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CASE STUDY

Hepatopulmonary syndrome following portopulmonary hypertension

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ABSTRACT: Portopulmonary hypertension (PPHTN) and hepatopulmonary syndrome (HPS) are distinct clinical entities that may accompany liver disease.

While PPHTN and HPS have been infrequently described as occurring in the same patient, to the present authors' knowledge, the order of occurrence has always been the initial onset of HPS, with pulmonary hypertension developing either concurrently or subsequently. In some instances, liver transplantation has been undertaken for HPS, followed by resolution of the HPS and subsequent development of pulmonary hypertension.

The current case study presents a patient with hepatitis C-related cirrhosis in whom PPTHN developed initially, followed 2 yrs later by the development of the HPS.

The current authors speculate that progressive imbalance in favour of endogenous vasodilators over vasoconstrictive factors led to normalisation of the pulmonary artery pressures.

KEYWORDS: Cardiopulmonary pathophysiology, cardiorespiratory, hepatopulmonary problems, hepatopulmonary syndrome, pulmonary circulation physiopathology, pulmonary hypertension

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STATEMENT OF INTEREST
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Hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHTN) are distinct clinical entities that may accompany liver disease. Although characterised by markedly different clinical and physiological features, HPS and PPHTN have been described as occurring within the same patient in five separate instances [1–5]. Among these five patients, the HPS either preceded the onset of pulmonary hypertension or manifested itself concurrently. Only in a single Japanese report [6] has a patient been documented to have pulmonary hypertension prior to developing HPS and, in this instance, the pulmonary hypertension was explicitly stated not to be due to PPHTN. The current case study presents a case of PPHTN and HPS that occurred metachronously within the same patient, with PPHTN preceding the HPS.

CASE REPORT

A 77-yr-old male with hepatitis C and cirrhosis presented to the Cleveland Clinic (Cleveland, OH, USA) in October 2005 for evaluation and possible surgical correction of aortic valve insufficiency. The patient had undergone coronary artery revascularisation surgery twice in the past (22 and 6 yrs earlier) and had a long-standing history of hepatitis C and compensated biopsy-proven cirrhosis. His past medical history also included hypercholesterolaemia, colon cancer (for which he had undergone resection 6 yrs earlier) and prostate cancer (treated by resection and hormonal therapy 10 yrs earlier).

Upon the patient's current presentation, hypoxaemia prompted an extensive evaluation, which established the presence of HPS. Specifically, supine pulse oximetry saturation on 5 $L \cdot min^{-1}$ of oxygen by nasal cannula was 88%, with a decline to 83% saturation when sitting. Multiple arterial blood gases were obtained (table 1), which confirmed severe hypoxaemia and orthodeoxia. The chest radiograph showed normal lung volumes, prominent basilar interstitial markings and calcified perihilar nodes. A computed tomography (CT) scan of the chest suggested bibasilar vascular dilatations and minimal interstitial fibrotic changes, and calcified, normal-sized hilar lymph nodes; no masses, nodules, thrombi or pleural effusions were identified. A Duplex ultrasound of lower extremities showed no evidence of deep vein thrombosis. Spirometry was normal and severe dyspnoea precluded measurement of the diffusing capacity of the lung for carbon monoxide. Doppler, contrast-enhanced, transoesophageal echocardiogram

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TABLE 1 Arterial blood gas measurements at the time of presentation (October 2005) performed in the supine, sitting and standing positions

Arterial blood gas	Sitting#	Sitting#	Standing	Supine
F_{I,O_2}	0.40	1.0	1.0	0.90
P_{a,O_2} kPa (mmHg)	5.46 (41)	12.40 (93)	11.60 (87)	33.46 (251)
$P_{a,O_2}/F_{I,O_2}$	102	93	87	279
S_{a,O_2} %	78	95	96	99
P_{a,CO_2} kPa (mmHg)	3.47 (26)	3.73 (28)	3.07 (23)	4.13 (31)
pH	7.52	7.45	7.45	7.46

F_{I,O_2}: inspiratory oxygen fraction; P_{a,O_2}: arterial oxygen tension; S_{a,O_2}: arterial oxygen saturation; P_{a,CO_2}: carbon dioxide arterial tension. #: two sets of arterial blood gas analysis were carried out: one on oxygen at 100% and one at 40% (see the second line, F_{I,O_2}). 1 mmHg=0.133 kPa.

