Hepatopulmonary syndrome: an unusual cause of dyspnea in the pulmonology ward – case presentation

Sindromul hepatopulmonar: o cauză neobișnuită de dispnee în secții de pneumologie – prezentare de caz

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Abstract

Hepatopulmonary syndrome is one of the possible complications of chronic liver disease, defined clinically by impaired oxygenation. The underlying cause of the respiratory failure is the presence of intrapulmonary shunting, as a result of abnormal vascular dilatations in the lungs. We report the case of 52-year-old male, ex-smoker, with a history of pulmonary TB and also of heavy drinking, who was admitted to the pulmonology ward for dyspnea at rest and limb cyanosis. His clinical exam was suggestive of liver cirrhosis, with signs of pneumonia, but also chronic lung disease. Variations in SaO2 with posture were noted: platypnea and orthodeoxia. Arterial gas assessment revealed severe hypoxemia, only partially corrected by high-flow oxygen therapy, while plethysmography showed only a mild obstructive syndrome, but with severely impaired alveolar-capillary diffusion. The suspicion of a hepatopulmonary syndrome was raised and a contrast echocardiography confirmed the diagnosis by revealing the presence of an intrapulmonary shunt. Although it is believed to be a fairly common complication of chronic liver disease, it is possible for a case of hepatopulmonary syndrome to be admitted solely for respiratory symptoms. The patient's poor socio-economic status is the main reason for both the lack of proper follow-up for his liver disease and the limited therapeutic options.
Keywords: ***Hepatopulmonary syndrome, liver cirrhosis, respiratory failure, contrast echocardiography***

Rezumat

Sindromul hepatopulmonar este una dintre complicațiile posibile ale afecțiunilor hepatice cronice, definit din punct de vedere clinic prin alterarea oxigenării. Substratul fiziopatologic al insuficienței respiratorii este reprezentat de șuntul intrapulmonar, ca rezultat al dilatațiilor vasculare anormale din plămâni. Este raportat cazul unui pacient de sex masculin în vârstă de 52 de ani, ex-fumător, cu antecedente de tuberculoză pulmonară și de consum important de alcool, care a fost internat în secția de pneumologie pentru dispnee de repaus și cianoza extremităților. Examenul clinic a fost sugestiv pentru ciroză hepatică, asociind semnele unei pneumonii. Au fost remarcate variații ale SaO2 în funcție de poziție: platipnee și ortodeoxie. Analiza gazelor arteriale a arătat hipoxemie severă (corectată doar parțial de administrarea oxigenului în debit mare), iar pletismografia a evidențiat doar un sindrom obstructiv ușor, dar cu alterare severă a transferului prin membrana alveolo-capilară. S-a ridicat suspiciunea unui sindrom hepato-pulmonar, confirmat ulterior prin efectuarea unei ecocardiografii cu contrast care a arătat prezența unui șunt intrapulmonar. Deși se consideră a fi o complicație relativ frecventă a afecțiunilor hepatice cronice, sindromul hepatopulmonar poate fi adresat mai întâi serviciilor de pneumologie pentru acuzele respiratorii din cadrul acestuia. Statusul socio-economic precar al pacientului a fost motivul principal de limitare a opțiunilor terapeutice și de pierdere a cazului din supraveghere.
Cuvinte-cheie: ***sindrom hepatopulmonar, ciroză hepatică, insuficiență respiratorie, ecocardiografie de contrast***

Introduction

The pulmonary complications of liver diseases are a heterogeneous group with different physiopathological mechanisms. Chronic hepatic dysfunction, accompanied by changes in the production or clearance of circulating cytokines, seems to be the underlying cause of pulmonary disease manifested in the hepatopulmonary syndrome (HPS), but also in the portopulmonary hypertension (PPH)[(1)].

HPS is diagnosed when the following triad is present: liver disease, impaired oxygenation and intrapulmonary vascular dilations (IPVDs)[(2)]. HPS isn't only seen in association with liver cirrhosis; virtually any chronic liver disease can evolve with IPVDs, and thus HPS, regardless of the presence of portal hypertension and without correlation to the severity of the liver disease[(3)].

