Clinical, Molecular, and Histopathological Aspect of Primary Biliary Cholangitis

Flora Dameria, Marini Stephanie**, Ria Kodariah***, Diah Rini Handjari**, Ening Krisnuhoni**, Nur Rahadiani***

*Department of Anatomical Pathology Residency Program, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

** Division of Gastroentero-hepatobilliary Pathology, Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

*** Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

Corresponding author:

Nur Rahadiani. Division of Gastroentero-hepatobilliary Pathology, Department of Anatomical Pathology, Dr. Cipto Mangunkusumo General National Hospital. Jl. Diponegoro No. 71 Jakarta Indonesia. Phone: +62-21-31930487; facsimile: +62-21-31934465. E-mail: nur.rahadiani@ui.ac.id

ABSTRACT

Primary biliary cholangitis (PBC), previously known as primary biliary cirrhosis, is an autoimmune liver disease which tends to be chronic and progressive in nature that is marked by the presence of cholangitis and small size biliary duct destruction which may cause cirrhosis or even liver failure. PBC incidence increases because PBC can now be diagnosed earlier and is due to the increasing survival rate of PBC patients. Diagnosis of PBC can be confirmed in asymptomatic state if in the indirect immunofluorescence (IIF) examination revealed antimitochondrial antibody (AMA) positive, and there is an abnormal liver function. Etiopathogenesis of PBC is multifactorial which involves genetic and environmental factors. Genetic factors which contribute to the incidence of PBC are human leukocyte antigen (HLA) and non-HLA genes, while in the environmental factors, the triggering factors of PBC are bacterial infection and xenobiotic. Interaction of these factors causes the development of E2 subunit pyruvate dehydrogenase complex (PDC-E2) and AMA as the causing autoantigen of biliary duct desctruction in PBC, mediated by the immune system. PBC stage is divided into minimal, mild, moderate and severe. Ursodeoxycholic acid (UDCA) is the first line therapy for PBC, while obeticholic acid (OCA) and fibrate is used as the second line. Liver transplantation is the definitive therapy for PBC where disease progresses into the advanced stage, although the patients have received medical treatment.

Keywords: *primary biliary cholangitis (PBC), pyruvate dehydrogenase complex (PDC-E2), antimitochondrial antibody (AMA), Ursodeoxycholic acid (UDCA)*

ABSTRAK

Primary biliary cholangitis (PBC) yang sebelumnya dikenal dengan primary biliary cirrhosis merupakan penyakit hati autoimun yang bersifat kronis dan progresif, ditandai dengan adanya cholangitis dan destruksi duktus bilier ukuran kecil yang dapat menyebabkan sirosis sampai dengan gagal hati. Insidensi PBC mengalami peningkatan disebabkan karena PBC sudah dapat didiagnosis lebih dini dan peningkatan angka bertahan hidup penderita PBC. Diagnosis PBC dapat ditegakkan pada status asimtomatik jika dalam pemeriksaan indirect immunofluorosence (IIF) didapatkan antimitochondrial antibody (AMA) positif dan terdapat fungsi hati yang abnormal. Etiopatogenesis PBC multikompleks yaitu faktor genetik dan faktor lingkungan. Faktor genetik yang berkontribusi terhadap

kejadian PBC yaitu gen human leukocyte antigen (HLA) dan non HLA, sedangkan faktor lingkungan yang sebagai pemicu terjadinya PBC yaitu infeksi bakteri dan xenobiotik. Interaksi faktor ini menyebabkan terbentuknya pyruvat dehydrogenase complex subunit E2 (PDC-E2) dan AMA sebagai autoantigen penyebab kerusakan duktus bilier pada PBC yang diperantarai oleh sistem imun. Stadium PBC dibagi menjadi minimal, ringan, sedang dan berat. Ursodeoxycholic acid (UDCA) merupakan terapi lini pertama untuk PBC sedangkan obeticholic acid (OCA) dan fibrat digunakan sebagai terapi lini kedua. Transplantasi hati merupakan terapi definitif pada PBC yang berkembang ke stadium lanjut walaupun sudah mendapatkan terapi medikamentosa.

