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Primary biliary cirrhosis in pregnancy

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Summary

Introduction

Primary biliary cirrhosis (PBC) is a chronic hepatic condition presumably of immune etiology. In genetically predisposed patients, progressing immunization of the liver is stimulated by

environmental or infectious agents. As a result of ill-targeted immune response antimitochondrial autoantibodies M2 (AMA-M2) are produced. They slowly damage fine intrahepatic biliary ducts with typical inflammatory response and subsequent cholestasis, often progressing to hepatic cirrhosis and liver failure, and if it has reached 4 stage, primary hepatic cancer.

PBC is most frequently diagnosed in women after the age of 30. It is 13 times more frequent in females than in males. Currently, PBC is often diagnosed at the asymptomatic stage or when nonspecific symptoms have developed, i.e. fatigue or pruritus. Biochemical tests present elevated cholestatic markers, and immune tests detect elevated autoimmune antibodies AMA and IgM. In advanced cases of hepatic cirrhosis, liver transplant is considered as a final treatment.

Case study

The patient, a 31-year old woman, CI PI, with PBC was first seen in 7 hbd. Her medical history revealed PBC had been diagnosed a year earlier. First clinical symptoms occurred 5 years ago, treated with Proursan. The patient was hospitalized 5 times, i.e. in 30, 36, 37, 38 and 39 hbd, among others, for threatening preterm delivery and cholestasis, and later for liver dysfunction associated with PBC, and for labor. In 39 hbd delivery was induced, and she gave birth (naturally) to a live neonate, female, weighing 2,830g, body length 52 cm, Apgar score 9-10. The liver function improved after the delivery and stabilized. The patient is followed up, treatment with Proursan continued.

Pregnancy in patients with PBC is associated with mother's exacerbated condition, especially in the third trimester and puerperium. The aforementioned case study shows that with proper care successful management and termination of pregnancy is safe for both mother and her baby.

Key words: primary biliary cirrhosis, pregnancy, labor

Introduction

Primary biliary cirrhosis (PBC) is a chronic liver disease of immune etiology. It is a progressive, autoimmune condition stimulated by environmental or infectious agents in genetically predisposed individuals. The prominent sign are anti-mitochondrial autoantibodies M2 (AMA-M2) resultant from improperly targeted immune response. [2, 19, 26].

In the course of PBC they slowly damage fine intrahepatic biliary ducts and produce typical inflammatory response and subsequent cholestasis, often progressing to hepatic

cirrhosis and liver failure, and primary hepatic cancer if it has reached 4 stage [4, 39]. In general, PBC is diagnosed in women over the age of 30 who are 13 times more likely than men to develop the disease [19]. The disease is usually diagnosed at an asymptomatic stage or when there are no specific symptoms, such as fatigue or itching of the skin. Family history of antigens HLA-DR3, -DR8, -DR52a is relatively common. Biochemical studies indicate elevated cholestatic markers and immunological studies usually detect elevated AMA and IgM antibodies. In advanced cirrhosis, the ultimate treatment is transplantation of this organ.

Case study

The patient, a 31-year-old woman was first seen at the gynecological office to confirm pregnancy. Medical history revealed she had been diagnosed with primary cirrhosis of the liver in 2015. First clinical symptoms associated with the disease developed 5 years before, i.e. chronic fatigue, weakness, lack of appetite, weight loss, intolerance of some fried, baked and fatty foods, tendency to constipation alternating with diarrhea, discomfort in the right hypochondrium and bloating, decreased libido and periodic pruritus. PBC was diagnosed on the basis of clinical examination and additional tests (in 2015). The patient was prescribed Proursan (ursodeoxycholic acid). Since liver tests were within normal range the patient was not qualified for liver transplant.

On admission USG scan showed single live embryo in the uterus, CRL-12 mm, 7 hbd, yolk sac normal, no signs of the chorion detachment.

Throughout the pregnancy the patient was monitored by specialists in infectious diseases, obstetrics and gynecology.

The patient was first hospitalized in 30 hbd. She reported at the Pregnancy Pathology Clinic for skin pruritus and abdominal discomfort. Ultrasound examination found fetal biometry normal for gestational age, cervical length 18mm. Cervical cultures (-) negative. Cardiotocography normal. Lab tests found no significant deterioration in the liver function.