The physiopathological process involved in inducing pulmonary vasodilatation seems to be the increased endogenous production of nitrous oxide; endothelin-1 and TNFα also play a role in regulating the microvascular tonus[(4,5)]. Other mechanisms that might be involved are impaired angiogenesis and vascular remodeling which lead to the development of pulmonary arterial-venous shunts[(6,7)]. The direct manifestation of this right-to-left shunting is clinically manifest oxygen desaturation, which is worsened by the impaired vasoconstrictor response to hypoxemia. An elevated alveolar-arterial (A-a) oxygen gradient of over 15 mmHg (or over 20 mmHg in older patients) is a highly sensitive index of desaturation which allows for early detection of HPS even before a significant drop in PaO_2 values is measured[(8)]. Conversely, once the A-a gradient is found to be elevated, the severity of the pulmonary disease is graded by the value of PaO_2, which is important in predicting the outcome of the patient.

Case presentation

The 52-year-old patient, a homeless male, was admitted as an emergency in the pulmonology department for dyspnea

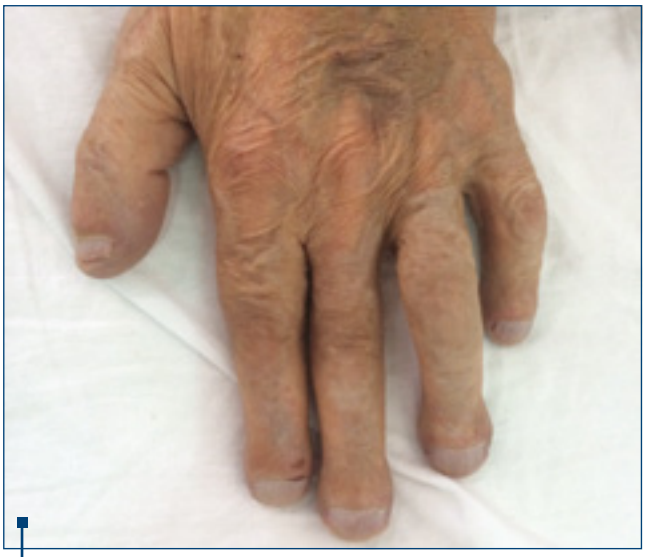

Figure 1. *Patient's left hand – finger clubbing*

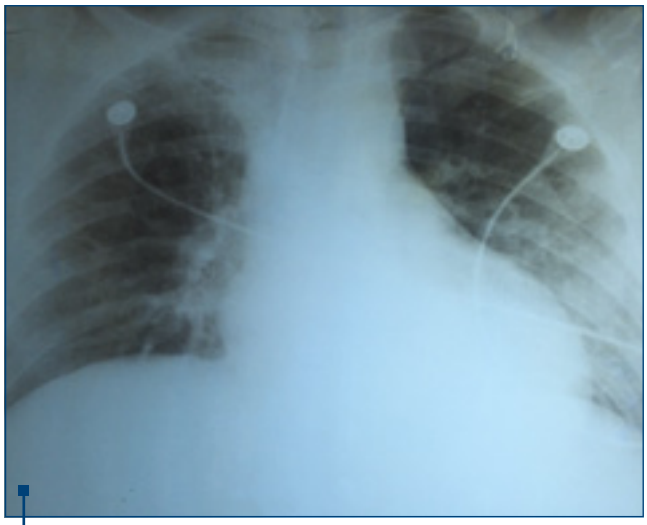

Figure 2. *Chest X-ray showing left lower lobe opacity with alveolar pattern*

at rest, perioral and limb cyanosis, productive cough (with intermittent haemoptysis), repeated episodes of epistaxis, gingival hemorrhages and melena in the previous 3 weeks, with no haematemesis. He was an ex-smoker (15 pack-years, stopped for 4 years), had had pulmonary tuberculosis in 1998 and 2011 (apparently correctly treated) and was diagnosed with alcoholic liver cirrhosis 2 years before.

The clinical evaluation showed marked cyanosis of mucosae and limbs, with spontaneous SaO_2=62%. Finger clubbing was present (Figure 1), as well as multiple spider angiomas in his thorax and abdominal collateral circulation. He was polypneic (RR=22/min) with crackles on the left side. The liver was firm and enlarged and the spleen was palpable. The rest of the clinical exam was unremarkable.

