



Case report

A rare cause of hypoxia in a patient with liver cirrhosis

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ABSTRACT

Pulmonary syndromes in the setting of hepatic disease with portal hypertension include portopulmonary hypertension (POPH), hepatopulmonary syndrome (HPS) and hepatic hydrothorax. POPH is defined as pulmonary arterial hypertension with portal hypertension in the absence of other causes of pulmonary arterial hypertension. HPS is a defect in arterial oxygenation as a result of pulmonary micro vascular dilatation in the setting of liver disease. We discuss a case of 63-year-old female with liver cirrhosis, exertional dyspnea and hypoxia associated with coexistence of POPH and HPS. The coexistence of POPH and HPS is rare entity which can generate a renewal of interest in further understanding the intricate pathologies behind these diseases.

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1. Introduction

Pulmonary syndromes in the setting of hepatic disease with portal hypertension include portopulmonary hypertension (POPH), hepatopulmonary syndrome (HPS) and hepatic hydrothorax. POPH is defined as pulmonary arterial hypertension associated with liver disease and portal hypertension in the absence of other causes. HPS is defined as classical triad of presence of chronic liver disease or portal hypertension, arterial deoxygenation and evidence of intrapulmonary vascular dilatations. We present a case of liver cirrhosis where both POPH and HPS were diagnosed simultaneously.

2. Case report

A 63-year-old woman came to the emergency department complaining of a one month history of progressive dyspnea on exertion and leg swelling. She had a past medical history of hepatitis C diagnosed four years ago which was untreated as patient could not tolerate pegylated interferon. On physical examination, she was found to be severely hypoxic. Chest was clear to auscultation. Abdominal examination showed hepato-splenomegaly and ascites. Her chest radiograph revealed mild cardiomegaly without any evidence of pulmonary edema. High resolution computed tomography showed a focal area of linear opacities within the right lower lobe in a reticular pattern with honeycombing and associated

septal thickening. Laboratory data was indicative of chronic liver disease, including a bilirubin of 2.8, an INR of 1.2, an albumin of 2.8, and a platelet count of 63,000. Arterial blood gas showed PaO₂ of 53 mmHg while breathing room air. Abdominal ultrasound showed features suggestive of portal hypertension (ascites, splenomegaly). Transthoracic echocardiogram revealed an elevated right ventricle systolic pressure (49 mmHg) accompanied by a mildly dilated right atrium and right ventricle with normal left ventricular function.

A contrast echocardiogram was done showing the appearance of micro bubbles in the left ventricle approximately 6 beats after their appearance in the right ventricle suggestive of hepatopulmonary syndrome (HPS). Right heart catheterization was performed which confirmed pulmonary arterial hypertension (PAH) with a pulmonary artery systolic pressure of 54 mmHg with a mean pulmonary artery pressure of 39 mmHg, a pulmonary vascular resistance of 266 (dyne*sec)/cm⁵ a wedge pressure of 15 mmHg and a cardiac output of 7.2 L/min. Investigation of other causes of pulmonary hypertension was unrevealing suggesting portopulmonary hypertension (POPH) as a cause of her worsening shortness of breath.

Our patient was treated on oxygen with aggressive diuresis. She was started on an endothelin receptor A antagonist, Ambrisentan. There was marked improvement in her shortness of breath and leg swelling. She was discharged home on oxygen and an endothelin receptor antagonist.

3. Discussion

Pulmonary syndromes in the setting of hepatic disease with portal hypertension include POPH, HPS and hepatic hydrothorax.¹ POPH is defined as pulmonary arterial hypertension with portal

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hypertension in the absence of other causes of pulmonary arterial hypertension.² HPS is a defect in arterial oxygenation as a result of pulmonary micro vascular dilatation in the setting of liver disease.⁸ There is no correlation between portal hypertension and the onset and severity of POPH.³ In the setting of cirrhosis, the incidence of HPS and POPH is 4 to 29% and 0 to 7% respectively.¹ The coexistence of POPH and HPS is rare but has been reported previously. So far there has been only one case report where HPS and POPH were diagnosed simultaneously.¹

The patho-physiology of both HPS and POPH is not clearly understood. Many theories have been proposed as an explanation of these alterations in pulmonary hemodynamics. In POPH these theories include the presence of an increased inflammatory response associated with portal hypertension leading to up-regulation of endothelin receptors and vasoconstriction without hypoxemia.¹ HPS is associated with vasodilatation causing intrapulmonary shunting leading to hypoxemia.³ It is a clinical paradox that both HPS and POPH coexist as the underlying mechanisms of the two diseases states are opposite.