Kata kunci: *primary biliary cholangitis (PBC), pyruvate dehydrogenase complex (PDC-E2), antimitochondrial antibody (AMA), ursodeoxycholic acid (UDCA)*

INTRODUCTION

Primary biliary cholangitis is a liver autoimmune disease which is chronic and progressive in characteristic, marked by the presence of cholangitis as well as small and medium biliary duct destruction which eventually causes cirrhosis or even liver failure.[1-2] The characteristics of this disease is the reactivity of specific antimitochondrial antibody (AMA) (> 90%), increase of alkaline phosphatase (ALP) with histopathological appearance of biliary duct destruction and lymphocytic chronic non-suppurative, granulomatous cholangitis.[3]

The incidence and prevalence of primary biliary cholangitis *(*PBC) increases as the capacity of earlier diagnosis and the survival rate of PBC patients increase, with yearly incidence and prevalence of 0.07-4.9 cases per 100,000 and 2.7-40 cases per 100,000, respectively. Primary biliary cholangitis is more common in females, with the ratio of female:male of 10:1 and in average occurs in the age of ± 50 years.[4] Based on the data in Anatomical Pathology Department Faculty of Medicine Universitas Indonesia/Cipto Mangunkusumo Hospital, there were only 3 cases diagnosed as PBC in the year 2007-2017.

The exact pathogenesis of PBC is still unclear. Genetic and environmental interaction become the aetiological factors of inflammation and destruction that leads to ductopenia. Genetic factors in PBC, which is the presence of change in X chromosome also related to human leucocyte antigen (HLA) and non HLA, while the environmental factor is supported by the molecular mimicry theory due to bacterial infection and xenobiotic compounds.[2,5] The pathological process in biliary duct is mediated by the adaptive immune response (humoral and cellular) and natural immune response which attack the biliary epithelial cells due to the loss of self-tolerance towards E2 subunit pyruvate dehydrogenase complex (PDC-E2) autoantigen.[5] The characteristics of biliary epithelial cells, apoptotic theory, and senescence in biliary epithelium are the reasons why biliary epithelial cells become the specific target in immune response although PDC-E2 is located in the mitochondria.[3] This literature review is aimed to discuss clinical, histopathological, and immune mechanism aspects in the pathogenesis of PBC.

Definition of Primary Biliary Cholangitis (PBC)

Primary biliary cholangitis is an autoimmune liver disease which is chronic and progressive, marked by the presence of cholangitis and small to medium biliary duct destruction (< 100 μm) and may progress into ductopenia, fibrosis, cirrhosis, and liver failure.[4] This disease is previously known as primary biliary cirrhosis. The changes in its nomenclature occur after a several of PBC patient were found to be not having cirrhosis. The presence of better screening and diagnostic tool enables the PBC diagnosis to be confirmed in early stage, while cirrhosis occur in advanced stage. [4,6]

Clinical Symptoms and Signs of Primary Biliary Cholangitis (PBC)

Primary biliary cholangitis comprises of four phases, which are preclinical/silent, asymptomatic, symptomatic, and pre-terminal or liver failure phase (figure 1). It is unnecessary for patient to follow all through available phases. Silent phase is characterized by positive AMA, but the liver function results are still normal. Patient who is diagnosed in the silent phase may survive up to 22 years without treatment, while in asymptomatic and symptomatic phase patient may survive in the range of 6-10 years. Asymptomatic phase is temporary and may develop into symptomatic phase after 4-18 years. Five percent of asymptomatic phase patients persist in this phase for 20 years. Cirrhosis is estimated to happen after 10 years in patients with asymptomatic PBC.[4]

PBC patient is frequently diagnosed in asymptomatic state (50-60%), which is a condition in which liver

function is abnormal but no clinical symptoms was observed. In Western countries and Japan, approximately 85% of PBC patients can be diagnosed in asymptomatic phase, while in other Asian countries only 20-74% patients can be identified in this phase.[9] Fatigue and pruritus are the most common symptoms in PBC. Other clinical symptoms are skin hyperpigmentation, xanthelasma, hyperlipidemia, osteoporosis, and fat-soluble vitamin deficiency.[1,4]