The chest X-ray revealed fibronodular sequelae at the right apex and an alveolar opacity in the lower half of the left hemithorax (Figure 2).

Blood work revealed mild anemia and thrombocytopenia, which together with a prolonged INR, mild hyperbilirubinemia and hypoalbuminemia, are to be expected in the setting of a known liver disease. The immunologic markers for hepatitis viruses were negative. Serum alpha1-antitripsine levels were slightly below the normal limit; later on, the genetic testing revealed a heterozygous genotype (MZ). Sputum samples were negative for *M. tuberculosis* infection.

Arterial gas assessment showed severe hypoxemia (PaO_2=31 mmHg) with hypocapnia ($PaCO_2$=22 mmHg) and respiratory alkalosis (pH=7,50; HCO_3=16,9 mmol/l). There was partial improvement with high-flow oxygen administration (PaO_2=42 mmHg; SaO_2=81,6%; alveolar-arterial gradient= 166 mmHg; estimated shunt fraction: 51%). Plethysmography revealed only a mild obstructive dysfunction, but severely impaired alveolar-capillary diffusion, with a very low transfer coefficient (DLCOc=37.5%, KCOc=46.8% of their predicted values, respectively).

To rule out pulmonary thromboembolism as the underlying cause of severe hypoxemia refractory to oxygen supplementation, a contrast CT scan was performed. The pulmonary arteries were normal, with no signs of thrombi. Some bronchiectasis were seen in both lungs, together with fibrous TB sequelae. There were also esophageal and gastric varices, expressions of portal hypertension, and moderate ascites, which are classic findings in a cirrhotic patient.

After further questioning, the patient revealed that he had been admitted almost a year before in another pulmonology ward for the same symptoms. A look into his records revealed much the same data: severe hypoxemic respiratory failure, well tolerated by the patient, refractory to supplemental oxygen, with minimal radiological findings and only a mild obstructive syndrome. After assessing SaO_2 variations with posture (55% upright vs. 70% supine), orthodeoxia and platypnea were found and there was strong suspicion of HPS as the cause of chronic hypoxemia.

To prove the existence of an intrapulmonary shunt we performed a contrast echocardiography. The right ventricle was slightly enlarged, with no signs of pulmonary hypertension. After the IV injection of microbubbles, which opacified the right cavities, the contrast material passed in the left cavities in about 3-4 cardiac cycles. This finding is highly suggestive of an intrapulmonary shunt and, in our case, settled our diagnosis as being HPS.

During his hospital stay, the patient received a full course of antibiotics and supportive treatment for bacterial pneumonia and also supplemental oxygen, first through a mask (with SaO_2 never rising above 80%), afterwards by CPAP, with no benefit after cessation. Upon discharge, we recommended long term oxygen therapy. Although the patient should be a candidate for liver transplantation, his social status as an uninsured individual with no stable address halted the proceedings.

Discussion

The clinical picture of HPS is composed of liver disease signs alongside dyspnea – particularly platypnea and orthodeoxia, explained by the gravitational increase in the flow of blood through the dilated veins in the lung bases while standing up[9]. Shortness of breath can have other causes in a cirrhotic patient: anemia, ascites, muscle wasting; still, the association of dyspnea with cyanosis and clubbing is highly suggestive of a pulmonary complication of the liver disease – either HPS or PPH.

