American Journal of Case Reports

ISSN 1941-5923
© Am J Case Rep, 2015; 16: 751-755
DOI: 10.12659/AJCR.895151

Received: 2015.06.28
Accepted: 2015.07.14
Published: 2015.10.22

A 45-Year-Old Undiagnosed Cirrhotic Patient with Hepatopulmonary Syndrome as First Presentation: A Case Report

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Male, 45
Final Diagnosis: Hepatopulmonary syndrome
Symptoms: Dyspnea • edema of feet
Medication: —
Clinical Procedure: None
Specialty: Gastroenterology and Hepatology

Objective: Unusual clinical course

Background: Hepatopulmonary syndrome (HPS) is a pulmonary complication characterized by a triad of chronic liver disease, arterial hypoxemia, and pulmonary vascular dilations. Agitated saline contrast echocardiography is a simple inexpensive criterion standard procedure for confirming the diagnosis of HPS.

Case Report: Here, we discuss a case of a 45-year-old male Indian patient with no medical history who presented to our hospital with exertional dyspnea, hypoxia, and classical signs of HPS. A diagnosis of cirrhosis was made on the basis of history, liver enzymes, and ultrasound, while HPS was diagnosed using transthoracic echocardiography with agitated saline.

Conclusions: HPS, although a complication of cirrhosis, can be the initial presentation in undiagnosed cirrhotic patients. Thus, it is important to include HPS in differentials when dealing with cases of progressive dyspnea. Also, the possibility of a liver disease etiology should be explored in patients with unexplained hypoxemia.

MeSH Keywords: Dyspnea • Hepatopulmonary Syndrome • Liver Cirrhosis

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/895151

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Background

Hepatopulmonary syndrome (HPS) is a pulmonary complication in the background of a liver disease and is mostly seen in a patient with end-stage liver disease. There are dilations in the pulmonary microvasculature, which causes anomaly in the arterial oxygenation. The dilations in pulmonary microvasculature are the hallmark of HPS. The incidence of HPS in cirrhotic patients is 11.1% [1]. The pathogenesis has not been defined. It presents with a combination of hepatic and pulmonary signs and symptoms like jaundice, nail changes like clubbing, palmer erythema, asterixis, spider angiomata, testicular atrophy, splenomegaly, large or small liver, gynecomastia, caput medusae, fatigue, and anorexia. The specific symptoms for HPS are hypoxemia and orthodeoxia [2]. Contrast-enhanced echocardiography using agitated saline, ventilation-perfusion lung scan, and pulmonary arteriography are employed for its diagnosis. Its prognosis is particularly poor if it occurs in the presence of an end-stage liver disease, with an average survival of 11 months [3]. Liver transplantation is the only established effective treatment for HPS.

Case Report

A 45-year-old native Indian male with no past medical history of cirrhosis presented to our hospital with history of progressive dyspnea on exertion for 2 months. He also gave history of change in shape of nails, and edema of feet which he neglected since 5 years. Review of systems was otherwise negative. His past medical history was negative for cardiac and pulmonary disease. He was an alcoholic since age 15 years. He quit alcohol 2 years ago, and was a non-smoker.

The patient appeared dyspneic, in severe distress, with hypoxia. On examination, his vitals were within normal limits except for the respiratory rate of 36. He demonstrated central cyanosis, and icterus. On physical examination, grade III clubbing (Figure 1), edema of feet, sparse axillary hair, and gynecomastia was present. The abdomen was distended, nontender, with splenomegaly. Cardiovascular, respiratory, and neurologic examination revealed no abnormalities.

