Case report of hepatopulmonary syndrome in patients with non-cirrhotic portal hypertension

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Abstract
We report the case of a female patient diagnosed with hepatopulmonary syndrome (HPS) which occurred in the context of chronic thrombosis of the portal and mesenteric veins resulting from primary thrombophilia (protein C and protein S deficiencies). This case of HPS was diagnosed when echocardiography with agitated saline contrast showed the patient was positive for extra cardiac shunt. Scintigraphy using albumin macro-aggregates showed evidence of uptake in the brain and persistent hypoxemia with elevated alveolar-arterial gradient for the age of the patient.

Key words
Hepatopulmonary syndrome, portal vein thrombosis, nodular regenerative hyperplasia.

INTRODUCTION
More than 50% of patients with hepatic diseases have respiratory symptoms and of these patients 30% may present pulmonary diseases as the cause of these symptoms (1).

Complications of chronic hepatic diseases cause changes in lung mechanics which can be manifested as hypoxemia, although patients with hepatopulmonary syndrome (HPS) may manifest in other ways from secondary hypoxemia to alterations in the pulmonary blood vessels. HPS is characterized by the appearance of persistent hypoxemia in a patient with hepatic disease and vascular lung dilation (2). The vascular component includes diffuse or local dilation of the pulmonary capillaries, and less commonly includes pulmonary arteriovenous shunts.

The term hepatopulmonary syndrome (HPS) was first introduced into the literature by Kennedy and Kudson in 1977, and many definitions have been proposed since then. Currently most of the evidence comes from isolated reports and case studies which use widely varying diagnostic criteria. Reported prevalence ranges from 15% to 32% among patients suffering from liver cirrhosis depending on the criteria used. This variability is explained by the lack of consensus about hypoxemia values and the use tests to confirm HPS (3). HPS can also occur in acute liver diseases such as viral hepatitis and hepatic failure (4). To date, there have been few cases and series that report the presence of HPS together with cirrhotic portal hypertension. The characteristics of these patients have not yet been fully studied (5).

The following is the case of a woman with portal hypertension of non cirrhotic origin who developed hepatopulmonary syndrome which was subsequently treated at the Liver Unit of Hospital Pablo Tobon Uribe.

CASE DESCRIPTION
The patient was a 21 year old student who resided in a rural area who had no relevant personal medical precedents. She was transferred from a second level complexity hospital after being diagnosed with cirrhosis and nonspecific...
pulmonary compromise due to persistent asymptomatic hypoxemia. Upon admission she had no supplemental oxygen. Her oxygen saturating was 80%, she presented oral and distal cyanosis and Hippocratic fingers. Physical examination showed no evidence of chronic hepatopathy. Her hepatic profile was AST: 41 U/L, ALT: 29 U/L, ALP: 114 U/L, GGT: 161 U/L, TP Ins 8.12, INR: 1.2, albumin 3.1 g/dL and her complete blood count showed 87,000 cells/mm3 of thrombocytopenia.

At that time there was no clinical, paraclinical or imaging evidence of cirrhosis. After hospitalization, a triphasic abdominal CAT scan showed chronic portal thrombosis with mesenteric extension and severe collateral circulation. The thrombophilia study found a deficit of C and S coagulation proteins. The hypoxemia study showed arterial gases had a PO2 of 57 mmHg and an A-a gradient of 30 mmHg (15 mmHg is expected for that age). An angio-thorax CAT-Scan resulted in rejection of pulmonary embolism. Normal cardiac structures were found in echocardiography, but after applying agitated saline solution it showed the passage of bubbles to left cavities after fifth heartbeat compatible with extracardiac shunt (Figure 1). Magnetic Resonance Angiography (MRA) of the heart revealed a structurally normal heart, and gammagraphy with albumin macroaggregates showed abnormal reception of the tracer at the brain level. Right heart catheterization was performed demonstrating pulmonary artery pressure of 40/10 mmHg, with a mean of 25 mmHg. The diagnosis of hepatopulmonary syndrome with presinusoidal portal hypertension without hepatic cirrhosis was then made. The patient is currently receiving anticoagulation treatment and oxygen at home. She is asymptomatic, has good functions and a strong family, social and work life.

DISCUSSION

HPS is characterized by permanent hypoxemia in patients with underlying secondary hepatic disease in the presence of vessel lung dilation (6).

Hypoxemia is associated with a broad alveolar-arterial gradient (Aa) of oxygen. This is defined as one above 15 mmHg, as over 25 mmHg in people older than 65 years, or defined as increasing with age by: Aa Gradient (0.26 x age - 0.43) + 10. Hypoxemia severity is classified according to PO2: it is low when PO2 is 80 mmHg, moderate at 60-80 mmHg, severe at 50-60 mmHg, and quite severe with PO2 less than 50 mmHg (7).

In early stages, a patient with hepatopulmonary syndrome remains asymptomatic. There are no pathognomonic symptoms or signs of this syndrome, though there were symptomatic findings suggestive of it. The patient may report dyspnea, especially when changing position from lying to sitting or standing (platypnea) and physical examination may show orthodeoxia (decreasing PaO2 or O2 saturation resulting from change of positions). Cyanosis, digital hippocratism and telangiectasias (as a manifestation of systemic vessel dilation) can also appear. Hypoxemia occurs as a result of several mechanisms: first, as an alteration of ventilation-perfusion, second, as the presence of truly anatomic shunts, and third as the decline in the diffusion-perfusion (8).