Due to threatening preterm delivery and shortened cervix, it was decided to insert a pessary. The patient was prescribed Celeston 2x12 mg for 2 days, Lutein, vaginally, 2x100 mg, and Ursopol 2x2 tabl. After conservative medication and four-day hospitalization, the pregnant woman was discharged home with Proursan 4x250mg, Lutein 2x100 mg vaginally, Macmiror complex 500 1x1 glob. vaginally every 3 days.

In 36 hbd the patient was again hospitalized for the severity of gestational cholestasis, generalized skin pruritus and threatening preterm labor. Hydroxyzine was started. Ultrasonography did not show abnormalities in fetal development. Cardiotocography was

normal. However, laboratory studies found liver function deterioration, elevated bile acid concentration 33.2 umol/l. After an eight-day hospitalization, the pregnant woman was discharged home with recommendations: Proursan 4x250mg, Hydroxyzine 2x100mg, Macmiror complex 500 1x1 glob. vaginally every 3 days.

In 37 hbd, the patient was admitted to the ward for intermittent uterine contractions. Pessary was removed. No liver deterioration was observed in laboratory findings. Ultrasonography found fetal biometry normal for gestational age. After a two-day hospitalization, the patient was discharged home with Proursan 4x250mg, Hydroxyzine 2x100mg, Macmiror complex 500 1x1 glob. vaginally every 3 days.

In 38 hbd the patient was admitted to the ward for a check-up. No liver deterioration was observed in laboratory findings. Ultrasonography found fetal biometry normal for gestational age. After a two-day hospitalization, the patient was discharged home with Proursan 4x250mg, Hydroxyzine 2x100mg, and recommended to report to the clinic in 7 days for the induction of labor.

In 39 hbd the patient was admitted to the pregnancy pathology ward to terminate her pregnancy. At the delivery room she was administered oxytocin to induce labor. After the onset of uterine contractions, at 4-cm cervix dilatation, epidural analgesia was given. The patient gave birth to a healthy neonate, 2,830g female, Apgar score 9 points in the first, 10 points in the third and fifth minute of life, umbilical cord blood pH 7.426. The puerperium was uneventful. The patient was discharged home on 5 day.

Since then the patient has been constantly followed-up at the Outpatient Clinic of Infectious Diseases, Proursan continued. No acute exacerbation of the disease was observed in the puerperium. Liver function is stable and at present the patient does not require liver transplantation. There was no abnormality in the development of the fetus during the entire course of pregnancy, but lab results found periodic deterioration of liver function. (Table 1).

Table 1. Liver function parameters

Biochemical parameters	Gestational age				
	Range	Hbd 30	Hbd 36	Hbd 37	Hbd 38
ALP	35-125 U/L		324U/L		259U/L
ALT	5-50 U/L	19 U/L	28U/L	21U/L	25U/L
AST	5-50 U/L	20 U/L	29U/L	25U/L	26U/L
Total protein	6.0-8.0 g/dl	6.70 g/dl	7.0g/dl	7.0g/dl	7.1g/dl
Bilirubin	0.10-1.30 mg/dl	0.40mg/dl	0.36mg/dl	0.39mg/dl	0.47mg/dl
CRP	0.1-5.0 mg/l	0.51mg/l			0.69mg/l
APTT	26.0-40.0 sek	24.6 sek	24.3sek	27.5sek	24.2sek
PT	9.7-14.5 sek	11.2 sek	11.0sek	10.5sek	10.8sek
INR PT	70-130 %	96%	99%	109%	100%
INR	0.8-1.2	1.0	0.9	0.9	0.9
TT	15.0-25.0 sek	15.8sek	20.7sek	14.8sek	20.9sek
GGTP	10-40 U/L		76U/L		69U/L
Kreatynin	0.70-1.30 mg/dl	0.74mg/dl	0.72mg/dl	0.76mg/dl	0.79mg/dl
Urea	20-45mg/dl	mg/dl		mg/dl	20.0mg/dl
Ureic acid	3.40-7.00mg/dl	3.5mg/dl	4.6mg/dl	5.0mg/dl	5.6mg/dl
Biliary acids	0-15.0 umol/l	10.7umol/l	33.2 umol/l	20.7umol/l	8.2umol/l
LDH	120-230 U/L	149U/L	216U/L	175U/L	161U/L
Urinalysis		b-0.21g/l	b-0.23	b-0.27	normal
HGB	12.0-15.6 g/dl	12.0g/dl	12.9g/dl	12.8g/dl	12.9g/dl
HCT	35.0-46.0 %	33.8 %	36.9%	36.0%	38.1%
RBC	3.6-5.2 M/ul	3.74M/ul	4.09M/ul	4.01M/ul	4.16M/ul
WBC	4.1-10.9 K/ul	12.8K/ul	12.8K/ul	11.83K/ul	10.10K/ul
PLT	140-440 K/ul	221K/ul	226K/ul	209K/ul	177K/ul
Na	137-146mEq/l	137mEq/l	134mEq/l	133mEq/l	133mEq/l
K	3.5-5.2 mEq/l	4.50 mEq/l	4.4mEq/l	4.2mEq/l	4.8mEq/l

