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SHORT REPORT

Pulmonary Hypertension After Liver Transplantation in Patients With Antecedent Hepatopulmonary Syndrome: A Report of 2 Cases and Review of the Literature

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Hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHTN) are distinct clinical entities that may complicate liver disease. Although HPS and PPHTN are different, several reports describe 6 patients in whom both conditions have occurred, either concurrently or sequentially, sometimes with the onset of PPHTN after liver transplantation. The current report extends this sparse experience by reporting 2 patients who underwent liver transplantation for HPS and who developed pulmonary hypertension after liver transplantation. This experience calls for better understanding of the pathogenesis of HPS and PPHTN and ways to better predict their occurrence. ***Liver Transpl 12:1278-1282, 2006.*** © **2006 AASLD.**

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Portopulmonary hypertension (PPHTN) and hepatopulmonary syndrome (HPS) are 2 distinct pulmonary vascular disorders that may accompany liver disease.[1-4] Indeed, the physiologic and clinical characteristics of these 2 entities vary markedly. For example, HPS, which may occur in approximately 20% of liver transplant candidates,[1] is characterized by a widened alveolar-arterial oxygen gradient and the presence of intrapulmonary vascular dilatations, sometimes accompanied by platypnea and orthodeoxia.[1-3] Patients with HPS characteristically have increased cardiac output, and decreased pulmonary artery (PA) pressures and pulmonary vascular resistance. In contrast, PPHTN is less common, having been estimated to occur in up to 4.7% of liver transplant candidates.[1] Patients with PPHTN present with findings of pulmonary hypertension, including dyspnea, impairment of the diffusing capacity, and edema.[1-4] Distinctive physiologic characteristics include increased PA pressures (by definition, with mean PA pressure >25 mm Hg at rest or 30 mm Hg with exercise), an increased pulmonary vascular resistance, and when advanced, with decreased cardiac index. Response to liver transplantation (LT) also distinguishes HPS from PPHTN because HPS is widely considered to be an indication for LT, with a high likelihood of reversal after transplantation,[1] whereas PPHTN is commonly considered a contraindication to LT because of the high associated mortality risk, especially when the mean PA pressure exceeds 45 mm Hg.[1]

Although HPS and PPHTN are clinically and physiologically distinct, several reports describe their occurrence within the same patient, either concurrently or sequentially, sometimes after LT.[5-10] The current report extends the available experience regarding the occurrence of HPS and pulmonary hypertension, possibly due to PPHTN, within the same patient; specifically, we describe 2 patients who developed pulmonary hypertension after LT that was undertaken to reverse HPS complicating cirrhosis.

Abbreviations: HPS, hepatopulmonary syndrome; PPHTN, portopulmonary hypertension; PA, pulmonary artery; LT, liver transplantation; PAOP, pulmonary artery occlusion pressure; CT, computed tomography.

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CASE PRESENTATION

Patient 1

A 31-year-old woman with end-stage liver disease due to autoimmune hepatitis developed HPS. She had platypnea and hypoxemia (room air Spo_2 73% 6 months before LT and while intubated during later LT surgery on Fio_2 60%, had a Pao_2 of 391 mm Hg, $Paco_2$ 24 mm Hg, pH 7.31). Contrast-enhanced echocardiogram showed evidence of an intrapulmonary shunt, consistent with HPS. Notably, right ventricular systolic pressure, as assessed by echocardiogram at the time of presentation, was normal (22 mm Hg). Pulmonary function tests were consistent with a mild restrictive ventilatory defect (FEV_1 80% predicted, FVC 89% predicted) that was ascribed to ascites. Oxygen requirements were 4 L/min at rest and 6 L/min with ambulation to maintain saturations of 98% and 96%, respectively.