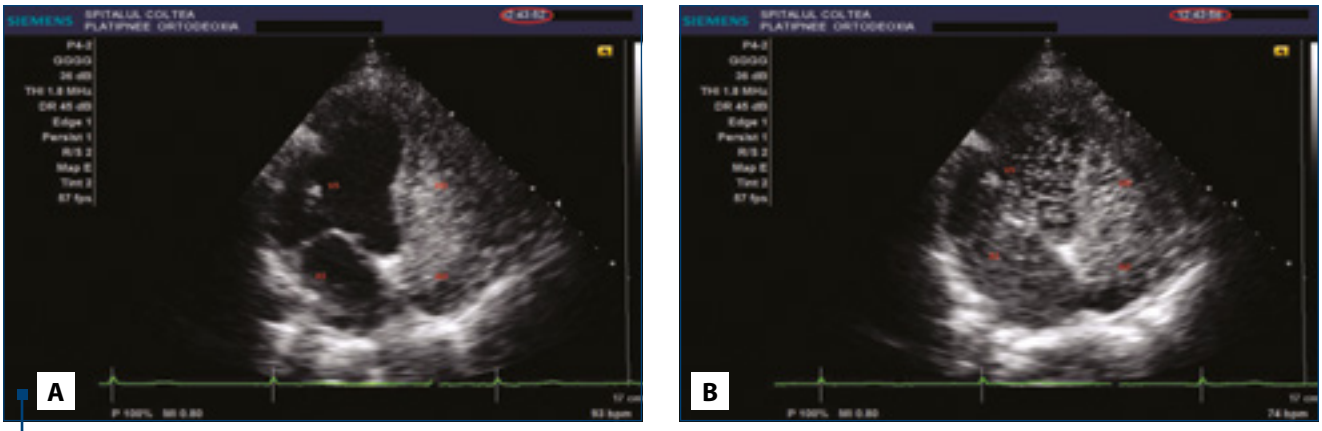

Figure 3A,3B: *Contrast transthoracic echocardiography – late appearance of contrast in the left cavities*

The diagnostic gold standard test for HPS is a contrast transthoracic echocardiography, which is a sensitive and non-invasive method for detecting pulmonary vasodilations. The contrast substance readily available is agitated saline injected in a peripheral vein. In a normal person, the microbubbles are absorbed in the alveolae at their first pulmonary passage, so they should only opacify the right heart. If there is early passage of bubbles in the left heart (in the first 3 cardiac cycles after injection), it is usually a sign of intracardiac shunting. However, with an intrapulmonary shunt, the contrast appears in the left cavities later, 3 to 6 heart beats after the opacifiation of the right heart (Figure 3a, 3b). Transesophageal echocardiography is more specific for the detection of microbubbles passing through the pulmonary veins, but is usually avoided when esophageal varices are suspected. Regardless of the method used, if an intrapulmonary shunt is detected by echocardiography in a patient with liver disease, it is usually indicative of IPVDs and thus HPS[10].

Regarding our patient, the severe type I respiratory failure, only partially corrected with high flow oxygen administration - in the absence of an underlying pulmonary or cardiovascular pathology - was what raised the suspicion of an intrapulmonary shunt. The presence of chronic hepatic disease (vascular and parenchymal decompensated alcoholic cirrhosis) moved the diagnosis forward to a hepatopulmonary syndrome. Consequently, this was readily established through assessment of blood gases and contrast transthoracic echocardiography. It is perhaps important to note that, although the distinction between PPH and HPS is not always clear, in this case we were able to rule out pulmonary hypertension as the underlying cause of dyspnea.

The presence of an alpha1-antitripsin deficiency, as evidenced by the low serum value and MZ heterozygous genetic testing result, begs consideration of a congenital hepatic and pulmonary disease. However, there is substantial proof against it – no sign of emphysema on the CT scan and only a mild obstructive syndrome in an ex-smoker with TB sequelae, which makes it a rather unlikely etiology of the respiratory symptoms. The degree in which this deficit could be an underlying contributor in the development of cirrhosis in our patient remains uncertain.

The therapeutic means in HPS are limited to long term oxygen supplementation. Patients with severe hypoxemia refractory to oxygen administration have a high priority liver transplant indication, with very good results – complete HPS resolution after transplant in more than 80% of cases[11]. The mortality rate in HPS cases who do not undergo liver transplantation is high (reportedly 41% at 2,5 years)[12]. The prognosis of our patient is reserved, due to his poor socio-economic status and his loss at follow-up.

Conclusions

Although liver cirrhosis was previously recorded in this patient's history, it progressed, in the absence of follow-up in a gastroenterology clinic, with the development of HPS. Consequently, the causation link between the liver disease and the respiratory failure had to be traced at the admittance in the pulmonology ward. HPS is not part of the usual differential diagnosis of dyspnea in a patient with multiple risk factors, therefore reaching the final conclusion of this case was a laborious process. ■

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