In terminal stage, splenomegaly and liver cirrhosis are found. Splenomegaly usually signifies the presence of portal hypertension. Portal hypertension gives poor prognosis in PBC. Signs of liver cirrhosis include ascites, jaundice, hepatic encephalopathy, and upper gastrointestinal tract bleeding. PBC patient with cirrhosis is at risk to suffer from hepatocellular carcinoma.[4]

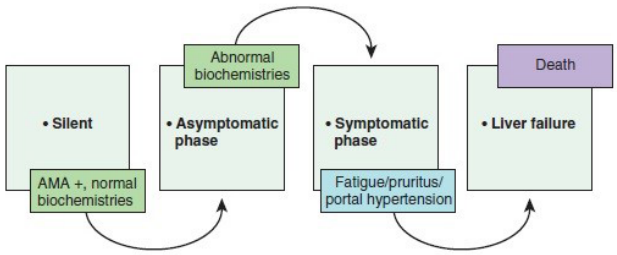

Figure 1. Clinical phase of primary biliary cholangitis (PBC)[4]

Diagnosis of Primary Biliary Cholangitis (PBC)

Diagnosis of PBC is confirmed by AMA examination using indirect immunofluorescence method with AMA titre ≥ 1:40 or AMA level > 0.1 unit, and the increase of alkaline phosphatase (ALP) > 1.5x normal for six consecutive months, and the increase of gamma glutamyltransferase (GGT).[4]

In PBC, the increase of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) may also happen, but less than 3x normal limit (< 300IU/L). ALP and bilirubin values are still in normal limit in early stage of PBC. The significant increase of ALP characterizes the severity of ductopenia and inflammation, while the gradual increase of bilirubin (< 20 mg/dL) follows the progressivity of the disease.[1,4]

Liver biopsy is required in several conditions, like in patient who has clinical symptoms of PBC with negative AMA. It also needed in patient with positive AMA, but the increase of ALP is < 1.5x normal limit and/or AST and ALT increases ≥ 5x normal limit with the significant increase of Immunoglobulin G (IgG). In addition to diagnosis purposes, liver biopsy is used to provide stage information as an evaluation of disease progressivity and response to therapy.[1,2,4]

Based on the activity of necroinflammation and histopathology variation, Nakanuma et al divide the PBC stages into minimal, mild, moderate, and severe. Necroinflammation activity refers to the area of cholangitis and hepatitis (interface hepatitis and lobular inflammation). Variation of histopathology comprises of three components, which are fibrosis, ductopenia, and copper precipitate (sign of chronic cholestasis) appearance.[7] Classification of PBC stage according to Scheuer and Nakanuma is summarized in table 1.[8]

Table 1. Histopathological staging system of primary biliary cholangitis (PBC)[8]

Stage	Scheuer	Nakanuma
Stage I	Florid duct lesions, biliary duct destruction, inflammation of the portal	No or minimal progression (fibrosis, ductopenia, copper binding protein = 0)
Stage 2	Duct proliferation, widening of the portal, interface hepatitis	Mild progression (fibrosis, ductopenia, copper binding protein = 1-3)
Stage 3	Scarring, ductopenia	Moderate progression (fibrosis, ductopenia, copper binding protein = 4-6)
Stage 4	Cirrhosis	Advanced progression (fibrosis, ductopenia, copper binding protein = 7-9)

Based on the development of lesion in the portal tract, Scheuer classified PBC into 4 stages (figure 2). In stage 1, there are florid duct lesions, biliary duct destruction, inflammation of the portal. Stage 2 is characterized by duct proliferation. Stage 3 is characterized by the presence of portal fibrosis and ductopenia and in stage 4, cirrhosis has occurred.[8]

