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Chronic Hypoxemia Inadvanced Liver Diseases: Hepatopulmonary Syndrome

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ABSTRACT

Hepatopulmonary syndrome (HPS) is one of the pulmonary complications from liver disease with or without cirrhosis.The prevalence of HPS varies from 4% to 47% in patients with liver cirrhosis.We present a case of chronic progressive dyspnea in an 18-year-old man with a history of chronic liver disease.Diagnosing can be particularly challenging, especially in cases involving prolonged dyspnea and comorbidities. Following thorough investigations, the patient's condition was attributed to a rarer condition: severe hepatopulmonary syndrome.Contrast-enhanced echocardiography with agitated saline is the gold standard for diagnosing pulmonary vascular dilatation which is the hallmark of HPS. There is currently no medical therapy approved for HPS. Oxygen therapy is recommended for patients with severe hypoxemia.

KEYWORDS: hepatopulmonary syndrome, chronic dyspnea, chronic hypoxemia, chronic liver disease

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INTRODUCTION

Hepatopulmonary syndrome (HPS) is one of the pulmonary complications from liver disease with or without cirrhosis. HPS characterizes as a series of poor arterial oxygenation and intrapulmonary dilatation resulting from chronic liver disease. This dilatation of the pulmonary artery contributes to impaired gas exchange, ventilation-perfusion mismatch, diffusion limitation, and shunting.The prevalence of HPS varies from 10% to 30% inpatients with liver cirrhosis.[1]

The diagnostic criteria for HPS involve the presence of liver disease and/or portal hypertension, along with a PaO2 < 80 mmHg or an alveolar-arterial oxygen gradient (P(A-a)O2) of ≥ 15 mmHg (or > 20 mmHg in patients older than 65 years) while breathing ambient air. Additionally, documented intrapulmonary vascular dilatation should be confirmed through contrast-enhanced echocardiography or lung perfusion scanning using radioactive albumin.[2] Recently, HPS's only definitive treatment is liver transplantation which canmodifythe natural history of HPS and improve arterial hypoxemia. Pharmacological treatments did not show significant results in a clinic.[3] HPS prognosis was calculated 41% mortality over 2.5 to 5-year-period in one case study.[4]

We present a case of chronic progressive dyspnea in an 18-year-old man with a history of chronic liver disease and portal hypertension. The diagnosis can be challenging, however, after thorough investigations, it was determined to be associated with a rarer condition known as hepatopulmonary syndrome.

CASE REPORT

A-18-year-old man with a history of portal hypertension was admitted to our hospital for an upper endoscopy procedure. During the pre-procedure evaluation, it was revealed that he had hypoxemia.

The patient has been experiencing dyspnea for the past 7 years, originating in childhood. His primary symptom has been escalating dyspnea in the two months leading up to admission, particularly occurring after extended periods of walking or standing. The dyspnea was improved in the prone position. He once had an episode of syncope after strenuous activities such as swimming. At present, there was no fever, cough, wheezing, chest pain, orother respiratory symptoms.

The patient had a history of liver cirrhosis with portal hypertension. Hepatitis viral marker results were negative. He also had history of anemia and thrombocytopenia. The patient had done bone marrow puncture examination before which revealed bone marrow hypoplasia with maturation dysfunction and there was no dominant marker in leukemic phenotyping.

There is no similar history in the family. The patient was not married. He is a high school student without a history of

smoking, promiscuity, alcohol abuse, or intravenous drug abuse.

His vital signs remained within the normal range (blood pressure: 120/80 mmHg, respiratory rate: 20 breaths per minute, heart rate: 70 beats per minute, temperature: 36.2°C), but his oxygen saturation was notably low (70% on room air). Subsequently, he was given 10 liters per minute of oxygen via a non-rebreathing mask, resulting in an improvement of his oxygen saturation to 95%. In physical examination, the patient had yellowish eyes (icteric eyes). The chest inspection and auscultation were normal, with no sign of rhonchi, wheezing, and abnormal heart sounds. In the upper abdomen, the spleen was palpated in the 4thSchuffner. Clubbing fingers were present.