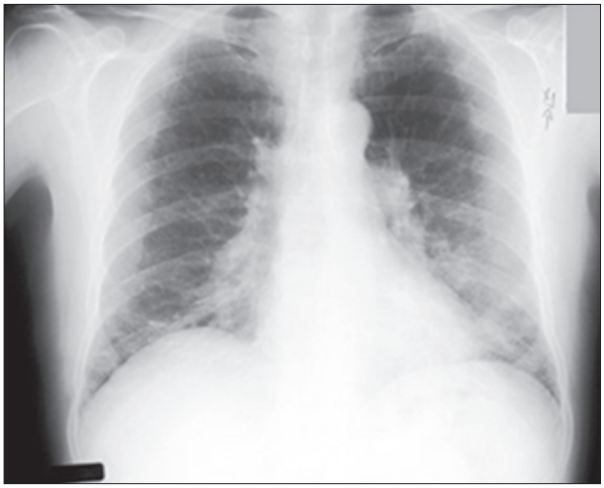

Figure 2. Chest X- ray showing reticulo-nodular pattern in bilateral lower zones.

On arterial blood gas (ABG), orthodeoxia was seen. The supine Po2 was 76 mm Hg, while standing Po2 was 57 mm Hg. With oxygen supplementation, the observed Po2 was 85 mm Hg in supine position and standing Po2 was 57 mm Hg. The CBC results showed high hemoglobin of 16 g/dL, low platelet count of 98 000/mcL, and normal leucocyte count. Liver function test showed elevated bilirubin of 3.8 mg/dL with increased indirect bilirubin of 3.2 mg/dL, ALT 80 units, AST 140 units, and decreased albumin of 2.8 g/dL. The INR, BUN, creatinine, D-dimer, and electrolytes were within normal limits. He screened negative for hepatitis A, B, and C.

The upper GI endoscopy revealed esophageal varices. The abdominal USG revealed a small shrunken liver with irregular margins. Cirrhosis of liver with early changes of portal

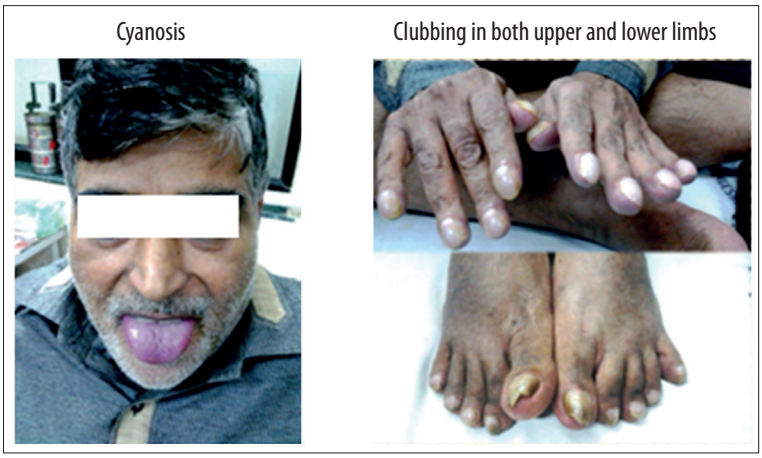

Figure 1. Severe central cyanosis and clubbing seen in the patient.

