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Case Report

Hepatopulmonary Syndrome Masked by Chronic Obstructive Pulmonary Disease-A Case Report

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Abstract

Hepatopulmonary syndrome (HPS) is an uncommon complication of hepatic cirrhosis, which presents with dyspnea, platypnea and orthodeoxia. We present a case of 61-year-old cirrhotic male whose symptoms were masked by chronic obstructive pulmonary disease (COPD). During admission, he became hypoxic requiring supplemental oxygen. Chest X-ray showed interstitial prominence. Work up for pulmonary embolism including Doppler of the lower extremities and Ventilation-Perfusion was negative. Patient was observed to exhibit platypnea hence an arterial blood gas was obtained which showed alveolar-arterial (A-a) gradient of 68.5 mmHg. A transthoracic echocardiogram with agitated saline was positive for shunting confirming our suspicion of hepatopulmonary syndrome. HPS diagnosis is based on a triad criterion of portal hypertension (PH), pulmonary vascular dilatation demonstrated by echocardiography and a partial pressure of oxygen (PaO2) <80 mm Hg or A-a gradient ≥ 15 mmHg while on atmospheric air. The pathophysiology is not fully understood however, a proposed mechanism involves intestinal bacterial translocation, which stimulates macrophage and monocyte accumulation in the lungs. These macrophages release vasoactive substances in the lungs causing vasodilation. No effective medical therapy has been documented. For now, liver transplantation is the only established modality. Our case highlights HPS as an important differential diagnosis in any cirrhotic patient irrespective of underlying pulmonary pathology.

Introduction

Liver cirrhosis is often associated with pulmonary complications such as hepatic hydrothorax, portopulmonary hypertension and hepatopulmonary syndrome [1]. Hepatopulmonary syndrome is characterized by poor arterial oxygenation and intrapulmonary shunting [1]. Prevalence in cirrhotic patients has been approximated at 5-32% [2]. It affects both adults and children, the later described in Abernathy and congenital malformations [3]. It is also more common in Whites compared to Blacks and Hispanics [4]. "Hepatopulmonary syndrome" as a term was invented in 1977, preceded by autopsy findings [5,6]. Pulmonary vascular dilation was first identified as a possible etiology in patients with liver cirrhosis in autopsy findings by Berthelot et.al, in 1966 [6]. The best diagnostic modality remains contrast-enhanced transthoracic echocardiography with

agitated saline, which shows the appearance of microbubbles in the left atrium in three to five cardiac cycles indicating shunting through a dilated pulmonary vasculature [7]. Till date, liver transplantation is the only proven treatment that has shown benefit in hepatopulmonary syndrome [8]. In this case report, we present a 61-year-old male with a history of alcoholic and hepatitis c-associated liver cirrhosis with a long smoking history and chronic obstructive pulmonary disease. He presented initially with bilateral lower extremity cellulitis and was found to have hepatopulmonary syndrome over the course of admission. Here we highlight the need to consider HPS as a differential in cases of liver cirrhosis even in the presence of a co-morbid pulmonary disorder.