(performed in October 2005) showed no significant intracardiac shunt but evidence of an intrapulmonary shunt, based on the delayed (*i.e.* more than five cardiac cycles after injection) appearance of contrast in the left-sided cardiac chambers. There was mild-to-moderate aortic regurgitation, with moderate sclerosis and a valvular area of 1.7 cm^2, mild mitral regurgitation with a minimally dilated left atrium and normal left ventricular systolic function. The pulmonary artery systolic pressure was estimated to be normal (28 mmHg). A technetium 99m macroaggregated albumin nuclear scan was performed and showed tracer activity in the brain and kidneys, indicating an ~10% quantitative right-to-left shunt fraction. In addition, a right heart catheterisation performed 2 months earlier (August 2005) showed normal pulmonary artery pressures and pulmonary vascular resistance, *i.e.* right atrium 6 mmHg, pulmonary artery 30/12 mmHg, pulmonary artery occlusion pressure 8 mmHg, cardiac output 6.5 and cardiac index 3.5 $L \cdot min^{-1}$, and pulmonary vascular resistance 125 $dyne \cdot s^{-1} \cdot cm^{-5}$ (normal <150 $dyne \cdot s^{-1} \cdot cm^{-5}$).

PPHTN had been diagnosed ~2 yrs before the patient's current admission (*i.e.* in November 2003). Specifically, dyspnoea, hypoxaemia and clubbing of the extremities prompted transthoracic and transoesophageal echocardiograms at that time, which showed moderate pulmonary hypertension (estimated pulmonary artery systolic pressure of 40 mmHg), with mild aortic regurgitation, normal left ventricular ejection fraction, normal-sized cardiac chambers and wall thickness, and mild tricuspid regurgitation. These findings were confirmed by subsequent transthoracic and transoesophageal echocardiograms, which showed pulmonary hypertension, but no evidence of severe aortic or mitral regurgitation (table 2). The echocardiographic studies showed progressive development of pulmonary hypertension, which was confirmed by right heart catheterisation and was not present during a cardiac catheterisation performed in 2002 at another institution. The catheterisation performed in 2002 showed near-normal pulmonary artery and capillary occlusion pressures, normal pulmonary vascular resistance and no evidence of mitral or aortic regurgitation. In the context of the patient's known liver cirrhosis and no other underlying causes of pulmonary hypertension, PPHTN was diagnosed. Specifically, there was no evidence of collagen vascular disease, anorexigen use, prior pulmonary embolism, obstructive sleep apnoea or atrial septal defect, and HIV testing had been negative. Ambulatory supplemental oxygen at 2 $L \cdot min^{-1}$ was prescribed at that time.

On physical examination on admission (October 2005), the patient's blood pressure was 110/70 mmHg, cardiac frequency was 100 $beats \cdot min^{-1}$ and respiratory rate was 22 $breaths \cdot min^{-1}$. The patient was in significant respiratory distress and was using accessory respiratory muscles. He was jaundiced and had multiple, large spider angiomas on the torso and upper extremities, facial telangiectasia and palmar erythema; no rashes or other lesions were noted. Chest examination showed bilateral gynaecomastia, symmetric respiratory excursions and normal resonance to percussion; no crackles, rhonchi or wheezes were audible on auscultation. There was no jugular venous distension and the heart sounds were normal, with a parasternal grade 2/4 protodiastolic murmur and an apical 3/6 pansystolic murmur; no gallops were audible. The abdomen was soft, with normal bowel sounds, no masses and no ascites. The liver felt small (span of 7 cm) and moderate splenomegaly was noted. The examination of the extremities showed peripheral clubbing and cyanosis, without evidence of oedema.

Additional laboratory examination showed pancytopaenia, normal renal function and electrolytes, normal serum brain natriuretic peptide level, mild hyperbilirubinaemia (total bilirubin 1.8 $mg \cdot dL^{-1}$), mildly elevated aspartate aminotransferase of 52 $U \cdot L^{-1}$ (normal <40), normal alanine aminotransferase, hypoalbuminaemia (3.4 $g \cdot dL^{-1}$) and normal coagulation tests.

The patient was deemed a poor candidate for liver transplantation on the basis of his age and past malignancies. Transtracheal oxygen was offered but declined, and the patient was discharged to go home on oxygen at 6 $L \cdot min^{-1}$ by nasal cannula and over-the-counter garlic tablets [7]. A follow-up

TABLE 2 Summary of echocardiographic features of the patient over time

Echocardiographic feature	November 2003	July 2004	September 2004	April 2005	August 2005	October 2005
Aortic valve regurgitation	+1	+1	+1	+1	+2– +3	+1
Mitral valve regurgitation	0	0	0	+2	+2	+1
Estimated right ventricular systolic pressure mmHg	40	45	45	Normal	Normal	Normal
Left ventricle ejection fraction	Normal	Normal	Normal	Normal	Normal	Normal

telephone interview 7 months after hospital discharge indicated that he was stable but with persistent, severely impaired functional capacity.

