to treat increased fatigue/weakness in liver disease, in particular PBC, as one of the most promising drugs, which has significant positive effect on the condition of patients [65]. The patient will require liver transplantation if cirrhosis develops.

CONCLUSION

Primary biliary cholangitis is an autoimmune disease that progresses to biliary cirrhosis at varying rates. Without treatment, the median survival for patients with PBC is 7.5 years in symptomatic patients and 16 years in asymptomatic patients. The disease predominantly affects women over 40 years of age. Currently, there has been a significant increase in PBC incidence and prevalence. Its etiology has not been adequately studied, but it has been established that antibodies to various mitochondrial antigens are formed. The autoimmune mechanism develops in genetically susceptible subjects when exposed to environmental factors. The targets in PBC are small and medium bile ducts with their progressive destruction and the development of cholestasis, leading to portal inflammation and eventually to cirrhosis. Most patients remain asymptomatic. Clinical symptoms include pruritus, dry complexion, fatigue, abdominal discomfort, arthralgia, and bone pain. Treatment is based on the use of UDCA, which is the first-line therapy and is effective in over 60% of patients. When there is no positive effect, treatment is continued in combination with other drugs, such as obeticholic acid and fibrates. Early diagnosis and timely treatment have reduced the number of patients requiring liver transplants. However, if primary biliary cholangitis progresses to an end-stage liver disease, liver transplantation remains the only treatment for such patients.

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