Case Description

A 61-year-old male with a past medical history of treated hepatitis C and alcoholic liver cirrhosis, chronic obstructive pulmonary disease (COPD), major depressive disorder with psychotic features and cognitive delay who presented to our emergency department with complaints of chronic bilateral lower extremity ulcers for about 7 months with concomitant lower extremity swelling and pain. Physical examination revealed an edentulous malnourished male with stigmata of chronic liver disease including spider nevi on the chest and caput medusa on his abdomen. Lower extremities showed chronic bilateral serous draining ulcers with intact margins and a clean base extending up to the shins. The ulcers were more extensive on the right leg. There was surrounding erythema and bilateral pedal enema with no fluctuance or purulence. Laboratory investigations showed a normal blood urea and creatinine. He was hypoglycaemic with a random blood sugar of 42 requiring dextrose 50 boluses. Complete hemogram showed a haemoglobin of 12.6 gm%, MCV-100.6 and white count of 5.97. Liver function tests showed SGOT-30 (1-40 U/L); SGPT-12 (1-40U/L); Alkaline phosphatase (ALP)-57 (40-129 U/L); Total Bilirubin -4.3 (0.1-1.2 mg/dl); Direct Bilirubin-1.7 (0.1-0.3 mg/dl) Serum albumin -1.9 (3.5-5.5 g/dl); PT-21.9 sec, INR- 1.9 (1.2 control). Chest radiography showed -interstitial prominence, and a small left pleural effusion with adjacent passive atelectatic changes (Figure 1). Doppler of the lower extremities showed no deep venous thrombosis. Magnetic Resonance Imaging (MRI) of the lower extremities ruled out osteomyelitis and he was prescribed antibiotics based on a diagnostic impression of cellulitis after blood cultures yielded no growth. He was also prescribed albuterol and ipratropium nebulization to manage his COPD. The general surgery team evaluated and recommended no surgical intervention but daily wound care and dressing as well as an outpatient follow-up at the vascular clinic. On admission patient was found to be persistently hypotensive requiring his mean arterial pressure (MAP) to be maintained by midodrine. He also began to be increasingly cyanotic and hypoxic with increasing oxygen requirements (4 L of O2 to maintain oxygen saturation of 88-92%). Of note, patient was never on home oxygen prior to presentation. Transthoracic echocardiography showed a normal left ventricular systolic function with an ejection fraction of 60%. Ventilation-Perfusion scan ruled out pulmonary embolism. Patient was observed to exhibit platypnea hence an arterial blood gas was obtained with him upright, as there was now a high index of clinical suspicion of HPS. Blood gas values were as follows PH-7.53, PO2 -50, PCO2-25, O2 Sat Arterial -88.2. A-a gradient was -68.5 mmHg. A transthoracic echocardiogram with agitated saline was done and this was positive for shunting after 4-5 cardiac cycles as illustrated in Figures 2 & 3 below. Also, his hospital stay was complicated by 2 episodes of melena stool, and a precipitous drop in Hb, which necessitated an elevation of care to the intensive care unit. The patient had a prior esophagogastroduodenoscopy (EGD) that was done in 2017, which showed mild portal hypertensive gastropathy with a non-bleeding duodenal ulcer, 5 mm in size with a clean base. The gastroenterology team for conservative management given his respiratory status forwent endoscopic intervention. Patient was transfused and received fresh frozen plasma given elevated INR. Vitamin K and proton pump inhibitors were also administered and prophylactic antibiotics prescribed for spontaneous bacterial peritonitis prevention. The decision was made to start lactulose given mild encephalopathy and octreotide infusion to decrease portal blood pressure. With the following interventions, he was stabilized and transitioned to the medical floor for further management. Unfortunately, due to complex social issues, he eventually elected to leave the hospital against medical advice.

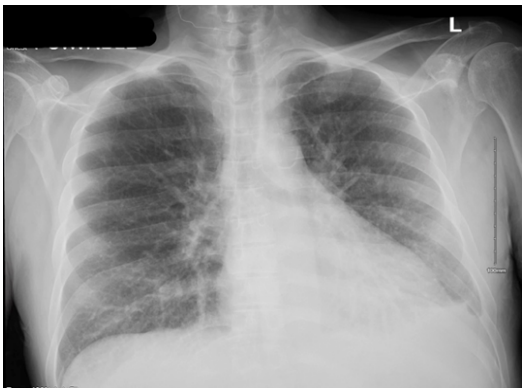
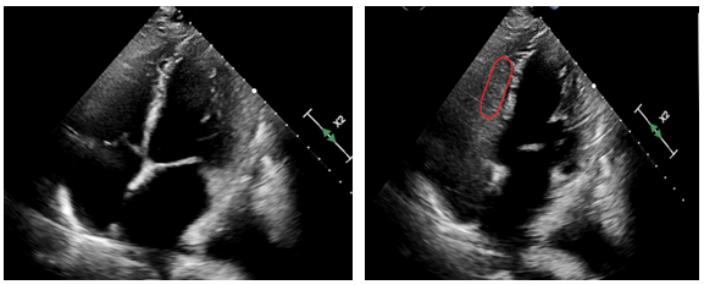


Figure 1: Chest X-ray (AP view) of our patient showing interstitial prominence initially suggestive of interstitial enema or atypical/ viral pneumonia.