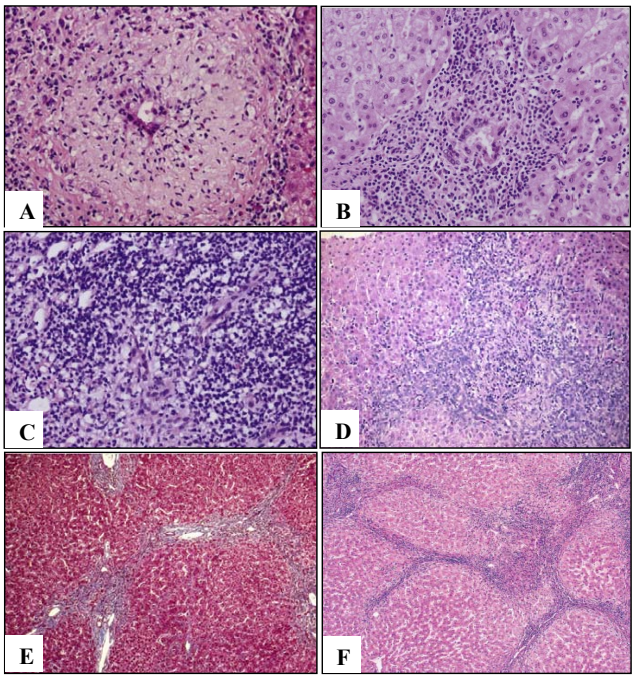

Figure 2. PBC stage according to Scheuer. A. Florid duct lesions. B and C. Biliary duct destruction and portal inflammation. D. Ductular proliferation (HE, 100x). E. Portal fibrosis and ductopenia (Masson trichome, 40x). F. Cirrhosis.[4,8]

Variation of Primary Biliary Cholangitis (PBC)

Primary biliary cholangitis (PBC) with negative antimitochondrial antibody (AMA)

The prevalence of this variation of PBC is 5-10% of total patients with PBC. The characteristics of this variant is that it has clinical and histopathology appearance of PBC but negative AMA, and tends to have positive antinuclear antibodies (ANA). This variant PBC slightly differ from positive AMA PBC in terms of clinical progression and response to therapy.[4,9]

Positive antimitochondrial antibody (AMA) primary biliary cholangitis (PBC) with no clinical symptom

The prevalence of this variation of PBC is 0.5%. It has several with characteristics like the absence of PBC symptoms, normal ALP with liver function, and positive AMA. This variant PBC can develop into symptomatic phase in 4-18 years time (36-89%), thus it is recommended that patient with this variant to undergo annual follow-up.[4]

Primary biliary cholangitis-autoimmune hepatitis (PBC-AIH) overlap syndrome

Overlap syndrome happens if there is PBC and AIH characteristics concurrently. The prevalence of this variant of PBC is 10%. This variant of PBC has higher risk towards fibrosis, portal hypertension, thus it has high possibility to be needing a liver transplantation. Therapy of this variant of PBC is the combination of UDCA and immunosuppressant with the aim to slow the progressivity of fibrosis. To diagnose this variant of PBC, clinical accuracy from hepatologist and information accuracy from pathologist are needed.[6]

Autoantibody and Autoantigen in Primary Biliary Cholangitis (PBC)

Serology marker of PBC is AMA. This marker can be detected in > 95% PBC patients and even can be detected before the presence of clinical symptoms and liver function abnormalities. AMA can be detected through indirect immunofluorescence (IIF), immunoblotting and enzyme linked immunosorbent assay (ELISA).[10] Antimitochondrial antibody recognizes oxoacid dehydrogenase complex subunits (2-OADC) inside the mitochondria which comprises of pyruvate dehydrogenase complex (PDC), 2-oxoglutarate dehydrogenase complex (OGDC), branch chain 2-oxoacid dehydrogenase complex (BCOADC).[5,10] In PBC patients, 30-50% of other specific autoantibodies which is antinuclear antibody (ANA) can be detected.[1,5] More than 99% ANA is detected in PBC patients with negative AMA, thus ANA can be used as diagnostic tool in PBC patient with negative AMA.[2] ANA

