Primary Biliary Cirrhosis

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ABSTRACT

Primary biliary cirrhosis (PBC) is an inflammatory disease or chronic liver inflammation, with slow progressive characteristic and is an unknown cholestatic liver disease and commonly happen in middle-aged women. The incidence of PBC is 0.03 – 5.8 per 100,000 people per year, prevalence of 1.91-40.2 per 100,000 people and continues to increase. Based on the American Association for Study of Liver Disease criteria, the diagnosis of PBC is made in the presence of two out of three criteria, which are increase of alkaline phosphatase, positive antimitochondrial antibodies (AMA), and histopathology examination.

We reported a case which is very rarely found; a 47-year-old women with the chief complaints of decrease consciousness and jaundice. In physical examination, there were anaemic conjunctiva, icteric sclera, hepatosplenomegaly, palmar erythema, and liver nails. In the patient, there was no evidence of obstruction in imaging with two-fold increase of alkaline phosphatase and positive AMA test. Patient was hospitalised to slow down the progression of the disease and to overcome the signs (e.g. pruritus, osteoporosis and sicca syndrome).

Keywords: *primary biliary cirrhosis, alkaline phosphatase, antimitochondrial antibodies*

ABSTRAK

Primary biliary cirrhosis (PBC) merupakan penyakit inflmasi atau peradangan hati kronik, bersifat progresif lambat dan merupakan penyakit hati kolestatik yang belum diketahui dan sering terjadi pada wanita usia pertengahan. Insidensi PBC 0,03-5,8 per 100.000 orang per tahun, prevalensi 1,91-40,2 per 100.000 orang dan semakin meningkat. Diagnosis PBC berdasarkan kriteria American Association for Study of Liver Disease didapatkan peningkatan alkali phosphatase, antimitochondrial antibodies (AMA) dan bukti histopatologi. Jika ditemukan dua dari tiga kriteria tersebut.

Kami melaporkan sebuah kasus yang sangat jarang ditemukan, seorang perempuan, berumur 47 tahun dengan keluhan utama penurunan kesadaran dan ikterik. Pada pemeriksaan fisik didapatkan konjungtiva anemis, sklera ikterik, ascites, hepatosplenomegali, palmar eritem dan liver nail. Pada pasien tidak didapatkan bukti dari imaging obstruksi dengan nilai alkali phospatase meningkat dan nilai AMA positif. Perawatan pasien untuk memperlambat perburukan penyakit dan untuk mengatasi gejala-gejala (misalnya: pruritus, osteoporosis dan sicca syndrome).

Kata kunci: *primary biliary cirrhosis, alkali phospatase, antimitochondrial antibodies*

INTRODUCTION

Primary biliary cirrhosis (PBC) is an inflammatory disease or chronic liver inflammation, with slow progressive characteristic and is an unknown cholestatic liver disease and commonly happen in middle-aged women.[1] The definitive mechanism of PBC is not clearly understood, but is believed to be a combination of genetic and environment factors. Chronic inflammation and recurrent damage to the small biliary duct provoke the proliferation of biliary duct cell and fibrosis caused by myofibroblast in the liver mesenchyme. Fibroproliferative biliary duct cells is commonly spread to the liver parenchyma, associated portal area, leading to biliary cirrhosis. Pathogenesis of fibrogenic response in the biliary duct damage has been studied with new concept "Hedgehog pathway" in the liver, which is a cell differentiation regulator. The Hedgehog pathway may help the growth of epithelial and stromal cells; disorder in this system may modulate the mechanism of biliary duct disturbance.[2]

The incidence of PBC is 0.03-5.8 per 100,000 people per year, prevalence of 1.91-40.2 per 100,000 people and continues to increase. The diagnosis of PBC based on American Association for Study of Liver Disease criteria requires the presence of two out of three criteria as follows: increase of alkaline phosphatase, positive antimitochondrial antibodies (AMA), and histopathology evidence .[1] The incidence of PBC is very rare, which interest the author to report this case with the expectation to diagnose this condition earlier, accurate, and give appropriate management which may increase the patient's life expectancy.

CASE ILLUSTRATION

A 47-year-old women with the chief complaint of decreased consciousness since 5 hours before hospital admission which was described as gradual. Initially patient slept more and later became difficult to be awakened. There were no complaints of terrible headache, projectile vomiting, slurred speech, or limb weakness. The complaint was accompanied with an episode of coffee-ground vomiting since 5 hours prior to the admission. The patient had no history of black stools. The aforementioned symptoms concurred with jaundice in both eyes and skin since 1 month before the admission. She also reported itching throughout her body that had been felt since 2 weeks prior to hospitalisation. The patient also lost 10 kg of her weight within two months period.

