Abstract

A 54-year-old Japanese woman with primary biliary cirrhosis (PBC) was admitted to our hospital due to hepatic coma and refractory pleural effusion. The physical examination revealed clubbed fingers and collateral veins. The patient had an increased alveolar-arterial oxygen gas tension difference. The levels of anti-mitochondrial antibody (AMA) and AMA M2 was 80 times normal. A technetium 99m-labeled macro-aggregated human albumin scintigram showed uptake in the spleen and the kidneys. A diagnosis of hepatopulmonary syndrome (HPS) was made. HPS may be overlooked because of the lack of symptoms. We conclude that closer attention should be paid to the occurrence of HPS.

Key words: HPS, PBC, contrast-echocardiography, orthoadoxia

Introduction

Liver dysfunction causes various disorders due to imbalance between vasoconstriction factors and vasodilatation factors such as NO, endothelin and others. Overproduction of vasoconstriction factors leads to portopulmonary hypertension (PPH), while increased levels of vasodilation factors leads to hepatopulmonary syndrome (HPS). In 1977, Kennedy and Knudson (1) proposed the term of HPS, being defined as a triad consisting of liver disease, an increased alveolar-arterial oxygen gas tension difference while breathing normal air, and evidence of intrapulmonary vascular dilation. Lymphocyte intestinal pneumonitis is a well-known complication of PBC, but alveolar diffusion capacity is also at times impaired in patients with PBC. Here, we report a case of primary biliary cirrhosis presenting as HPS.

Case Report

In 2000, a 54-year-old Japanese woman visited her local hospital due to pruritus. The laboratory data showed liver abnormalities: aspartate aminotransferase (AST) 94 IU/l; alanine aminotransferase (ALT) 62 IU/l; alkaline phosphatase (ALP) 594 IU/l; gamma-glutamyl transpeptidase (GGT) 195 IU/l (normal <71); anti-nuclear antibody (ANA) 2,560 times; and AMA 970 times. The patient had been treated with ursodeoxycholic acid (UDCA) at a dose of 600 mg/day, and required repeated hospitalization because of intractable ascites and pleural effusion since 2000. In January 2003, she was admitted to our hospital due to general fatigue and hepatic encephalopathy.

On physical examination, the patient’s skin had slight jaundice, marked spider nevi, and collateral veins on the abdomen. Her oral cavity was dry and she had considerable tooth decay. The vesicular sound of the right lung was reduced due to pleural effusion. Routine laboratory data were as follows: white blood cell count 7,700/µl; red blood cell count 304×10⁴/µl; hemoglobin level 8.7 g/dl; platelet count 21.6×10⁴/µl; total protein 6.4 g/dl; albumin 2.9 g/dl; total bilirubin 2.1 mg/dl; AST 24 IU/l; ALT 17 IU/l; lactic dehydrogenase (LDH) 252 IU/l; ALP 394 IU/l; GGT 37 IU/l; cholinesterase 40 IU/l; total cholesterol 122 mg/dl; and ammonia 151 µg/dl. The serum was negative for hepatitis B surface antigen (HBsAg) and hepatitis C antibody. Additional studies revealed a prothrombin time of 52.7%; a plasma retention rate of indocyanine green of 57%; IgG 1,470 mg/dl; IgA 436 mg/dl; IgM 192 mg/ml; ANA 160 times (speckled type and cytoplasmic type); AMA 80 times; AMA M2 80 times; and the patient was negative for anticientromere antibody. Based on these data, the patient was diagnosed as PBC. A Schirmer test gave results of 1 mm/5 min and 3 mm/5 min for the right and left eye. Keratoconjunctival inflammation was also noted.
tivitis sicca with a complication of Sjögren’s syndrome was present.

Arterial blood gas analysis in the supine position showed the following results: pH 7.474; arterial carbon dioxide pressure (PaCO₂) 44 mmHg; arterial oxygen pressure (PaO₂) 56.9 mmHg; arterial oxygen saturation (SaO₂) 88.3%; and alveolar-arterial oxygen pressure difference 43.7 mmHg. A decrease in PaO₂ of 7 mmHg was observed in the standing position. Electrocardiography, plain chest radiography, echocardiography, and enhanced computed tomography showed no significant findings. A respiratory function test showed the following results: forced expiratory volume in 1 second (FEV₁) 74.81%; %FEV₁ 94.9%; vital capacity (VC) 2.58 l; %VC 97.0%; and DLCO 6.55 ml/min/mmHg. Pulmonary perfusion imaging using Tc-99m MAA showed uptake to the spleen and the kidneys, in addition to uptake to the lung, suggesting an intrapulmonary shunt (Fig. 1). Pulmonary arteriography revealed no abnormal findings (Fig. 2), but contrast-enhanced echocardiography suggested delayed opacification in the left chamber. The patient was diagnosed with HPS, and home oxygen therapy for hypoxemia was initiated.