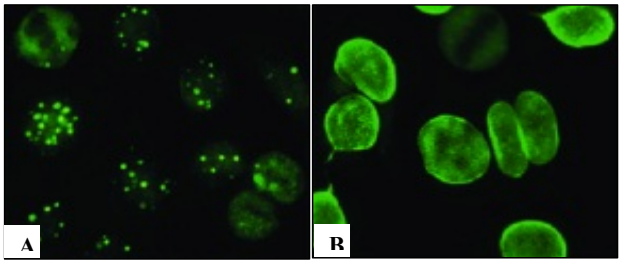

Figure 3. ANA appearance in PBC. A. Multiple nuclear dots pattern. B. Nuclear rim pattern[11]

examination with IIF method give a nuclear rim and multiple nuclear dots pattern appearance (figure 3).[1,5,7]

Pathogenesis

The aetiopathogenesis of PBC is the interaction between genetic and environmental factors which eventually causes immune reaction towards biliary epithelial cells, involving the natural and acquired immune response towards an autoantigen.[1,5]

Genetic Factors

There are several evidences that genetic factors have a strong role in the etiopathogenesis of PBC. Six percent of PBC patient has a first line family hereditary of PBC or other autoimmune disease.[1,2,4,12] PBC is more dominant to happen in female, which is predicted to be caused by the changes in X chromosome.[13]

According to genome-wide association studies (GWAS), human leukocyte antigen (HLA) gene class II such as HLA-DRB1, HLA-DQA1 and HLA-DQB1 has a strong relation to individual susceptibility to PBC.[5,13,14] Possessing non-HLA gene may also contribute to the pathogenesis of PBC in 80-90% of PBC patient with no HLA gene associated with susceptibility to PBC. These genes include IRF5, SOCS1, TNFAIP3, which function as antigen presentation; TNFSF15, IL12R, TYK2, STAT4, which function to activate T cell and IFN production; and ARID3A which function on B cell activation and immunoglobulin production.[14]

Environmental Factors

Bacterial infection and xenobiotic are environmental factors that can cause the diminished ability of tolerance toward autoantigen, hence produce AMA.[2,3] In several studies, consistently stated that there is an association between PBC and bacterial infection, which can be caused by *Escherichia coli*, *Chlamydia*

pneumoniae, Lactobacillus delbrueckii, Helicobacter pylori, Novosphingobium aromaticivorans. Human PDC-E2 molecule mimics the PDC-E2 of the before mentioned microorganisms, located in ExDK sequence which is important in the recognition of CD4+ T cells. Therefore, infection of those microorganisms can trigger the destruction of immune tolerance towards PDC-E2 through molecular mimicry and cross reaction.[2,3,4,5,15]

Xenobiotic is also involved in the etiopathogenesis of PBC.[10] Several pharmaceutical and household compounds like detergent can potentially be harm, especially those which have molecular similarity to PDC-E2. 2-octynamide compound, a derivation form of 2-Octynoic acid, can modify PDC-E2 in lipoyl domain. This compound is widely used for perfumes, beauty products particularly lipstick and nail polish, and also in artificial flavour for food and bubble gum.[2,4,5,12,15,16]

Biliary epithelial cells

The target of PBC destruction is very specific, i.e. the destruction in biliary epithelial cells. Several factors such as molecular expression, mucosal immunity, and contribution in bile acid transportation and apoptosis characteristics, senescence, and autophagy in biliary epithelial cell are known to be involved in the development process of PBC.[5]

Molecular expression

Biliary epithelial cell may play role as APC, expressing adhesion and accessories molecules. Adhesion molecules function to adhere and recognise lymphocyte, which include ICAM-1, VCAM-1, LFA-1 and E-selectin.[3] Biliary epithelial cell expresses accessory molecules as co-stimulator signal to T cell which are CD 80, CD 86 (B7-1, B7-2). Additionally, biliary epithelial cell also express MHC class I and II, TNFα, IFN-γ and IL-1, IL-4, IL-6, and MCP-1, which secretion occur due to stimulation from proinflammation cytokines.[4,5]