There was no history of fever, dark-coloured urine, or clay-coloured stools. No past history of herbal medication was reported. None of her relatives had a history of jaundice or liver disease. Similar symptoms were experienced by the patient 9 years ago that was said related to contraceptive pills that she had used for 4 years prior to that period. Recently, she resumed using contraceptive pills for the last 4 months.

She was treated in Hasan Sadikin Hospital for the same symptoms for 1 month and was discharged home two days ago. The patient was previously examined for the presence of hepatitis marker with a non-reactive result. On physical examination, the patient looked severely ill and was somnolent. Her blood pressure was 120/70 mmHg; pulse 88x/minute, regular, equal on both arms, and adequate filling; respiratory rate 20x/minute; body temperature 36.8 degree Celsius. Upon examination the conjunctiva looked anaemic and the sclera was icteric. Neck and chest examinations revealed no spider naevi. The abdomen was rounded, soft, and showed no venous enlargement; the liver was palpated 3 cm below the costal margin and 3 cm below the xiphoid process, soft, and had obtuse angle; and percussion on Traube's space was dull. Limb examination showed palmar erythema and liver nails.

Laboratory tests revealed hemoglobin 6.4 gr/dL; haematocrit 18.0%; leukocytes 22.910 10^3/uL; thrombocytes 36.000 thousand/uL; mean corpuscular volume (MCV) 102.3 fL; mean corpuscular hemoglobin (MCH) 36.4 pg; mean corpuscular hemoglobin concentration (MCHC) 35.6 %, basophil 0 %, eosinophil 0 %, band neutrophil 3 %, segmented neutrophil 73 %, lymphocyte 16 %, monocyte 6 %, metamyelocyte 1 %, myelocyte 1 %, random blood glucose 93 mg/dL, ureum 48 mg/dL, creatinine 1.02 mg/dL, sodium 135 mEq/L, potassium 4.2 mEq/L, aspartate aminotransferase (AST) 155 U/L, alanine aminotransferase (ALT) 201 U/L, gamma glutamyl transferase (gamma GT) 676 U/L, alkaline phosphatase 498 U/L, prothrombin time (PT) 12.90 second, activated partial thromboplastin time (APTT) 43.20 second, international normalized ratio (INR) 1.20, serum protein 4 gr/dL, serum albumin 1.5 gr/dL reactive antinuclear antibody (ANA), positive for antimitochondrial antibody (AMA), total cholesterol 493 mg/dL, high density lipoprotein (HDL) 9 mg/dL, low density lipoprotein (LDL) 514 mg/dL, triglycerides 212 mg/dL, non-reactive for HBsAg, non-reactive for anti-HCV, positive 3 for direct Coombs test, negative for indirect Coombs test, dark yellow urine, urine was turbid, mass density

1.015, pH 7.5, negative nitrites, positive 1 for urine protein, negative urine glucose, negative ketone in urine, normal urobilinogen, positive 3 for bilirubin in urine, negative for leukocyte esterase, positive 3 for blood in urine, abundant erythrocytes, leukocyte 2, epithelial cells 4; negative for bacteria, crystals, and cylinders. She underwent abdominal ultrasound that showed enlarged liver, moderately increased liver echogenicity, homogenous, no mass, portal and hepatic veins were not widened; gallbladder collapsed and widened; no intraluminal sludge was observed; no sonographic Murphy sign was identified; spleen was enlarged; parailiac and paraaortic lymph nodes were not enlarged; minimal ascites was observed. The impression from ultrasound was hepatosplenomegaly with thickening of the gallbladder possibly due to inflammation, hypoalbuminemia, minimal ascites.

The patient was diagnosed with decreased consciousness due to hepatic encephalopathy, cholestatic jaundice due to primary biliary cirrhosis with upper gastrointestinal bleeding due to ruptured esophageal varices with differential diagnoses of portal hypertension gastropathy, autoimmune haemolytic anaemia, thrombocytopenia due to chronic liver disease. The patient was treated with bed rest, 3 litres per minute of oxygen when she was difficult to breath, NaCl 0.9% infusion 1500 cc/24 hours, dark-coloured production from NGT (nothing by mouth temporarily), albumin 25% transfusion over 6 hours, thrombocyte transfusion with a target of > 50.000, WRC transfusion if Hb < 8 or signs of hypoxia were present; ursodeoxycholic acid (UDCA) 2 x 500 mg, lactulose 1 x 15 cc to be taken orally; liver biopsy, vital signs, and intake-output monitoring.