Blood examination showed leukopenia (2.34 x 10^3/µL), thrombocytopenia (50 x 10^3/µL), and prolonged aPTT (49.1 s) **(Table 1)**. There were also sign of liver dysfunction in the form of elevated liver enzyme (SGOT = 59 U/L), hypoalbuminemia (2.1 g/dL) and elvatedbilirubin total, direct, indirect : 3.38 mg/dL, 1.57 mg/dL, 2.26 mg/dL respectively. Arterial blood gas was done under oxygen supplementation of 10 liter per minute which showed respiratory alkalosis (pH 7.582, pCO2 20.3 mmHg) with PO_2 210 mmHg and oxygen saturation 99.8%.

Table 1. Laboratory results

Lab	Results	Reference
Hemoglobin	14.8	13.0-17.0 g/dL
Hematocrit	42.8	40.0-50.0%
Leucocyte	2.34	4.00-10.00 x 10^3/µL
Thrombocyte	50	150 – 410 x 10^3/µL
PT	14.2 (11.5)	9.9-12.6 s
aPTT	49.1 (32.9)	31-47 s
SGOT	59	5-34 U/L
SGPT	22	9-68.8 U/L
Albumin	2.1	3.5-5.2 g/dL
Total Bilirubin	3.83	0.2-1.2 mg/dL
Direct Bilirubin	1.57	0.0-0.5 mg/dL
Indirect Bilirubin	2.26	0.2-0.8 mg/dL
Ureum	6.8	18-45 mg/dL
Creatinine	0.4	0.73-1.18mg/dL
pH	7.582	7.35-7.45
pCO_2	20.3	35-45 mmHg
pO_2	210	75-100 mmHg
HCO_3^-	19.3	21-25 mmol/L
Base Excess	-0.3	-2.5 - + 2.5
O_2 Saturation	99.8%	95-98%

Plain chest radiography showed no sign of abnormality in lung and heart **(Figure 1).**Splenomegaly was evident along with dilation of the portal, hepatic, and splenic veins, as observed in the contrast-enhanced abdominal CT scan**(Figure 2)**. Tortuous branches of the splenic vein were noted in the hilus, accompanied by tortuous veins paraesophageal and peri-gastric in location. These results indicate portal hypertension. The hypodense lesion in splenic veins with hyperdense figure intralesional shows thrombus in a splenic vein or an infarct in the mesenteric vein. The dilatation and filling defect in the superior mesenteric vein indicate thrombus