Mucosal immunity

The role of mucosal immunity in PBC is shown by the biliary epithelial cells which transfer IgA actively through epithelial mucosa. Immunoglobulin A (subtype AMA) recognizes PDC-E2 which can be found in serum, saliva, urine and bile. This has been proven by the detection of IgA and PDC-E2 deposit in the apical surface and cytoplasm of biliary epithelial cells.[2,5]

Bile Acid Transportation

Biliary epithelial cell has anion exchanger 2/AE2 (SLC4A2) regulation which plays role in the defence of "bicarbonate umbrella bilier", functioning as bile protection. In PBC, SCL4A2 regulation is destructed causing the excessive accumulation of bile acid (cholestasis). This causes progressive biliary lesion up to ductopenia due to the toxic characteristics of bile. Bile acid accumulation is a ligand to Farnesoid x receptor (FXR) that functions in the regulation of bile acid homeostasis, lipid, glucose metabolism and for immune regulation. FXR activation inhibit the signalling cascade of nuclear factor κB (NF-κB) by decreasing the production of TNF-α, IL-1, IL-17 and IFN-γ.[4,5,17]

Apoptosis

Biliary epithelial cell (BEC) is prone to apoptosis. Several stimuli originating from immune system, oxidative stress, toxin, and infectious agent can induce apoptosis of BEC.[18] Biliary epithelial cell will phagocytize apoptotic biliary epithelial cell and form apotop which later becomes the endogen source of new autoantigen formation. Circulating AMA will recognise apoptop and forms AMA autoantigen complex. This complex will cause apoptosis around the cell.[2,5,12]

Senescence

In PBC, it was found that accumulation of biliary epithelial that has undergone senescence is marked by the increased expression of senescence marker, like the senescence-associated beta-galactosidase (SA-βgal), $p16^{INK4A}$, and $p21^{Waf1/Cip1}$. The mechanism is still unclear. After senescence, injured cells will normally be substituted with new cells, but in PBC cell undergoes transition to senescence-associated secretory phenotype (SASP), that is marked by the secretion of chemokines (CX3CL1, CXCL8 and CCL2), cytokine (IL-6, IL-1), growth factors and metalloproteinase matrix (MMPs) which function is to repair/remodel and attracting immune cells.[12]

Autophagy

Autophagy is a cell defence mechanism when cell suffers from lesion or nutritional deprivation. It works by destructing and recycling intracellular organelles. Autophagy regulation is maintained by immunity signal molecules, which are toll like receptors (TLR), IFN-γ and NF-κ. Autophagy process can be a signal for apoptosis.[18]

In PBC, autophagy and deregulation of autophagy is disrupted. Immunohistochemistry examination can be used to detect autophagy using markers like LC3 (accumulation of abnormal autophagosome) and p62 (insufficient autophagy capacity).[18]

Mechanism of development of biliary epithelial cell injury in PBC

Bacterial component with the structure mimicking epitope PDC-E2, xenobiotic compounds which modify PDC-E2 and biliary epithelial cells which undergo apoptosis will produce autoantigen, causing destruction of biliary epithelial cells in PBC. This antigen will activate macrophage to present antigen to CD4+ T cell through class II MHC and produce cytokines IL-23, IL-12, IFNγ, TNFα. CD4+ T cells then activate and produce cytokines IFNγ and TNFα. IFNγ cytokine function to activate cytotoxic T cell, TNFα function to induce apoptosis and senescence of biliary epithelial cells, IL 12 function to activate Th1 cell and IL-23 which function to activate Th17 cell. CD4+ T cell to activate B cell through costimulary molecule CD40/CD40L and produce IL-4 to differentiate B cell into plasma cell which later develop antibody, particularly AMA.[12]

Primary Biliary Cholangitis (PBC) Treatment

United States Food and Drug Administration recommend Ursodeoxycholic acid (UDCA) as the first line treatment of PBC. Ursodeoxycholic acid plays role in decreasing periportal inflammation process and repair ductular proliferation to slow down development of fibrosis and, in some cases, to reduce the risk of oesophageal varices in PBC. Administration of UDCA in early stage can inhibit disease progression and mortality risk thus decrease the need of liver transplantation. UDCA treatment give response after 6 months up to 2 years after therapy is initiated. Combination of UDCA and budenoside is used in the case of PBC and AIH overlapping syndrome. This combination is contraindicated for PBC patient with cirrhosis due to the increased of portal vein thrombosis.[2,4,19]