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Figures 2&3: A transthoracic echocardiogram with agitated saline was done and this was positive for shunting after 4-5 cardiac cycles (red circle).

Discussion

The diagnosis of hepatopulmonary syndrome involves a triad criteria of a) portal hypertension, b) pulmonary vascular dilation typically by contrast-enhanced echocardiography and c) a partial pressure of oxygen (PaO2) <80 mm Hg or alveolar-arterial oxygen gradient (A-aO2) ≥ 15 mm while on atmospheric air [9]. It is mostly seen in scenarios of portal hypertension and cirrhosis, but it may also occur in patients with acute or chronic hepatitis, fulminant liver failure and cavopulmonary shunts [10]. Typical presentation is dyspnoea on exertion or at rest. Other common findings include digital clubbing and cyanosis [11]. Platypnea and orthodeoxia may or may not be present, but incidence increases with severity of HPS [12]. The triad was fulfilled by our patient who had portal hypertension, was hypoxemic on admission (SpO2 75-80%, PaO2 -50 mmHg, Aa gradient-68.5 mmHg) with echocardiographic findings suggestive of intrapulmonary shunting. He also had the hallmark findings of dyspnoea, cyanosis, platypnea, and orthodeoxia. Slight delay in initial diagnosis was because the patient had a long smoking history and imaging findings suggestive of chronic obstructive pulmonary disease and atypical viral pneumonia. In this case, the principles of Occam's razor were far-fetched and the more complex HPS was at play. The pathophysiology of HPS, though not fully understood is thought to involve a complex interplay of vasodilator production and inhibition of pulmonary vasoconstriction. Intestinal bacterial translocation in the setting of portal hypertension is key [13]. This stimulates macrophage and monocyte accumulation in the lungs [13]. These macrophages release tumour necrosis-alpha (TNF-alpha) in the lung vessels stimulating inducible nitric oxide synthetase (iNOS) and eventual nitric oxide release, a potent vasodilator. Another potent vasodilator carbon monoxide (CO) is also released by heme oxygenase degrading heme. Heme oxygenase induction is also caused by bacterial translocation and elevated NO levels. Meanwhile, macrophages, monocytes and TNF-alpha increase angiogenesis by vascular endothelial growth factor (VEGF) [1,14]. A combination of vasodilation and angiogenesis leads to A-V shunt formation and resultant ventilation-perfusion mismatch. No effective medical therapy has been documented for HPS. For now, liver transplantation is the only established modality that has resulted in improved hypoxemia within 6-12 months [8]. Indomethacin, norfloxacin, aspirin and plasma exchange have been tried without success [1,12,15,16]. Results for pentoxifylline, an inhibitor of TNF-alpha and NO is equivocal [17]. Trans-jugular intrahepatic shunt (TIPS) has shown mixed results too. Meanwhile, mesenteric angiography may assist in identifying congenital portosystemic shunts in children with embolization as a viable therapeutic intervention [18].

Conclusion

HPS is an uncommon complication of hepatic cirrhosis and non-cirrhotic portal hypertension. Clinical features of cyanosis, platypnea and orthodeoxia are commonly associated findings. Medical pharmacotherapeutic interventions have yielded poor results with liver transplantation as the only proven therapeutic intervention. Clinicians should always consider HPS as a differential diagnosis in any cirrhotic patient regardless of underlying pulmonary pathology. Prompt and early diagnosis could affect clinical decision-making and inform therapeutic management. In the case of our patient, overt symptoms of HPS were masked by underlying COPD and possible pneumonia. More research is also needed on therapeutic interventions for patients with HPS as there is a dearth in the literature on comprehensive strategies for management. There needs to be more guideline directives from thought leaders and experts in the field of gastroenterology for a holistic approach to HPS research and clinical translation of research findings.

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