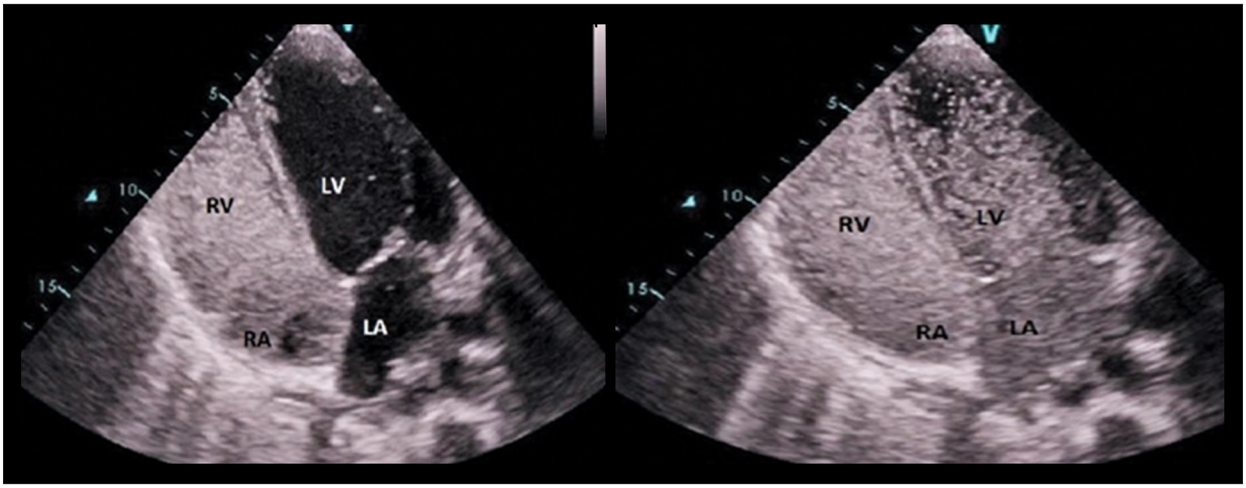

Figure 3. Agitated saline echocardiography (Bubble study) elucidating the microbubbles and delayed opacification of left atrium.

hypertension, and splenomegaly with dilated splenic vein was also observed. Chest X-ray showed reticulo-nodular pattern in lower zones bilaterally (Figure 2). The ECG revealed no abnormalities. A high-resolution CT of the thorax was done to exclude pulmonary embolism; it revealed abnormally profuse, dilated terminal pulmonary arterial branches, giving 'spider nevi appearance' seen in the right upper lobe, right lower lobe, left upper lobe, and left lower lobe. We also noted multiple enlarged venous channels communicating terminal end of splenic vein with left renal vein, and signs of collaterals along the porto-systemic anastomosis.

An agitated saline transthoracic contrast echocardiogram (bubble study) was done. Microbubbles were initially observed in the right ventricle. They were observed in the left ventricle after 7 cardiac cycles. The bubble study confirmed the diagnosis of HPS (Figure 3). A CT pulmonary angiography confirmed the diagnosis of HPS via demonstration of early filling of pulmonary veins more on left side with contrast opacification of left atrium in early phase. Based on these results and history findings, a diagnosis of HPS was made.

Discussion

HPS occurs in one-third of patients with decompensated cirrhosis [4], and is defined by perturbed gas exchanges, arterial hypoxemia, and vasodilatation in the lungs in the absence of primary cardiopulmonary disease [5]. In HPS, when the person changes his position from supine to upright, there is increase in the blood flow to lower zones of the lungs. As there are abnormalities in the vasculature of lower zones of the lungs in HPS, hypoxemia is induced. Platypnea and orthodeoxia are the characteristic features of HPS [2,6]. This leads to the patient presenting with cyanosis (mostly central), and there may be clubbing, which results from formation of microscopic intrapulmonary arterio-venous dilatation in patients with liver failure. In the present case, all the characteristic features of hepatopulmonary syndrome, like platypnea and orthodeoxia, were present. He also presented with the typical cirrhotic features, like gynecomastia, jaundice, cyanosis, and clubbing, which aided in establishing the possible etiology of HPS. Additionally, the labs supported the diagnosis. The mechanism of HPS is unknown, but the most common theory proposed is based on imbalance between vasodilators and vasoconstrictors with domination of vasodilators, like endothelin 1, nitrous oxide, prostaglandins, serotonin, glucagon, and interleukin-1 and 6 [7,8]. In HPS, 2 types of intrapulmonary vascular dilations (IPVD) are seen. Type 1 IPVD appears as diffuse pulmonary vascular dilations on angiography. They are more common than Type 2 IPVD, and are located close to normal gas exchange units of lungs. They have a good response to 100% oxygen treatment. Type 2 IPVD appears as distinct localized dilations with poor response to 100% oxygen therapy because true anatomic shunting is present. A variety of imaging techniques are employed for diagnosis of HPS. The simplest and most economical screening test is to measure the difference in oxygen saturation by pulse oximetry between standing and sitting position. Studies claim pulse oximetry is one of the most sensitive (100%) and specific (88%) tests, especially with an oxygen saturation cutoff of <96% [9]. In the present case, we used it as a screening tool for diagnosis of HPS. When orthodeoxia was observed, we performed an abdominal USG to look for the liver morphology. A nuclear study with 99m technetium-labelled macro-aggregated albumin scan can be used to document IPVDs, but the disadvantage is that it cannot differentiate intra-cardiac shunt from intra-pulmonary shunt [10]; therefore, we did not include this study in the present case. This microbubble transthoracic echocardiography is the criterion standard test to diagnose IPVD. Trans-esophageal echocardiography is more sensitive [11] but is not practical because HPS patients have a high prevalence of esophageal varices, which