Discussion

The lowest incidence of PBC is reported in Africa, Asia and Australia, the biggest incidence in the United Kingdom, Scandinavia, Canada and the USA, in the northern hemisphere it is more frequent in urban areas than in villages [19, 26]. In one study at the University of Newcastle the highest incidence was reported among relatives - the daughters of the sick [22]. Family history of PBC (associated with antigens HLA-DR3, DR8, DR52a) [19,

39] is often reported. Clinical trials in many centers in the world have confirmed PBC related with DRB1*08 allele, and protective significance of DRB1*11 and DRB1*13 [3, 16, 21]

No relationship between PBC and cigarette smoking, mean age of menopause, first pregnancy, and the number of children was found [7]. The disease is usually diagnosed at an asymptomatic stage or when nonspecific symptoms such as fatigue or itching occur. A characteristic symptom of PBC is the onset of small bile duct destruction [18]. Histological characteristic markers include the destruction of bile duct epithelial cells, damage to the intrahepatic fine bile ducts, infiltration of portal circulation by CD4, CD8, B lymphocytes, macrophages, eosinophils and NK cells [19, 26,2 9]. Inflammatory infiltration leads to cholestasis which in turn induces inflammation and necrosis caused by bile acids, strong detergents. Destruction of hepatocytes activates HLA class I antigens, which triggers cytotoxic T lymphocytes [7, 26]. Eventually, progressive fibrosis of the liver in the periportal region results in cirrhosis.

The presence of serum autoantibodies indicates that the underlying cause of the disease is autoimmune in nature, as evidenced by the relationship between the disease and the presence of antimitochondrial antibodies (AMA) found in 90-95% patients [19]. AMAs recognized as serologic markers of this disease are targeted against cholangiocytic mitochondrial membrane antigens of high specificity for E2 component (dihydrolipoamide acetyltransferase) of pyruvate dehydrogenase complex (PDC-E2). It was first discovered in 1965 by Walker using indirect immunofluorescence. The antigens for AMA are pyruvate dehydrogenase complexes (PDC), dehydrogenases of branched 2-oxy acids and 2-oxyglutaric acid dehydrogenase found in the mitochondrial inner membrane [6, 13, 32].

In healthy liver, AMA mainly bind to bile ducts epithelium, much less with hepatocytes. E2 and E1 subunits of 2-oxy-acids dehydrogenases in complexes initiate apoptosis of cells via TRAIL (TNF-related apoptosis inducing ligand) [5, 27]. Antimitochondrial M4 antibodies and anti-M8 antibodies, which occur together with anti-M2 antibodies, react with antigens located on the outer mitochondrial membrane, and may account for a more severe course of the disease [24].

M2 antigens may occur aside anti-mitochondrial anti-M9 antibodies targeted against glycogen phosphorylase. Testing for anti-M9 antibodies may help identify early stages of PBC [31]. In the course of the disease other antibodies are detected, including antibodies against nuclear membrane antigens, i.e. nuclear pore complex proteins of the nuclear envelope gp 210, gp 62, or the inner lamina proteins of the nuclear envelope which is Lamina B receptor (anti-LBR, Lamina B Receptor) [15, 28]. It is not known why the immune response is directed

against biliary cell antigens while the same molecules are found in other cells of the body. What triggers this reaction remains unexplained [13].