Discussion

In the literature, cases of HPS have been reported in about 4–29% of liver transplant candidates who have abnormal arterial oxygenation (2, 3). The first report of HPS was in 1987.

PBC is associated with various respiratory disorders. Lymphocyte interstitial pneumonitis is a well-known, but rare complication of PBC patients with Sjögren’s syndrome and CREST syndrome (4). Esophagogastric varices (EGV) usually reflect the existence of a severe liver disease, such as symptomatic PBC. Recently, Takeshita et al (5) reported that EGV is a common complication in asymptomatic PBC patients, and suggested that it may be an important factor in progression to symptomatic PBC. Similarly, abnormal diffuse capacity is frequently observed in patients with PBC in the absence of clinical manifestations of the disease (6). Some reports have suggested that reduced diffusion capacity is present in 36–39% of PBC patients (7, 8). The present patient may have had chronic respiratory disorders for years, and had no symptoms.

The present patient showed no clinical symptoms, but had severe hypoxemia, intrapulmonary shunt and clubbed fingers. Clubbed fingers are often observed as a complication of chronic respiratory disease, and these findings may be useful for screening for HPS in liver disease patients without dyspnea.

Hypotheses of the pathogenesis of HPS invoke an imbalance between vasoconstriction and vasodilatation. The former are endothelin-1, serotonin, and angiotensin 1, the latter are nitric oxide (NO), glucagon, histamine and prostacyclin. This may be partly associated with liver injury causing a disorder in the production and metabolism of these factors (9). However, it may also be related to the presence of portal hypertension, to the hyperdynamic circulation, and to the degree of liver injury. Reports of HPS in patients with prehepatic portal hypertension and the presence of inferior vena cava obstruction without cirrhosis suggest that the presence of severe hepatic dysfunction is not a prerequisite for the development of intrapulmonary vasodilation. In addition, although most patients who were diagnosed with HPS subsequently developed portal decompression, the recognition that only a subset of all patients with cirrhosis and hyperdynamic circulation develop HPS suggests that other factors contribute to the onset of intrapulmonary vasodilation.

When vascular abnormalities appear to be predominant in the middle to lower lung fields, patients can experience

Figure 1. A Tc-99m MAA scintigram showed uptake over the bilateral lung fields, the spleen, and the bilateral kidneys.

Figure 2. Pulmonary arteriography revealed no dilation or shunt of the pulmonary artery.
worsening hypoxemia when moving from the supine to the standing position. This condition is called orthodeoxia, and arises because gravitational effects in the standing position result in more intrapulmonary blood flow to the lower lung fields.

Contrast-enhanced echocardiography and dynamic pulmonary perfusion imaging using Tc-99m MAA are useful for the diagnosis of pulmonary venous dilatation. MAA or micro-bubbles made from indocyanine green can be detected in the left chamber through the dilated pulmonary vessels. In the present patient dynamic pulmonary perfusion imaging using Tc-99m MAA revealed significant uptake in the spleen and the kidneys. Contrast enhanced echocardiography is able to detect delayed micro-bubble opacification in the left ventricle 4 beats after detection of micro-bubbles in the right ventricle. In our patient the results from these examinations suggested dilation of the pulmonary capillary. Two types of angiographic findings have been reported (10). The first of these (type 1) includes normal pulmonary vessels or a diffuse “spongy” appearance of the pulmonary vessels during the arterial phase, while the second (type 2) is characterized by small discrete arteriovenous contacts. HPS patients often have a normal angiogram, regardless of severe hypoxia. However, pulmonary angiography may be an invasive and insensitive diagnostic modality for detecting intrapulmonary vasodilation in HPS, and the embolization of arteriovenous dilation is a therapeutic option for type 2 patients who are usually poor responders to 100% oxygen (11, 12).

Various therapeutic options, such as treatment with a somatostatin analogue (4), N(G)-nitro-L-arginine methyl ester (L-NAME) (13), aspirin (14), and other drugs have been tried for HPS patients, but no clear therapeutic effect of these drugs has been established. Hence, liver transplantation is the most effective current therapy for patients with mild to moderate HPS. Recently, transjugular intrahepatic porto-systemic shunting (TIPS) is reported as a useful therapeutic option of HPS (15).

The prognosis for HPS patients who do not undergo liver transplantation is thought to be poor; 50% mortality is expected in 2 or 3 years. Liver transplantation increases the probability of long-term survival, but postoperative complications following liver transplantation are an important problem. Severe hypoxemia (PaO₂ <50 mmHg) and Tc-99m MAA uptake of over 20% are predictive of a higher postoperative risk (16, 17), and these data will be considered for our patient, who may be a candidate for a future liver transplantation.

In conclusion, the present patient was diagnosed with HPS as a complication of PBC. However, since HPS is often asymptomatic, early diagnosis is necessary for determination of appropriate therapeutic options, including liver transplantation. In cases where patients with chronic liver disease also have clubbed fingers, the possibility of HPS complication should particularly be considered.

References