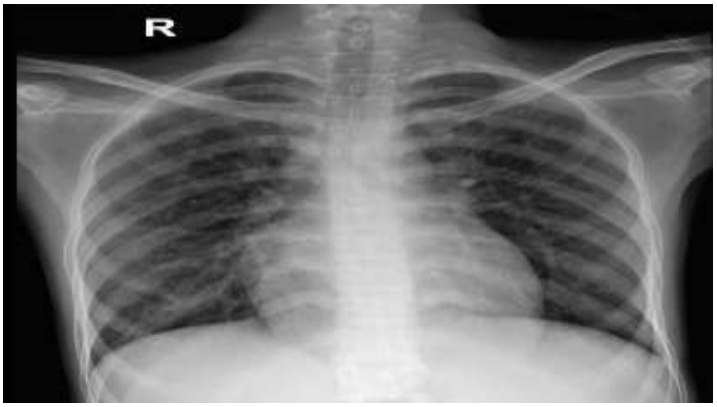

Figure 1. Plain chest radiograph showing no abnormality

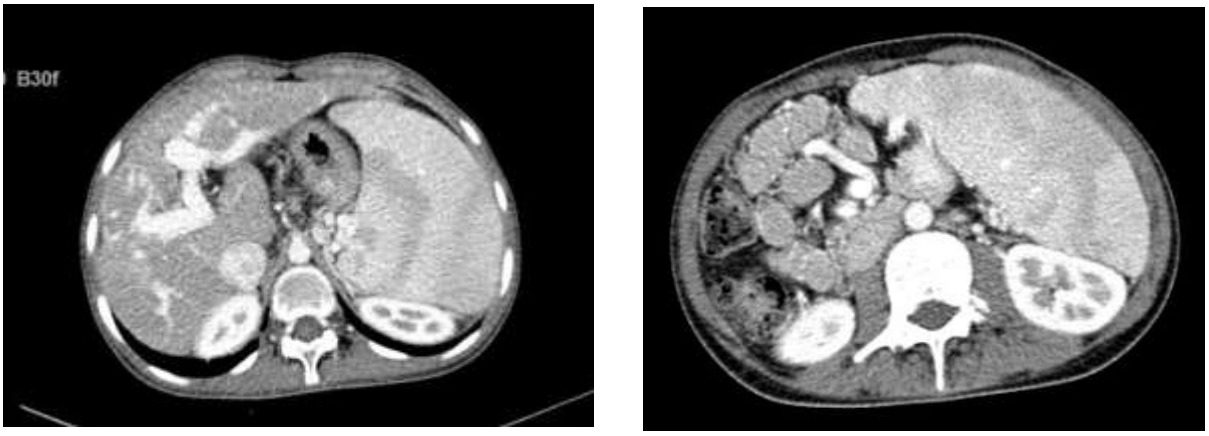

Figure 2. Contrast-enhanced abdominal CT scan showing sign of cirrhosis, portal hypertension, and thrombusin splenic vein

The finding of an abdominal thrombus led us to look for another thrombus in the lung using a CT thorax angiography **(Figure 3)**. There were no signs of thromboembolic in pulmonary artery and veins, and intrathoracic vascular. There was also non-significant subpleural nodule and ground-glass opacity (GGO) in both lungs.

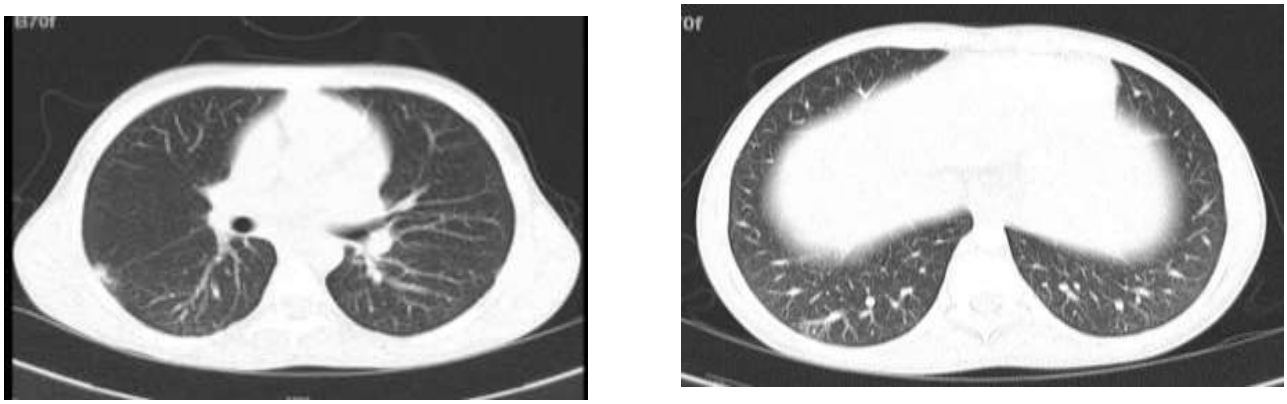

Figure 3. CT thorax angiography showing non-significant subpleural nodule and GGO

Cardiology examination was done to find the cause of hypoxemia. The patient undergo transthoracic echocardiography (TTE) with a bubble test was conducted. During the saline contrast echocardiography, bubbles displaying complete opacity were observed; however, they did not traverse from the right atrium (RA) to the left atrium (LA). Between cycles 4 and 6, bubbles originating from the left pulmonary vein entered and filled the left atrium and left ventricle. This observation indicated a positive bubble test, revealing an intrapulmonary shunt devoid of any cardiac shunting, which strongly suggests the presence of a hepatopulmonary shunt.