DISCUSSION

HPS and PPHTN are distinct clinical entities that can complicate liver disease and may, in rare instances, occur either simultaneously or metachronously in the same patient. While the present authors' review of the literature showed five such instances [1–5], the current case is distinctive in reporting for the first time, to the present authors' knowledge, the onset of the HPS following PPHTN. Indeed, in all previously reported instances of co-occurrence of HPS and PPHTN in the same patient, development of HPS either preceded PPHTN [1, 2, 4, 5] or occurred simultaneously [3]. In several instances, pulmonary hypertension followed liver transplantation, for which HPS was an indication [1, 2, 5]. The present authors are aware of only a single reported case [6] in which pulmonary hypertension preceded HPS and, in this Japanese report [6], the authors specifically stated that the cause of the patient's pulmonary hypertension was not PPHTN.

The evidence supporting the diagnoses and the metachronous occurrence of PPHTN and HPS in the current patient is strong. Initially, the patient had echocardiogram-confirmed pulmonary hypertension, modest supplemental oxygen needs (*i.e.* 2 $L \cdot min^{-1}$ of nasal cannula) and no evidence of right-to-left shunt by echocardiography. Furthermore, no alternative explanation for the pulmonary hypertension was evident. Then, ~24 months later, the patient satisfied criteria for HPS, with worsened hypoxaemia, evidence of intrapulmonary vascular dilatations based on contrast-enhanced echocardiographic evidence of right-to-left intrapulmonary shunt, and parenchymal markings on chest CT that were deemed consistent with IPVDs. No alternative explanation for intrapulmonary shunt (*e.g.* arterio-venous malformations) was evident.

The metachronous occurrence of PPHTN followed by the HPS is of interest because of the different proposed pathogenetic causes of PPHTN and HPS. Although the specific pathogenesis of both conditions is unknown, many mechanisms leading to PPHTN have been proposed [8, 9]. For example, a widely held view is that in the setting of a specific genetic predisposition [10, 11], a humoural vasoconstrictive substance produced in the splanchnic circulation and normally metabolised by the liver reaches the pulmonary vessels through the diseased liver or through portosystemic collaterals. Pulmonary vasoconstriction results either directly or by tipping an established equilibrium between natural vasodilators and vasoconstrictor substances in favour of the latter. Candidate humoural mediators include serotonin, endothelin, preproendothelin, interleukin-1, vasoactive intestinal peptide, thromboxanes, and other prostanoid substances [12–14]. Furthermore, prolonged pulmonary vasoconstriction is felt to predispose to structural changes, such as plexogenic pulmonary arteriopathy and/or microvascular *in situ* thrombosis.

Similarly, the development of HPS is felt to reflect the effect of vasodilatory substances that appear in the face of liver disease. Specifically, in both human HPS and animal models [15, 16], nitric oxide (NO) has been implicated as an important mediator of vasodilation. NO exerts its effect either through upregulation of NO synthase in the pulmonary endothelium [17] or through increased NO production, the latter being due to intestinal absorption of bacterial endotoxins and lack of clearance by the liver. Moreover, in severely hypoxaemic patients with HPS, the concentration of exhaled NO is high [18]. Finally, administration of antagonists of NO synthesis, such as methylene blue or others, can enhance oxygenation [19–23].

In the context of uncertainty about the pathogenesis of both entities, why PPHTN and HPS occurred metachronously and in this order in the present patient is still unknown. The sequence may be explained by the following mechanisms. 1) PPHTN developed due to excessive, unbalanced pulmonary vasoconstriction; and 2) several hepatic or portal circulation changes (*e.g.* the development of shunts or progressive hepatic parenchymal failure) led to vasomotor changes in favour of vasodilatation and possibly NO-mediated pulmonary vessel dilatation (''autotherapy''). That the development of the HPS reflected the prevailing influence of vasodilation is supported by the concomitant appearance of cutaneous spider angiomata and telangiectasias and the improvement of mitral and aortic regurgitation.

Overall, the current case extends the spectrum of described pulmonary complications of liver disease in presenting, to the authors' knowledge, the first instance of portopulmonary hypertension and hepatopulmonary syndrome in the same patient in which portopulmonary hypertension preceded the development of hepatopulmonary syndrome. In the event that such patients are offered liver transplantation to reverse the hepatopulmonary syndrome, clinicians will need to be vigilant for the reappearance of pulmonary hypertension following transplant, as has occasionally been previously described [1, 2, 5].

REFERENCES

1 Shah TJ, Isaac J, Adams D, Kelly D. Development of hepatopulmonary syndrome and portopulmonary hypertension in a paediatric liver transplant patient. *Pediatr Transplant* 2005; 9: 127–131.

