The Hepato-Pulmonary-Cutaneous Syndrome: Description of a Case and Suggestion of a Unifying Hypothesis

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Abstract

We report a 54-year-old patient with the association of hepatic dysfunction with cyanosis, severe hypoxemia, platypnea-orthodeoxia, diffuse cutaneous spider nevi, telangiectasia, palmar erythema, digital clubbing and findings of marked intrapulmonary vascular dilation and arterovenous shunt. The diagnosis of hepato-pulmonary-cutaneous syndrome, a term we think more appropriate and inclusive than that of hepato-pulmonary syndrome for this clinicopathological picture, is proposed. The putative underlying mechanism for these connected pulmonary and extrapulmonary syndromic features is discussed.

Introduction

Dyspnea and cyanosis are rare in patients with cirrhosis, except when ascites or pleural effusion are present. A diminished arterial partial pressure of oxygen (PaO_2) is however observed in 50% of decompensated cirrhotic patients, with PaO_2 levels in the range of 60–70 mm Hg [1, 2]. Contributing factors are multifactorial and include: altered ventilation-perfusion relationship, especially in patients with ascites and pleural effusions; reduced pulmonary diffusing capacity, sometimes due to interstitial edema or dilation of precapillary pulmonary vessels; decreased oxygen affinity of red blood cells; pulmonary

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arterovenous (A-V) anastomosis, either microscopic or involving large vessels; and combinations of these factors. Moreover, some patients present the hepato-pulmonary syndrome (HPS), characterized by diffuse intrapulmonary vasodilation, A-V shunts or both that can lead to abnormal arterial oxygenation, orthopnea, platypnea, and orthodeoxia in the setting of liver disease [3]. In fact, patients with the HPS usually have chronic liver disease that can be asymptomatic under other aspects, but are often admitted to hospital due to chronic respiratory failure and other extrahepatic manifestations. Here we describe the case of a woman with HPS, palmar erythema, diffuse cutaneous spider nevi, telangiectasia, and digital clubbing, that is a clinical picture we could name hepato-pulmonary-cutaneous syndrome (HPCS), and a unifying hypothesis for these pulmonary and cutaneous vascular abnormalities is suggested.

Case Report

A 54-year-old woman had been well until 15 years before the current observation when elevation of serum liver enzymes was noted. Subsequently, she was admitted numerous times in various medical departments due to abnormal liver function tests, hypoxia, polyglobulia and dismissed without a definite diagnosis. Two years before the current observation, due to increasing grievous exertional dyspnea and weight loss (20 kg in the last 2 years), the patient was admitted to another medical ward where anti-HCV antibodies enzyme immunoassay, HCV RNA and subsequent liver biopsy confirmed the diagnosis of chronic active hepatitis of high severity due to hepatitis C virus infection. The source of infection was most probably a blood transfusion 26 years before after postpartum hemorrhage.

Due to worsening of the exertional dyspnea, even to mild exercise, the patient was admitted to our department. Physical examination disclosed superficial polypnea, central cyanosis, digital clubbing, palmar erythema, telangiectasia, diffuse spider nevi (**fig. 1**), and systemic hypotension with a widened differential pressure and hepatosplenomegaly. No ascites was detectable on physical examination or by ultrasound. Orthodeoxia was observed, since blood gas analysis showed a PaO_2 of 38 mm Hg in the supine position and of 30 mm Hg in the erect position, only partially corrected with 100% O_2. Chest radiography and spirometry were negative. Contrast-enhanced echocardiography with saline showed evidence of passage of air bubbles from the right ventricle to the left atrium after 4 cardiac cycles, in absence of intracardiac right-to-left shunt. Radionuclide imaging with 99mTc-macroaggregated albumin showed rapid distribution of radionuclide to the brain and kidney (**fig. 2**), and a hyperkinetic heart syndrome. Thus a diagnosis of HPCS was made with an estimated A-V shunt of 18% while the patient was supine and of 40% while the patient was sitting. Additional laboratory evaluation consisted of nitric oxide (NO) plasma levels, which were 148 μM (normal 10–60 μM), measured by the Grease method, wherase endothelin-1 plasma levels were 58 pg/ml (normal <20 pg/ml) determined by a commercially available RIA kit (Amersham).