can lead to variceal bleeding during the procedure. Also the patient has to be sedated, and it is a costly procedure, so it is not preferred. The bubble study can differentiate between intra-cardiac and intra-pulmonary shunting [12]. The procedure involves administration of intravenous saline, which is shaken by hand to create microbubbles. The results are analyzed based on the number of cardiac cycles completed before the microbubbles appear in the left atrium. In normal healthy individuals the microbubbles get captured in pulmonary capillaries and do not appear in the heart because they are absorbed by the alveoli. In HPS the microbubbles appear in the left atrium, typically 1–3 cycles in intra-cardiac shunt and 4–6 in intra-pulmonary shunt. Invasive procedure like pulmonary angiography can be used when the possibility of large arteriovenous shunts is high. It also differentiates between Type 1 and Type 2 IPVDs. CT chest can be used to reveal evidence of IPVD, as we found in our case. It also ruled out the possibility of pulmonary embolism. To confirm the HPS, we used the criterion standard bubble study, which revealed intrapulmonary shunts.

The current best recommended treatment for HPS is liver transplantation. It has revolutionized the treatment of HPS, with improvement or complete resolution in hypoxia in 85% of cases within 1 year. The drawback of liver transplantation is the cost of operation and waiting time for the organ transplant. Additionally, the 1-year survival rate in HPS cases undergoing a transplant is 71%, indicating high mortality [13,14]. Recommended supportive treatment includes oxygen supplementation with the aim to maintain a PaO2 >60 mm Hg. Supportive treatment includes drugs like almitrine and methylene blue [15], which increase pulmonary vascular resistance and pulmonary arterial pressure. It was found in various studies that in HPS patients, regular intake of garlic powder capsules can improve arterial oxygenation [16,17]. TIPS may be used in some cases [18]. Our patient had most of the signs and symptoms of cirrhosis, and HPS were found. After the prompt diagnosis with the bubble study and other lab investigations, we counseled this patient for liver transplant. The patient preferred supportive oxygen therapy due to expense issues and is currently on methylene blue and garlic powder supplementation, propranolol, and spironolactone. He has mild dyspnea. During his last check up on June 2015, the ALT was 70 units and AST was 84 units. His bilirubin has decreased to 2.8 mg/dL, while the albumin is 3.1 g/dL. His pulse oximetry parameters and platelet count did not reveal any change.

Conclusions

Here, we presented an unusual case of a cirrhotic patient, without any documented history of cirrhosis, presenting with HPS as his first clinical presentation. Although HPS is a complication in cirrhosis, it can be the initial presentation in a few cases, as seen in our patient. Thus, HPS should be considered as a differential diagnosis in patients with unexplained hypoxemia. The patients should be promptly diagnosed with simple methods like ABG initially, and can be confirmed with the criterion standard bubble study. Also, the possibility of a liver disease etiology should be explored in patients with unexplained hypoxemia.

Acknowledgement

We are grateful to Dr. Tabitha Watts for finding out time to reply to our emails and for giving her precious and kind advice regarding the topic of our case report. We are grateful to Dr. Cedric Coleman whose expertise, understanding, and generous guidance and support me possible for us to work on topic that was of great interest to us. We are highly indebted and thoroughly grateful to Dr. Julie Taylor for her immense interest in our topic of research, for providing us with materials and links that I could not possibly have discovered by our own.

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