Obeticholic acid (OCA) and fibrate is used as the second line treatment for PBC. Obeticholic acid is a farnesoid x receptor (FXR) agonist which play role to regulate bile acid haemostasis, antiinflammation, and antifibrosis. Fibrate give anti-inflammatory effect and modulate bile acid synthesis through activation of peroxisome proliferator-activated receptor α (PPAR-α) pathway.[2,4,20]

Liver transplantation is a definitive therapy for PBC that develops into advanced stage even though pharmacological treatment has been administered. The survival rate of PBC after transplantation is 80% for 2 years and 70% for 7 years. New regiment for PBC has been identified, serves as an immunomodulator targeting immune response. Rituximab and Abatacept is the example of this line which is still evaluated for its effectiveness.[2,4]

Differential Diagnosis of Primary Biliary Cholangitis (PBC)

Mechanical Obstruction of Biliary Duct

Biliary duct obstruction due to stones, biliary stricture and benign or malignant tumour can give appearances similar to PBC. Using USG, CT scan, and AMA examination, we can differentiate them from PBC. Histopathology appearances of mechanical obstruction are edema of the portal tract and varied duct reaction with lymphoplasmatic inflammation, which are not distinct from PBC. Cholestasis usually happen in the mechanical obstruction of biliary duct, while cholestasis in PBC is not seen in early stage.[4]

Primary Sclerosing Cholangitis (PSC)

Histological appearance of PSC alone cannot be used as a fundamental finding to differentiate PSC from PBC since there is a lot of overlap morphology. Information regarding history of inflammatory bowel disease (IBD), AMA negative and a positive biliary tree cholangiography (gold standard) can confirm the diagnosis of PSC.[4]

Adverse Drug Reaction

Appearance of liver biopsy due to adverse drug reaction may be similar to PBC. Adverse drug reaction can be confirmed if the results of AMA examination are negative and there is history of drugs use, such as hormonal steroid (estrogen and androgen), phenothiazine, anticonvulsant, tricyclic antidepressants or antibiotics such as erythromycin, clavulanate amoxicillin.[9]

Autoimmune Hepatitis (AIH)

In AIH, there is an increase of ALT ≥5x normal range, increased IgG 2x normal range, slightly increased or normal ALP, positive ANA and SMA, with negative AMA. There is 20% cases of AIH show

positive AMA. Histopathological appearance in the form of hepatocellular injury without the involvement of bile duct and lymphocytic interface help to differentiate AIH from PBC. Therefore, combination from clinical appearance, liver function and serology examination results, and histopathological appearance are needed to confirm the diagnosis.[9]

Viral hepatitis

Chronic hepatitis C can have histopathological appearance of biliary duct lesion and granuloma in portal tract (particularly with interferon therapy) which can also be seen in PBC. Information about negative AMA, positive viral serological examination, ALT/AST increase, normal or slight increase of ALP and absence of copper periportal deposit can help the diagnosis of viral hepatitis.[4]

CONCLUSION

Primary biliary cholangitis is an autoimmune liver disease which is chronic and progressive, marked by the presence of cholangitis and small bile duct destruction, which eventually may cause cirrhosis or even liver failure. Diagnosis of PBC is established if AMA titre is ≥1:40 or AMA level > 0.1unit, increased ALP >1,5x normal range for 6 consecutive months, and increased GGT. Based on the necroinflammation activity and histopathology variation, PBC is classified into mild, moderate, and severe stage. Liver biopsy is needed in PBC suspected patients with negative AMA and in PBC-AIH overlap syndrome and to evaluate the progressivity of the disease and response to therapy. The etiopathogenesis of PBC is an interaction between genetic factors (HLA and non-HLA genes) with environmental factors (bacterial infection and xenobiotic) which cause PDC-E2 as an autoantigen and the formation of AMA.

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