Since no widely accepted therapy for HPCS exists, along with the active and untreated liver disease, a course of α-interferon was started at a dose of 3,000,000 IU 3 times per week, together with continuous low-flow oxygen therapy.

Discussion

End-stage liver disease is accompanied by several circulatory abnormalities. Cardiopulmonary dysfunction in cirrhosis includes hyperkinetic systemic and splanchnic circulation, cirrhotic cardiomyopathy and HPS [1, 2]. HPS generally refers to hypoxemia and vascular pulmonary dilation in the setting of liver disease and appears to be relatively common, although often subclinical. Severe HPS is rare and has an estimated prevalence of 5% in cirrhotic patients. However, the pathogenesis of this syndrome is still unclear. It has been postulated that during HPS an impairment of hypoxic vasoconstriction exists, which may ultimately lead to marked pulmonary vascular dilation, diffusion-perfusion impairment, A-V shunts and ventilation-perfusion mismatch. These gas exchange abnormalities may be clinically evident in patients with profound hypoxia, platypnea

and/or ortodeoxia, which have already been associated with classic right-to-left shunts. In fact, patients with HPS may have venous blood flowing through nonventilated alveoli, or bypassing of capillary-alveolar interfaces by venous blood through A-V shunts or ineffective oxygenation of deoxygenated hemoglobin molecules due to dilated capillary and precapillary beds [3, 4]. Moreover, patients have peripheral A-V vasodilation, extrinsicable as spider nevi and pleural vascular abnormalities that resemble cutaneous spider nevi, called lung spiders [5, 6]. Systemic vasodilation and hypotension with widened differential pressure and elevated cardiac output are often found in HPS patients. Although there are not signs, symptoms or hallmarks of HPS on physical examination, the presence of cyanosis, severe hypoxemia (partial pressure of oxygen <60 mm Hg) and platypnea-orthodeoxia, spider nevi, and digital clubbing strongly suggest HPS [7]. The use of contrast-enhanced echocardiography with saline, lung scanning quantification with uptake in the brain, or both can distinguish hypoxemia induced by HPS from all other causes of hypoxemia [4, 8].

The underlying intermediate pathogenetical and biochemical mechanisms are probably common to these different pulmonary and extrapulmonary manifestations, so we propose the new term of HPCS, which more encompasses the spectrum of coexisting clinicopathological abnormalities in this liver-related vascular disorder. Of note, patients with cutaneous spider nevi have been reported to have more systemic and pulmonary vasodilation, more profound gas exchange abnormalities, and less hypoxic pulmonary vasoconstriction, suggesting that spider nevi might be a cutaneous index of intrapulmonary vascular dilation [5–7]. Moreover, it seems possible to speculate that arterial oxygenation in these patients is dependent on the degree of pulmonary and systemic vascular changes. For example, blunted hypoxic pulmonary vasoconstriction is a common feature of HPS [3, 4]. We can assume that spider nevi, telangiectasia and cutaneous vasodilation when extensively present as in the case of our patient, or the lung spiders, can have profound hemodynamical effects that can quite alter PaO_2, since the shunting of blood from arterial to venous compartments decreases O_2 availability to tissues, but also decreases oxygen consumption and hypoxemia. Since hypoxia is a potent vasoconstrictor, a less marked peripheral arterial deoxygenation can partially influence vasodilation and A-V anastomosis, and thus the spider angiomas can modulate vascular pulmonary changes. If pulmonary vasodilation and A-V shunts are prevalent, the patient will have marked hypoxia, whereas if extrapulmonary vasodilation and A-V communications are prevalent, the patient will have a relatively less marked hypoxia in pulmonary arterial blood, and this could be involved in the blunted hypoxic pulmonary vasoconstriction reported in patients with HPS. Moreover it could help to explain also the possible occurrence of both intrapulmonary vascular dilation and anatomical shunt without associated hypoxemia that some authors claimed to challenge the definition of HPS in some patients [3].