Physiopathologically, HPS reflects an abnormal dilation of the pulmonary bed which has been attributed among other factors to the overproduction of nitric oxide. This molecule is one of the most potent pulmonary vessel dilators and appears to be responsible not only for the hyperdynamic and splanchnic vessel dilation, but also for the HPS (9).

At the microvascular level, endothelial synthesis of nitric oxide and increased expression of the inducible form of this enzyme in macrophages result in increased production of nitric oxide. This is augmented as the endothelin-1 production at the hepatic level and overexpression of endothelin receptors in the pulmonary vascular bed also stimulate production of nitric oxide (10).

There is then a significant hemodynamic change. The pulmonary capillaries expand to reach diameters of up to 100 microns, thereby generating short circuits from left to right and the alterations described in oxygenation.

These hemodynamic changes, pulmonary vessel dilation and extracardiac short circuiting, are the foundations for the confirmed diagnosed methods of HPS.

The echocardiography contrasted with agitated saline solution is a procedure applied via a peripheral vein. The agitated saline solution forms bubbles larger than 10 microns. Under normal conditions the bubbles go to right

![Figure 1. Echocardiography with contrast medium of patient with portal vein thrombosis and hepatopulmonary syndrome. The flow of the contrast medium after the 5th beat is shown together with the presence of bubbles in the right and left chambers.](image-url)
left cardiac cavities. If the passage of bubbles occurs before or after application of the solution completely shadowing the left cardiac chambers between the third and sixth beat and at a diameter of 15 microns, bubbles pass through the capillaries and enter the HPS context, where capillaries measure much more than 20 microns in diameter are injected. Any acquisition (primarily cerebral or renal) of the contrast media is considered to be positive for left-right shunt (without differentiating whether it is intra-cardiac or extracardiac) (11, 12).

Any form of acute or chronic hepatic disease can coexist with hypoxemia due to dilatation of the pulmonary vessels. Consequently, portal hypertension is not essential for manifestation of this syndrome. Although cases of hepatic failure and acute hepatitis have been reported, they are the exceptions because what they have in common is the description of the syndrome in cirrhotic patients with portal hypertension. These cases have no association with the etiology of cirrhosis, and the relationship with the severity of hepatic dysfunction or portal hypertension is not yet clear.

Despite advances in knowledge about HPS, there are few publications about patients with portal hypertension, who do not have cirrhosis, but who do have this syndrome. There are a number of hepatic entities for which there have been reported cases of HPS other than cirrhosis. They include idiopathic portal hypertension, portal thrombosis, congenital hepatic fibrosis, Budd – Chiari syndrome, hepatic metastases, neonatal hepatitis and nodular regenerative hyperplasia. Still, there are no clearly known mechanisms by which HPS develops in these pathologies (13). Currently, it is calculated that 4% to 8% of the hepatopulmonary cases occur in patients with non-cirrhotic portal hypertension. The literature about the coexistence of HPS in patients with non-cirrhotic portal hypertension is limited to case reports and controlled studies with small sample sizes. In 2000, Binay and his collaborators (14) demonstrated the presence of HPS in non-cirrhotic patients. They defined the HPS diagnostic criteria for the study as positive CE, PaO2 less than 70 mmHg and A-a gradient greater than 20 mmHg. They evaluated 25 patients with non-cirrhotic portal hypertension with contrast echocardiography with agitated saline solution. Two patients met the criteria for HPS, and both had normal hepatic and pulmonary functioning. During the same year, the author described the characteristics of two other patients with HPS and Budd – Chiari syndrome. Both underwent derivation through cavoplaty, one successfully, the other unsuccessfully. The patient who could be diverted was given oxygen for eight weeks and recovered from dyspnea (15).

One of the largest studies of HPS was conducted between 1996 and 1998 and published in 2003 (13). In that study the incidence of HPS among 45 patients with hepatic cirrhosis patients and 31 patients with non-cirrhotic portal hypertension was compared. It was found that five (10.8%) of patients with cirrhosis and three (9.7%) patients without cirrhosis met the diagnostic criteria for HPS. The conclusions were that cirrhosis is not a prerequisite for the development of this syndrome and that patients with idiopathic portal hypertension and portal vein thrombosis may also develop HPS, as described in our case above.

So far there is no effective medical therapy for HPS. Liver transplantation, with 5 year survival rates of about 75%, is the only therapeutic option (16). In these cases, mortality and resolution of hypoxemia are related to the severity of the hypoxemia prior to transplant. Therapies that have been tried in an anecdotal way, but which have no support from the literature, include antibiotics, beta blockers, glucocorticoids, nitric oxide inhibitors, somatostatin, and cyclophosphamide, but none have been successful.

Isolated cases of the use of interventional therapies such as intrahepatic transjugular portosystemic shunts (TIPS, cavoplaa and embolization of arteriovenous shunts to improve the portal pressure gradient have also been reported in. For this reason, patients with contraindications for liver transplantation only receive symptomatic management with ambulatory oxygen therapy.

There are no descriptions of treatment of HPS in patients with non-cirrhotic portal hypertension. In 2011, Maganty and Ghanta reported the case of a 26 year old patient with portal hypertension secondary to nodular regenerative hyperplasia who had dyspnea and platypnea and who required home oxygen. The patient had a MELD of 10, and her only indication for transplant was lung compromise. After undergoing orthotopic liver transplantation her post operative examination showed persistent hypoxia. During the following three weeks she gradual improved and oxygen was totally removed (17).

The patient described above is now being managed with anticoagulation indicated for the thrombophilia described and with ambulatory oxygen. At the moment no interventional therapy is planned, and she has contraindications for liver transplantation due to the extension of portal vein thrombosis and the technical limitations of this complication.

REFERENCES


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