2 Martinez-Palli G, Barbera JA, Taura P, Cirera I, Visa J, Rodriguez-Roisin R. Severe portopulmonary hypertension after liver transplantation in a patient with preexisting hepatopulmonary syndrome. *J Hepatol* 1999; 31: 1075–1079.

3 Jones FD, Kuo PC, Johnson LB, Njoku MJ, Dixon-Ferguson MK, Plotkin JS. The coexistence of portopulmonary hypertension and hepatopulmonary syndrome. *Anesthesiology* 1999; 90: 626–629.

4 Mal H, Burgiere O, Durand F, Fartoukh M, Cohen-Solal A, Fournier M. Pulmonary hypertension following hepatopulmonary syndrome in a patient with cirrhosis. *J Hepatol* 1999; 31: 360–364.

5 Kaspar MD, Ramsay MA, Shuey CB, Levy MF Jr, Klintmalm GG. Severe pulmonary hypertension and amelioration of hepatopulmonary syndrome after liver transplantation. *Liver Transpl Surg* 1998; 4: 177–179.

6 Tasaka S, Kanazawa M, Nakamura H, *et al.* [An autopsied case of primary pulmonary hypertension complicated by hepatopulmonary syndrome.] *Nihon Kyobu Shikkan Gakkai Zasshi* 1995; 33: 90–94.

7 Abrams GA, Fallon MB. Treatment of hepatopulmonary syndrome with *Allium sativum* L. (garlic): a pilot trial. *J Clin Gastroenterol* 1998; 27: 232–235.
8 Lebrec D, Capron JP, Dhumeaux D, Benhamou JP. Pulmonary hypertension complicating portal hypertension. *Am Rev Respir Dis* 1979; 120: 849–856.
9 Mandell MS, Groves BM. Pulmonary hypertension in chronic liver disease. *Clin Chest Med* 1996; 17: 17–33.
10 Deng Z, Morse JH, Slager SL, *et al.* Familial primary pulmonary hypertension (gene PPH1) is caused by mutations in the bone morphogenetic protein receptor-II gene. *Am J Hum Genet* 2000; 67: 737–744.
11 Morse JH, Deng Z, Knowles JA. Genetic aspects of pulmonary arterial hypertension. *Ann Med* 2001; 33: 596–603.
12 Egermayer P, Town GI, Peacock AJ. Role of serotonin in the pathogenesis of acute and chronic pulmonary hypertension. *Thorax* 1999; 54: 161–168.
13 Panos RJ, Baker SK. Mediators, cytokines, and growth factors in liver–lung interactions. *Clin Chest Med* 1996; 17: 151–169.
14 Maruyama T, Ohsaki K, Shimoda S, Kaji Y, Harada M. Thromboxane-dependent portopulmonary hypertension. *Am J Med* 2005; 118: 93–94.
15 Rolla G. Hepatopulmonary syndrome: role of nitric oxide and clinical aspects. *Dig Liver Dis* 2004; 36: 303–308.
16 Nunes H, Lebrec D, Mazmanian M, *et al.* Role of nitric oxide in hepatopulmonary syndrome in cirrhotic rats. *Am J Respir Crit Care Med* 2001; 164: 879–885.
17 Fallon MB, Abrams GA, Luo B, Hou Z, Dai J, Ku DD. The role of endothelial nitric oxide synthase in the pathogenesis of a rat model of hepatopulmonary syndrome. *Gastroenterology* 1997; 113: 606–614.
18 Cremona G, Higenbottam TW, Mayoral V, *et al.* Elevated exhaled nitric oxide in patients with hepatopulmonary syndrome. *Eur Respir J* 1995; 8: 1883–1885.
19 Schenk P, Madl C, Rezaie-Majd S, Lehr S, Muller C. Methylene blue improves the hepatopulmonary syndrome. *Ann Intern Med* 2000; 133: 701–706.
20 Lange PA, Stoller JK. The hepatopulmonary syndrome. *Ann Intern Med* 1995; 122: 521–529.
21 Rodriguez-Roisin R, Krowka MJ, Herve P, Fallon MB, ERS Task Force Pulmonary-Hepatic Vascular Disorders (PHD) Scientific Committee. Pulmonary-hepatic vascular disorders (PHD). *Eur Respir J* 2004; 24: 861–880.
22 Gómez FP, Barbera JA, Roca J, Burgos F, Gistau C, Rodriguez-Roisin R. Effects of nebulized *N*(G)-nitro-L-arginine methyl ester in patients with hepatopulmonary syndrome. *Hepatology* 2006; 20: 1084–1091.
23 Fallon MB. Hepatopulmonary syndrome: more than just a matter of tone? *Hepatology* 2006; 43: 912–913.