DISCUSSION

Primary biliary cirrhosis (PBC) is a chronic inflammation, slow progressive liver disease, and is also a cholestatic liver disease with an unknown cause that often affects middle-aged women.[1] The precise mechanism of PBC has not been elucidated but was believed to be a combination of genetic and environmental factors. The damage of biliary duct epithelial cells mediated by the immune system was deemed as a trigger in the pathogenesis. The targets for antimithochondrial antibodies (AMA) are 3 M2 components of mithocondrial antigen: PDC-E2, 2-oxoglutarate dehydrogenase complex (OGDC) and branched chain 2-oxo-acid dehydrogenase complex (BCOADC). Of these three components, the most identifiable one by T and B cells is the inner lipoyl domain of PDC-E2. It is unknown, however, if PDC-E2 that is localised on mithochondrial membrane of the selective biliary epithelial cells and salivary duct cells is also a target of autoimmune destruction. The cell death presumably increases the exposure of PDC-E2 to immune system which resumes as autoimmune attacks. Apoptosis or the death of cholangiocytes, unlike any other cell death, is a potential source of immunogenic PDC-E2 in patients with PBC. Chronic inflammation and recurrent injury of the small biliary duct triggers

Table 1. Laboratory examination

Blood examination				**Urine**	
Hemoglobin (gr/dL)	6.4	AST(U/L)	155	Colour	Yellow
Haematocrit (%)	18.0	ALT(U/L)	201	Turbidity	Hazy
Erythrocyte (million/uL)	1.76	Gamma GT(U/L)	676	Mass density	1.015
Leukocyte (10^3/uL)	22.910	Alkaline phosphatase(U/L)	498	pH	7.5
Thrombocyte (thousand/uL)	36.000	Total bilirubin (mg/dL)	39.766	Nitrite	Negative
MCV (fL)	102.3	Direct bilirubin (mg/dL)	28.677	Protein	+1
MCH (pg)	36.4	Total protein (gr/dL)	4.0	Glucose	Negative
MCHC (%)	35.6	Albumin(gr/dL)	1.5	Ketone	Negative
Diff. count (%)	0/0/3/73/16/6/1/1/1	PT (second)	12.90	Urobilinogen	Normal
Glucose random (mg/dL)	93	APTT (second)	43.20	Bilirubin	+3
Sodium (mEq/L)	135	INR	1.20	LE	Negative
Potassium (mEq/L)	4.2	HbsAg	Non-reactive	Blood	+3
Urea (mg/dL)	48	Anti HCV	Non-reactive	Erythrocyte	2
Creatinine (mg/dL)	1.02	AMA	Reactive	Leukocyte	4
ANA test	Reactive	HDL(mg/dL)	9		
Total cholesterol (mg/dL)	493	Triglyseride	212		
LDL (mg/dL)	514	Coomb test	Direct +3		

MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; Diff count: differential blood count; ANA test: antinuclear antibody test; LDL: *low*-density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Gamma GT: gamma-glutamyl transferase; PT: prothrombin time; APTT: activated partial thromboplastin time; INR: international normalized ratio; HbsAg: hepatitis B surface antigen; Anti HCV: anti hepatitis C virus; AMA: anti-mitochondrial antibody; HDL: high density lipoprotein; LE: Lupus erythematosus

the proliferation of biliary duct cells and fibrosis caused by myofibroblast cells within the hepatic mesenchyme. Fibroproliferative biliary duct cells often expands to liver parenchyme and associated portal area towards a process of biliary cirrhosis. The pathogenesis of fibrogenic response in biliary duct injury has been studied using a new concept of "Hedgehog pathway" in the liver that regulates the cell differentiation system. The Hedgehog pathway shows its ability to promote the growth of epithelial and stromal cells and the interruption of such system can modulate the disruptive mechanism in biliary duct.[2]

The patient came with problems of decreased consciousness and coffee-ground vomiting since 5 hours prior to hospital admission, as well as yellowing of eyes and body since 1 month prior to admission. The determination of diagnosis and aetiology needs a thorough anamnesis to identify the cause of this patient's loss of consciousness. From the history taking, it was found that the patient suffered from jaundice of eyes without an episode of fever nor history of certain drugs and alcohol consumption, tuberculosis treatment, familial history of jaundice, and upper abdominal discomfort. Physical examination suggested signs of hepatic failure and portal hypertension which were hepatosplenomegaly, ascites, palmar erythema, and liver nails. Findings from history taking and physical examination hinted a diagnosis of liver cirrhosis that was supported by following additional examinations.