The exact biochemical mechanisms behind the production of pulmonary and extrapumonary vascular dilation and A-V shunt are not yet known. However, it can be supposed that an imbalance between vasoconstrictive and vasodilatory substances that are abnormally metabolized by the impaired liver exists. Of note, the criteria for this syndrome have been met in patients with any form of liver disease, including acute liver failure and ischemic hepatitis [9]. On the contrary, no relationship between the presence or severity of HPS and the severity of liver disease as assessed on the basis of Child-Turcotte-Pugh classification or the Model for End-Stage Liver Disease has been found [10]. Some hypotheses assign a crucial role to NO as a mediator of pulmonary vasodilation and impaired arterial oxygenation reported in patient with advanced liver disease, and a correlation between the decrease in exhaled NO concentration after liver

transplantation and the improvement in oxygenation in these patient has been reported [4, 11]. Little is known about the behavior of plasmatic endothelin-1 levels in these patients, and there are no data on a possible correlation between the humoral modification(s) leading to HPS and cutaneous abnormalities.

NO of our patient was above physiologic level. Increase in plasma NO may be involved in the systemic and pulmonary vasodilation, whereas increased levels of endothelin-1 may counteract the effects of NO. High plasma levels of endothelin-1 may also reflect decreased availability of endothelin-1 receptors or decreased clearance [12]. In addition, since the endothelin-converting enzyme, which transforms pro-endotelin to endothelin-1, is situated in the lungs, it is tempting to speculate that the high concentration of endothelin-1 in the lungs increases pulmonary vasoconstriction, which favors the formation of A-V shunts. Moreover, it has been reported that endothelin-1 produced during hepatic injury may contribute to HPS by modulating eNOS and inducing pulmonary microcirculatory vasodilation [4, 13].

Our patient developed digital clubbing, besides pulmonary insufficiency and spider nevi. In fact, it is well known that patients with chronic liver disease, chronic inflammatory bowel disease, congenital heart diseases with right-to-left shunts, congenital anomalous hepatic drainage and type 1b Abernethy malformation can develop digital clubbing [4]. Of note, these rare congenital cardiac disorders without liver injury in which either hepatic venous blood flow does not reach the lung or portal venous blood reaches the inferior vena cava without passing through the liver have clinical similarities to the HPS, suggesting that blood from the gut must cross the liver to prevent pulmonary vascular dilation [4]. It is thought that digital clubbing develops from the presence in the systemic circulation of one or more growth factors that are normally inactivated in the lungs [14]. Moreover, one of the known physiologic effects of endothelin-1 is mesenchymal cell hyperplasia. In the presence of pulmonary A-V shunts these substances find their way to the systemic circulation where they could stimulate digital hyperostosis.

Even though a number of mechanisms have been proposed to explain pulmonary and systemic vascular change in these patients, increased levels of NO and endothelin-1 seem to be usual findings in this clinical syndrome [4, 15]. In conclusion, we suggest that the new term of HPCS is more appropriate and inclusive than that of HPS to summarize the diversity, similarity and physiopathological correlations for this unique clinicopathological syndrome.

Fig. 1. Clinical features of severe HPCS in a 54-year-old woman. Prominent and diffuse spider nevi on the thorax. The patient had physical traits of cirrhosis and characteristic signs and symptoms of HPCS including severe hypoxemia, platypnea-orthodeoxia, diffuse cutaneous spider nevi, telangiectasia, palmar erythema, digital clubbing and findings of intrapulmonary diffusion-perfusion impairment and A-V shunt.

Fig. 2. Radionuclide imaging of the brain, kidneys and lungs (anterior and posterior lungs) showing the positive and rapid distribution of the 99mTc-labeled macroaggregated albumin to the kidneys and brain.
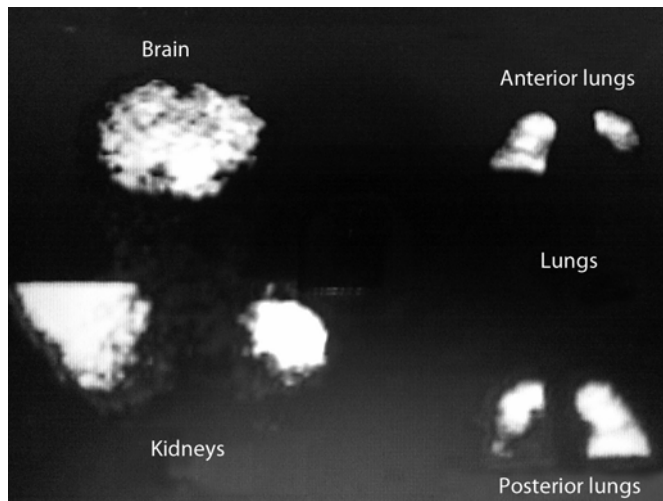
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