DISCUSSION

Hepatopulmonary syndrome is defined as the triad of a defect in arterial oxygenation, vasodilation of intrapulmonary arteries, and the presence of liver disease. Cirrhosis may or may not be present with HPS, but 4-32% of cirrhotic patients develop HPS as one of the complications.[5]

The primary factor behind HPS is the dilation of intrapulmonary arteries, which leads to an imbalance in ventilation-perfusion, constriction of oxygen diffusion, and the formation of a shunt in arteriovenous connections. This leads to compromised gas exchange. Our current understanding of the fundamental mechanisms behind HPS is largely derived from animal models used in experimental studies. The primary pathophysiological characteristics of experimentally induced HPS caused by common bile duct ligation (CBDL) cirrhosis involve changes in the pulmonary microvasculatureencompass vasodilation, accumulation of monocytes within blood vessels, and the initiation of new blood vessel formation (angiogenesis).[3]

Limited information is available regarding the pathogenesis of HPS and how the mechanisms identified in the development of experimental HPS contribute to human disease. Three pathways leading to the occurrence of low oxygen levels (hypoxemia) in human HPS have been proposed: a mismatch between ventilation and perfusion (possibly due to increased blood flow in capillaries, potentially caused by vasodilation), a mismatch between diffusion and perfusion (resulting in the hindered movement of oxygen from air sacs to blood vessels, possibly due to vasodilation or angiogenesis), and structural arteriovenous shunting (potentially arising from vasodilation or angiogenesis). Pulmonary vascular dilatation has been linked to an overproduction of vasodilators, notably nitric oxide

(NO).Genetic variations also has been linked to the growth and formation of blood vessels andto be a contributing factor to the vulnerability of HPS.[3] Lastly, the questions of whether monocytes attached themselves to the pulmonary vasculature in human HPS and if inhibition of tumor necrosis factor (TNF) or the movement of bacteria through the gastrointestinal tract can reduce severity of HPS is still unknown.[7]

HPS is categorized into two types depending on the site of expanded pulmonary vessels. Type I HPS is when dilation occurs in the pre-capillary levels near the gas exchange units, and Type II HPS, which results in arteriovenous shunting situated distantly from the exchange units. These distinctions serve as valuable indicators for assessing the need for oxygen supplementation in HPS patients (oxygen supplementation proves beneficial solely in increaing PaO2 levels for Type I HPS).[8]

HPS is evident not only in varying degrees of cirrhotic conditions but also in non-cirrhotic individuals, as observed in cases like portal vein thrombosis, nodular regenerative hyperplasia, congenital hepatic syndromes, and Budd-Chiari syndrome.[9]The occurrence of HPS is not solely linked to chronic liver dysfunction; there have been documented cases of transient HPS, even in cases of acute Hepatitis A.[10]In our case, there was underlying liver cirrhosis with symptoms of icteric and splenomegaly (4thSchuffner). The lab results also showed thrombocytopenia, elevated transaminase enzyme and bilirubin, hypoalbuminemia, and elongation of APTT up to 1.5 times. The abdominal CT scan revealed a reduction in liver size. Additionally, there was enlargement observed in the portal vein, hepatic vein, and splenic vein, accompanied by an enlarged spleen. Furthermore, thrombus was found within the lumen of the splenic vein. These observations collectively pointed towards the presence of cirrhosis accompanied by portal hypertension.

The signs and symptoms of HPS are similar to chronic liver disease with insidious and worsening in exertion dyspnea. However, in the early stages, most patients are symptomatic. In physical examination, individuals could present signs such as cyanosis, digital clubbing, spider naevi, diffused telangiectasia, paroxysmal nocturnal dyspnea (exacerbation of shortness of breath upon transitioning from supine to upright position), and orthodexia (a decrease of PaO2 by more than 5% or 4 mmHg upon changing from supine to upright position). In our specific case, the breathing difficulties had been experienced over the course of the past 7 years, and these symptoms had recently shown a progression. The dyspnea intensified when shifting from a lying position to sitting or engaging in excessive physical activity. During the physical examination, we identified finger clubbing. The oxygen saturation level was measured at 70% in room air and increased to 95% when utilizing a non-rebreathing mask at a flow rate of 10 lpm. Blood gas analysis showed respiratory alkalosis with pH 7.58, pCO2 20.3 mmHg, pO2 210 mmHg, $HCO3^-$ 19 mEq/L,and SpO2 99% (with 10 litter oxygen supplementation).Chest plain radiograph and chest CT angiography revealed no significant result.