Additional tests revealed thrombocytopenia, ratio of albumin-globulin with APRI score > 2 which explained the presence of liver cirrhosis in this patient. Decreased consciousness is a part of cirrhosis complication, which is grade III hepatic encephalopathy. In this patient, there was no evidence of infection nor acute liver failure. In addition, coffee-ground vomiting in this patient was a part of liver cirrhosis complication, i.e. upper gastrointestinal bleeding (variceal bleeding). From this data, it was concluded that the diagnosis was a decreased consciousness caused by hepatic encephalopathy.[1,2,3,4,5]

The diagnostic approach was based on the icterus that the patient experienced since 1 month prior (Figure 1).[6] This patient had yellowing of eyes and body since 1 month ago, accompanied by body

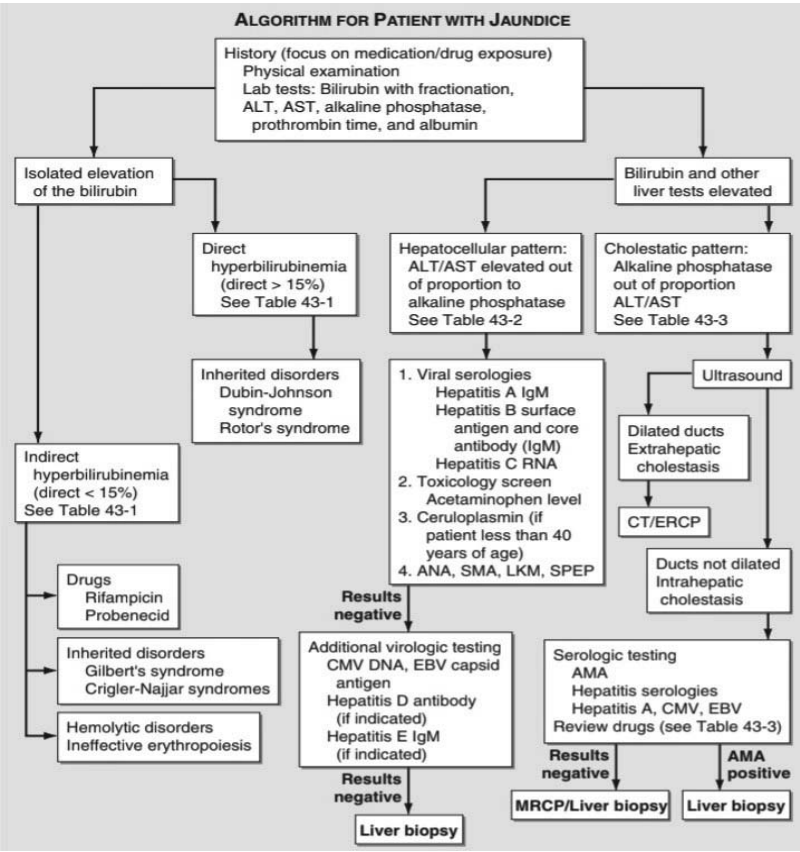

Figure 1. Diagnostic approach in jaundice[6]

weakness, generalised itching throughout the body and coffee-ground stools. There was neither history of fever, colour change of urine looking like dark tea, clay-coloured stool, nor upper abdominal pain. There was also no history of drugs consumption, tuberculosis treatment, or drinking alcohols. Laboratory data with R value < 2 supported the diagnosis of cholestatic jaundice.

From the above algorithm, jaundice can be caused by pre-hepatic, hepatic, and post-hepatic causes.

Table 2. Differential diagnosis in jaundice[7]

Pre Hepatic	Haemolytic Antibiotic medications Thalassemia
Hepatic	Viral hepatic Alcoholic hepatic Primary biliary cirrhosis Primary sclerosing cholangitis Infiltrative disease (TB, lymphoma, amyloidosis) Infection (malaria, leptospirosis) Gilbert's syndrome Crigler-Najjar syndrome
Post hepatic	Cholestatic extrahepatic Gallstones Biliary duct tumour Pancreatic carcinoma Carcinoma of Vater ampulla

Diagnostic approach in the suspect of primary biliary cirrhosis (Figure 2).[1] Patient with two-fold increase of alkaline phosphatase serum and no evidence of obstruction in biliary duct from USG examination.