Antimitochondrial AMA antibodies are not specific only of this disease and their elevated values bear no relationship with the onset of PBC. They are detected in other pathological conditions, e.g. medication-induced liver damage, visceral lupus, cardiomyopathy, tuberculosis and other diseases. In 5-10% of patients AMA in the serum are absent so diagnosis is based on clinical picture and biochemical findings [19, 26]. The most characteristic are anti-mitochondrial antibodies, anti-M2, M4, M8 and M9 [1, 34]. Anti-M2 antibodies are detected in 98% patients. Antigen M2 comprises subunits E1, E2 and E3 of 2-oxy-acids dehydrogenase complex, mainly pyruvate dehydrogenase (E1), lipoic acid dehydrogenase (E3) and acetyltransferase (E2) located in the inner mitochondrial membrane, and protein X [35]. Markers like anty-M9, glycogen phosphorylase, non-specific anti-M4, thiol oxidase correlate with the severity of PBC.

The number of mitochondria is higher than in the bile duct epithelial cells [28]. The expression of BB1 and B7 antigen and intercellular adhesion molecule 1 (ICAM-1) have been detected on the epithelial lining of fine bile ducts. The occurrence of lymphocyte transformation disorders and inhibition of leukocyte migration speak for immune background of the disease. The presence of Tc lymphocytes with CD8 co-receptors for proteins encoded by *MHC I* genes and Th-lymphocytes with CD4 co-receptors for proteins encoded by *MHC II* genes was demonstrated in inflammatory infiltrates of damaged bile ducts [13].

To activate Tc or Th lymphocytes the cells with antigen expression simultaneously send two types of signals. The first is an antigen on the surface of the protein encoded by the MHC genes recognized by the receptor on the surface of T lymphocyte. The second signal is sent by the co-stimulating proteins B7 (CD80 and CD86) recognized by co-receptor CD28 on the surface of T lymphocyte. If T cell receives only the first signal, it loses the ability to proliferate and differentiate, even when the second signal appears [3]. Expression of BB1 and B7 and ICAM-1 antigens creates chances for cytotoxic T lymphocytes to damage bile ducts [30]. As a result, bile duct destruction, cell apoptosis and progressive hepatic fibrosis occur.

That very specific type M2 AMA is detected in 95% patients with PBC. PBC often co-occurs with other immune pathologies, e.g. rheumatoid arthritis, diffuse systemic sclerosis, Sjögren syndrome, CREST, autoimmune thyroiditis, tubular acidosis [11,13]. The disease is diagnosed when other serum antibodies are detected, like rheumatoid factor (RF) (66%), anti-smooth muscles antibodies (ASMA) (66%), anti-thyroid antibodies (40%), antinuclear antibodies (ANA) (30–35%) [13, 14].

Moreover, infectious background was also considered among the causes of the disease. It was supposed to be due to cross-generated response to pyruvate dehydrogenase complex (PDC) contained in bacteria [19]. Some authors suggest possible molecular mimicry [1, 19, 34]. The microorganisms involved in this process include: *Escherichia colli, Novosphingobium aromaticivorans, Lactobacillus, Chlamydia pneumoniae, Helicobacter pylori and Mycobacterium gordonae*. [1, 12, 34].

Some authors postulate PBC is induced by external agents, i.e. xenobiotics, which react with dehydrogenase E2, impair body tolerance and production of anti PDC-E2 (IgG and IgM) antibodies [8]. Xu et al. suggest the involvement of human β-retrovirus in PBC formation [19, 43].

In 60% patients with PBC no clinical signs may be observed. Others may develop nonspecific symptoms like chronic fatigue increased after physical activity that does not pass after rest and skin pruritus that may precede other symptoms. Skin pruritus is the most troublesome and thus the most significant clinical symptom of PBC. Initially, it affects the hands and feet, later the whole body, and eventually excoriation disorder develops, The severity of itching does not correlate with the severity of cholestasis, blood bile acid concentration, and clinical stage of the disease. It has not been explained whether the cause is in the neuronal structures, bile salts metabolites, progesterone, histamine or endogenous opioids. Skin pruritus intensifies at night, influenced by heat. Reduction of symptoms occurs with the progression of the disease [26].