HPS diagnosis criteria are the presence of liver disease and/or portal hypertension, and PaO2 <80mmHg or alveolar-arterial oxygen gradient (P(A-a)O2) ≥ 15mmHg (or >20mmHg in > 65 years old patient) while breathing ambient air and documented intrapulmonary vascular dilatation by contrast-enhanced echocardiography or lung perfusion scanning with radioactive albumin.[2]During this assessment, saline is agitated to produce microbubbles with a diameter >10 μm. These microbubbles are then injected into a peripheral vein. Under normal conditions, these microbubbles do not traverse the pulmonary capillary bed, which has a diameter of less than 8-15 μm. Consequently, they remain detectable within the right heart. The presence of intrapulmonary vessel dilatations or shunts is suggested when microbubbles are detected in the left heart after a lapse of three or more cardiac cycles from their initial observation in the right heart.[6]In our case, saline contrast echocardiographshowed bubbles from the left pulmonary vein fulfilling LA and LVbetween 4-6 cycles, good right ventricle function, and low probability of pulmonary hypertension. These findings suggested hepatopulmonary syndrome.

HPS severity is determined using PaO2 levels: (1) Mild: PaO2 ≥ 80 mmHg with A-aO2 ≥ 15 mm Hg while breathing room air;(2) Moderate: PaO2 ≥ 60 mmHg to <80 mmHg with A-aO2 ≥ 15 mmHg while breathing room air; (3) Severe: PaO2 ≥ 50 mmHg to <60 mmHg with A-aO2 ≥ 15 mmHg while breathing room air, and (4) Very severe: PaO2 <50 mmHg with A-aO2 ≥ 15 mmHg while breathing room air Or PaO2 <300 mmHg while breathing 100% oxygen.[8] In this case, patient's oxygen saturation was 70% in room air. If correlated with the oxyhemoglobin dissociation curve the PaO2 is around 40mmHg. The patient is categorizedwith severe HPS.

HPS management and therapy include oxygen supplementation especially for severe hypoxemia (PaO2<60 mmHg). Liver transplantation is the only definitive treatment that provides survival advantages for patients. Improvement in hypoxemia is noticeable within 6 to 12 months post-transplantation. Certain medical interventions,such as octreotide norfloxacin, and methylene blue have shown some efficacy in enhancing symptoms for a subset of HPS patients. Nevertheless, research has not demonstrated significant symptom improvement in a substantial number of patients.[2] The utilization of a transjugular intrahepatic portosystemic shunt (TIPS) is considered as an alternate treatment option, offering diverse results. Another therapy uses in patients with a large shunt is pulmonary arterial coil embolization in selected cases.[8] In our case, no particular medical treatment was administered for managing HPS, given that the existing evidence supports liver transplantation as the definitive therapy capable of enhancing the long-term survival of HPS patients. The patient and their family were educated on the

necessity of long-term oxygen supplementation for home care. Preparations were made for the patient to undergo liver transplantation through outpatient treatment.

In one case study, the prognosis for HPS indicated a 41% mortality rate over a span of 2.5 to 5 years. Among HPS patients, there was a recorded survival rate of 63% within an average period of 2.5 years post-diagnosis.[4]Higher mortality was found in HPS patients compared to cirrhotic patients in 5-year survival. Mortality is mostly related to liver failure rather than respiratory failure.[1]

CONCLUSION

Hepatopulmonary syndrome (HPS) is a serious vascular complication of liver disease that occurs in patients with cirrhosis. Chronic liver diseases patients with sign of chronic hypoxemia (clubbing finger) and orthodexia, in the absence of riskof intrinsic cardiopulmonary disease, should be evaluated for HPS.Contrast-enhanced echocardiography with agitated saline is the gold standard for diagnosing pulmonary vascular dilatation which is the hallmark of HPS. There is currently no medical therapy approved for HPS. Oxygen therapy is recommended for patients with severe hypoxemia. Liver transplantation is the definitive therapy that capable of enhancing the long-term survival of HPS patients.

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