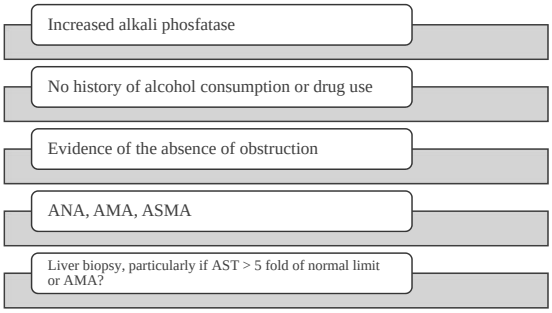

Figure 2. Diagnostic approach in the suspect of Primary Biliary Cirrhosis[1]

The diagnostic approach for primary biliary cirrhosis was based on the criteria from American Association for Study of Liver Disease (AASLD): (1) biochemical evidence of cholestasis shown by increased alkaline phosphatase activity (the magnitude of increased activity correlates with the severity of ductopenia and inflammation, there was no consensus on the degree of escalation in primary biliary cirrhosis), for at least 6 months; (2) the presence of AMA (antimithochondrial antibodies); (3) histopathological evidence of non-suppurative destructive cholangitis and injury of interlobular biliary duct on liver biopsy. The recommended diagnosis of primary biliary cirrhosis develops if two of these three criteria are found.[1,2]

Based on the findings from history taking, physical examination, laboratory and further tests, it was concluded that the cause of jaundice in this patient was primary biliary cirrhosis. It was supported by the results from ultrasound that showed enlarged liver, moderate increase in liver echogenicity, homogenous, without mass, no enlargement of vena porta and vena hepatica, widened of collapsed gallbladder, no intraluminal sludge, no sonographic Murphy sign, enlarged spleen, no enlargement of parailiac and paraaortic lymph nodes, and minimal ascites. The impression from ultrasound was hepatosplenomegaly with thickening of gallbladder possibly due to inflammation, hypoalbuminemia, and minimal ascites. Loss of consciousness in this patient was caused by hepatic encephalopathy as seen in patients with primary biliary cirrhosis and portal hypertension. From the case report, the patient had PBC with the feature of low haemoglobin with patterns of autoimmune haemolytic anaemia. This patient had low haemoglobin level and positive 3 direct Coombs test that matched the findings from autoimmune haemolytic anaemia.

It was concluded that the patient was diagnosed with decreased consciousness due to hepatic encephalopathy, cholestatic jaundice due to primary biliary cirrhosis with upper gastrointestinal bleeding due to ruptured oesophageal varices with differential diagnosis of portal hypertension gastropathy, Evans syndrome due to primary biliary cirrhosis based on gradual loss of consciousness since 5 hours prior to hospital admission and jaundice since 1 month before that. Physical examination revealed signs of chronic liver disease. On additional tests, increased alkaline phosphatase and positive AMA results were identified while ultrasound showed no obstruction. Liver biopsy has not been performed in this patient.

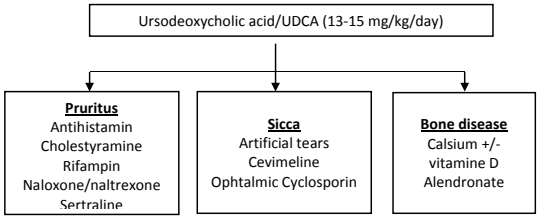

Figure 3. Management symptoms of primary biliary cirrhosis[1]

The aim of treatment in primary biliary cirrhosis is to diminish the disease progression and to alleviate accompanying symptoms (e.g. pruritus, osteoporosis, and sicca syndrome). Below is the treatment algorithm based on the recommendation from American Association for Study of Liver Disease: [1,3,8,9,10]

UDCA treatment using the recommended dose of 13-15 mg/kg/day is considered as the first line treatment for PBC. UDCA is a natural hydrophilic bile acid that has a function related to hydrophilic bile acid pool with a direct choleretic, anti-inflammation, and anti-apoptosis of the liver epithelial cells effects. Various adjunct treatment can be given to patients with suboptimal UDCA response, including steroids, azathioprine, mycophenolate mofetil, methotrexate, colchicine, sylmarine, and bezafibrate. Corticosteroids is known for its effect in improving serum liver function and liver histological appearance, but it may deteriorate the bone mineral density. The combination of prednisolone (10 mg/day, for 9 months) with UDCA (10 mg/kg/day) is better in improving liver histology in PBC during early phase than UDCA alone.[1,3]

The patient was treated with UDCA but only received it when her condition was affected by hepatic encephalopathy. This treatment has not shown a significant improvement.

Liver transplantation may increase the survival of patients with PBC and is effective for decompensated cirrhosis or liver failure. Approximately 20% of patients have recurrent PBC within five years after transplantation. Pruritus is often refractory to medical treatment and might influence the patient's quality of life. The first line of mild-moderate pruritus is antihistamine, which should be taken cautiously in patient with cirrhosis and signs of encephalopathy because antihistamine may suppress brain function even further.[1,3] Detection of patients with PBC should be performed during early signs of jaundice so that proper treatment can be given since the presence of its early symptoms.

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