As the disease progresses, other symptoms develop, such as dry eye syndrome, xerostomia, discomfort in the right hypochondrium, hepatosplenomegaly, jaundice, hyperpigmentation of the skin resulting from pituitary dysfunction, digestive disorders caused by decreased bile secretion, and fatty stools. In advanced stage other symptoms appear, e.g. jaundice with advanced vanishing biliary ducts (ductopenia), without signs of cirrhosis - on histopathological examination premature ductopenic PBC, cirrhosis and portal hypertension [13]. The first clinical symptom of the disease may be bleeding from esophageal or gastric varices, despite maintained function of the liver to synthetize [26]. Ascites and hepatic encephalopathy are observed in patients with histologically advanced cirrhosis. The dynamics of the disease and the progression of clinical symptoms are variable in individuals.

PBC may co-occur with osteoporosis, which is also a complication of other cholestatic liver diseases resulting from impaired absorption of fat-soluble vitamins, including vitamin D [19, 26]. This inhibits osteoformation, low or normal resorption, osteoblasts demonstrate low activity, while osteoclasts activity is enhanced. Calcium ion absorption and vitamin D

production are impaired [5]. Patients with PBC have lipid disorders associated with elevated total cholesterol and LDL. These changes develop due to lipoprotein X (LpX) molecule formed from bile acids in cholestatic liver disease. It prevents LDL from oxidation, which reduces its atherosclerotic activity by protecting the vascular endothelium [19, 37, 38]. However, despite lipid disorders, patients with PBC do not belong to the group of cardiological risk. Lipid abnormalities in PBC patients may also appear as yellow tufts, most commonly on the eyelids. One of the late consequences of PBC is hepatic cell carcinoma, which occurs in 3% of patients [40].

Biochemical studies show elevated cholestatic markers, i.e. alkaline phosphatase (ALP) and γ-glutamyltranspeptydase (GGTP). ALT and AST activity is usually slightly enhanced. Bilirubin level, normal in the early stages of the disease, increases during the course of the disease, which signals the progression and gives unfavorable prognosis. According to the Paris and Barcelona criteria, bilirubin and ALP levels are the parameters that assess the response to treatment of PBC [3,5]. If the level of ALP is more than 5 times greater than the reference value, then viral and autoimmune diseases, overlap syndrome, and autoimmune hepatitis should be considered [5]. PBC is characterized by high levels of serum IgM. If serum AMA is detected, PBC is highly likely; AMA ≥ 1/40 is considered positive test result [14]. Autoantibodies from ANA family are most characteristic of PBC. These are specific antibodies against anti-Sp100 and anti-gp210 proteins [16]. When AMA is not detected, those can be used as markers to diagnose this disease.

Liver biopsy allows assessment of PBC severity, is decisive for the diagnosis in patients without AMA detected, however it is not necessary for the diagnosis [14, 22]. Histopathological evaluation is significant for the prognosis. Histopathological changes do not correlate significantly with AMA and ANA titers [9, 23].

Abdominal ultrasonography is useful to assess general state of the internal organs. Patients should have liver parameters assessed: ALP, aminotransferases, bilirubin and GGTP and bile acids every 3-6 months. Gastrofiberoscopy should be performed every 1-3 years, with densitometry (bone mineral density) every 2 to 4 years, and thyroid hormones every year [26]. To diagnose PBC at least two out of the following three criteria are necessary:
-elevated ALT, GGTP, bilirubin and IgM,
-antibodies AMA, against 2-oxy acid (M2) dehydrogenase complex, SMA, anti-thyroid and anti-nuclear,
-liver biopsy with typical histological picture.

Only in advanced stages jaundice occurs, and autoantibodies AMA, ANA, SMA are detected. AMA anti-M2, M4, M8 and M9 antibodies are most important in the diagnosis [33].

Treatment

There is no one effective treatment. The recommended medication is ursodeoxycholic acid (UDCA) preparations that exhibit cholestatic activity, and help reduce the amount of bile and improve blood parameters. In Europe and in the United States, an optimal dose of 13-15 mg / kg bm/24h is recommended. Survival in patients treated was better compared to those left untreated [11, 17]. UDCA treatment aims to protect damaged cholangiocytes from toxic bile acids, it also stimulates impaired secretion in the hepatic cells, counteracts hepatocytes and cholangiocytes apoptosis induced by bile acids [14]. Moreover, studies confirmed reduction of serum bilirubin, ALP, GGTP, cholesterol and IgM. The use of UDCA decreases the number of liver transplants, however, there is no direct influence on survival [14, 26, 43].