Different expressions of endothelin-1 receptor have been proposed to explain the hemodynamics of both disease entities. There is an up regulation of endothelin B receptors in HPS leading to up regulation of nitric oxide synthetase resulting in increase production of nitric oxide. Nitric oxide causes pulmonary vasodilatation, intrapulmonary shunting and hypoxemia.² HPS is also associated with orthodeoxia which is defined as oxygen desaturation when assuming the upright position⁴ and platypnea, defined as dyspnea induced by the upright position and relieved by recumbency. In POPH, there is an increased expression of endothelin A receptor leading to vasoconstriction in pulmonary vasculature causing vascular remodeling with the subsequent development of pulmonary hypertension.¹ The high cardiac output seen with portal hypertension along with pulmonary vasoconstriction likely plays an important role in the development of POPH.³

Dyspnea on exertion is the most common symptom of POPH.³ Increased pulmonary artery pressure (PAP) seen on Doppler echocardiography in a patient with portal hypertension is an important clue towards the diagnosis of POPH. Diagnosis is made by right heart catheterization and is defined by the presence of the following features in a patient with portal hypertension; a mean PAP greater than 25 mmHg at rest or greater than 30 mmHg on exertion, a raised pulmonary vascular resistance more than 250 dyne/cm², a transpulmonary gradient (difference between mean PAP and pulmonary capillary wedge pressure) >12 mmHg and left ventricular end diastolic pressure of <15 mmHg in the absence of other causes of PAH.³

The presence of hypoxemia in a patient with portal hypertension should raise the suspicion of HPS. Usually the PaO₂ is less than 80 mmHg and alveolar-arterial gradient is greater than 15 mmHg on room air.⁷ Contrast echocardiography is a vital diagnostic tool for HPS. The appearance of agitated saline in the left atrium after three cardiac cycles is diagnostic of intrapulmonary shunting.⁷

POPH and HPS also differ in terms of their treatment options. Pulmonary vasodilatation is the mainstay of treatment in POPH. Intravenous epoprostenol has been shown to cause improvement in hemodynamics and symptoms in POPH but requires constant intravenous access for drug infusion and a highly compliant patient.⁴ Also, both oral and nebulized forms of prostacyclin have been used in POPH and have demonstrated comparable results to intravenous prostacyclin.⁵ The oral dual endothelin receptor antagonist bosentan has the beneficial effects of improvement in

exercise capacity and hemodynamics in POPH. Bosentan blocks endothelin receptors thereby decreasing the targets for endothelin-1 levels of which are increased in POPH.⁴ PAH of any severity in a cirrhotic patient with portal hypertension carries a poor prognosis and severe PAH carries a high mortality after liver transplantation.³ In many transplant centers, a mean PAP >50 mmHg is considered as an absolute contraindication for liver transplantation.³ Therefore PAH is generally treated with vasodilators with the aim of reducing mean PAP below 35 mmHg before liver transplantation.⁶ Austin et al. described a case of POPH where the pulmonary arterial pressure was reduced successfully with triple therapy including iloprost, sildenafil and bosentan before liver transplantation.⁵ The treatment of HPS includes correction of hypoxemia by oxygen and liver transplantation. Liver transplantation is the only treatment that has been shown to alter the natural course of the disease with improvement in hypoxemia.⁷ Patients with refractory hypoxemia carry a higher mortality and morbidity when undergoing liver transplantation in both the preoperative and postoperative periods.⁷

The 5 year survival rate of POPH is 14% without any treatment as compared to 45% for those who receive medical vasodilator therapy.⁶ The 5 year survival for HPS without liver transplant is 23%.⁷

The treatment strategy in a patient who presents with both HPS and POPH is challenging. Liver transplantation is required for HPS but the presence of POPH carries a poor prognosis before and after liver transplantation. The aim of the treatment is to lower the PAH with vasodilators before liver transplantation and use oxygen for hypoxemia. Further studies are needed to understand more about the patho-physiology of the coexistence of these two syndromes.

There should be a low threshold in getting a contrast echocardiogram and right heart catheterization in liver disease patients with either dyspnea or hypoxemia to investigate the existence of HPS and/or POPH.

Conflict of interest

Authors confirm that there is no conflict of interest amongst them and the submitted manuscript is not under simultaneous consideration by any other publication. Patient described in the case report is not alive at the time of submission.

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