Cholestyramine is used to alleviate pruritus due to elevated levels of bile acids. In addition, cholestyramine eliminates them from the intestine without allowing them to re-enter the bloodstream. Alternative medications are stanozolol, naltrexone and rifampin. Others include betamethasone, prednisolone, azathioprine, phenobarbital, diazepam, hydroxazine, antihistamines, naloxone, ondansetron. Some of them cause drowsiness and therefore are unacceptable.

If the treatment of pruritus is unsuccessful, other methods such as plasmapheresis 2-3 times a month is used to reduce the symptoms to an acceptable level [36]. Persistent pruritus, unresponsive to pharmacological treatment and preventing from daily functioning, is an indication for liver transplantation. Drugs used to reduce skin pruritus and gastric acidity may interact with UDCA, so they should be given every 2-4 hours after UDCA administration.

In addition, the efficacy of such medicines as chlorambucil, penicillamine, cyclosporin, glucocorticosteroids, azathioprine, mycophenolate mofetil, thalidomide, methotrexate, malothilate, colchicine, and silymarin was tested. They have not been shown to inhibit the progression of the disease or longer survival in patients [26,39].

Glycocorticosteroids (prednisolone, budesonide) improve biochemical and histological parameters but reduce bone mineral density. The EASL recommendation states that the beneficial effect of steroids is only in the early stages of the disease and should not be used in patients with cirrhosis [28].

The beneficial effect of bezafibrate in reducing ALP, as well as positive effect of fibrates on the treatment of chronic fatigue and itching, in the reduction of ALP, GGT, ALT AST, and

IgM values have been reported [20, 38]. Reports from the years 2013-2014 on the combination of UDCA with bezafibrate indicate beneficial effect of this combination on many parameters, such as decreased ALP, LDL, cholesterol, triglycerides and other biochemical markers, and reduction of the severity of itching. Obeticholic acid is used in the treatment is important for intestinal-hepatic bile acid transport [10, 36]. The studies also demonstrated beneficial effect of rituximab, a monoclonal anti-CD20 antibody if there was no response to UDCA monotherapy. The mechanism consists in the reduction of B cell count, increase in Treg lymphocyte count and influence on cytokine production [13, 20, 41].

In patients with PBC hypolipemic drugs have not produced a definitive answer. As a side effect statins triggered acute cholestatic hepatitis. Those drugs are excreted with the bile, so it is difficult to reach therapeutic blood concentration [10, 28]. Some studies indicate that Provigil can work effectively without damaging the liver. However, the drug is not patent-protected, and therefore is very expensive.

Liver transplant is considered in patients with advanced disease. The risk of recurrence in the transplanted organ is 18% to 25-30% and increases with the passage of time from transplantation [3, 7, 11, 18, 42]. Management of PBC also includes recommendation to completely eliminate alcohol consumption and hepatotoxic medication.

There is no potent cure for PBC. However, it is possible to slow the disease progression so that patients can live normally and enjoy good quality of life. In PBC lipid vitamins A, D, E, K are hardly absorbed. Therefore when bilirubin is elevated, adequate supplementation is recommended.

Prognosis

Prognosis is good when the disease is diagnosed in stage I or II on histological examination or in patients without clinical symptoms. In other cases the prognosis is worse, the average survival time is about 12 years.

Concomitant cirrhosis of the liver and pregnancy is extremely rare, since endocrine and metabolic disorders often cause gynecological problems, including difficulty conceiving, spontaneous abortions, premature deliveries and stillbirths. If a pregnant woman has alcoholic cirrhosis of the liver, the prognosis for the fetus is more serious and the baby may be born with the symptoms of fetal alcohol syndrome.

Pregnant woman suffering from cirrhosis requires strict regimen to monitor liver function and must follow proper diet. Excessive effort should be avoided during labor and

therefore it is recommended to terminate pregnancy by caesarean section or forceps or vacuum delivery.

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