One year after onset of HPS, she underwent a cadaveric LT in the hope of reversing HPS. Intraoperative hemodynamic measurements before reperfusion showed PA systolic and diastolic pressures of 18 and 11 mmHg, respectively (mean 13 mm Hg), PA occlusion pressure (PAOP) of 10 mm Hg, cardiac output of 7.6 L/min; after reperfusion, values were PA 26/17 mm Hg (mean 20 mm Hg), wedge pressure 12 mm Hg, cardiac output 11.8 L/min. After a postoperative course characterized by neurologic complications of seizures and right hemiparesis, she was discharged to a rehabilitation center on postoperative day 22, with improving respiratory symptoms (i.e., no shortness of breath and minimal fatigue). Oxygenation had normalized with a room arterial blood gas showing a Pao_2 97 mm Hg, $Paco_2$ 35 mm Hg, and pH 7.44 (alveolar-arterial oxygen gradient of 5 mm Hg).

One month later, she developed an acute episode of chest and abdominal pain accompanied by hypotension and loss of consciousness, for which she was admitted to a local hospital and subsequently transferred to our institution. Initial assessment showed oliguria and significant ascites. Right heart catheterization showed severe pulmonary hypertension and low cardiac output consistent with cor pulmonale (PA 67/30 mm Hg [mean 42 mm Hg], cardiac output 2 L/min, PAOP 14 mm Hg, pulmonary vascular resistance 1120 dyne-s/cm^5). Also, a transthoracic echocardiogram revealed a severely dilated right ventricle with profoundly decreased systolic function and 4+ tricuspid regurgitation. Notably, pursuit of an alternative explanation for severe pulmonary hypertension and right heart failure included a chest computed tomographic (CT) angiogram, which showed no evidence of pulmonary embolism but enlarged right cardiac chambers and a dilated main PA. A CT scan of the abdomen showed dilation of the hepatic veins, thickening of the colonic and small bowel wall, and a large amount of ascites. Head CT scan showed no acute changes. Key laboratory values showed impaired renal and liver function (serum creatinine 1.5 mg/dL, prothrombin time 30.7, international normalized ratio 2.8, alanine transaminase 424 U/L, aspartate aminotransferase 1,826 U/L, serum lactate 14.6 mmol/L), leukocytosis (14,500/μL with left shift), platelets 193,000/μL, and slight increase in cardiac enzymes (creatinine kinase myocardial biomarker 9.1 ng/mL).

Concern about intraabdominal sepsis prompted an exploratory laparotomy, which showed generalized ischemia of the bowel and clear ascites ascribed to hypoperfusion accompanying the severe pulmonary hypertension. The patient died 48 hours later. All cultures were negative. A postmortem examination showed an acute myocardial infarction (estimated to be of 8-12 hours' duration), severe right ventricular dilatation with hypertrophy, no atrial septal defect, and no pulmonary emboli. Examination of the pulmonary arteries showed no evidence of plexogenic arteriopathy or in situ thrombosis.

Patient 2

A 40-year-old woman with hepatitis C cirrhosis and HPS underwent cadaveric LT. She had developed progressive dyspnea and hypoxemia 10 months before the transplantation, so that by the time of surgery, she required 6 L/min of oxygen at rest and 12 L/min (6 L/min through nasal cannula and 6 L/min of transtracheal oxygen) during activity to maintain an Spo_2 up to 93%. Results of a room air arterial blood gas 5 months before LT showed Pao_2 67 mm Hg, Pco_2 28 mm Hg, pH 7.48 (alveolar-arterial oxygen gradient of 47 mm Hg). The diagnosis of HPS before LT was confirmed by a saline contrast-enhanced echocardiogram, which showed definite evidence of an intrapulmonary right-to-left shunt associated with hypoxemia and normal left and right ventricular size and function. Intraoperative hemodynamic measurements before reperfusion showed a PA diastolic pressure of 25 mm Hg, central venous pressure of 20 mm Hg, PAOP of 13 mm Hg, and a cardiac output of 7.8 L/min; postreperfusion values were PA diastolic of 15 mm Hg, central venous pressure of 16 mm Hg, PAOP of 10 mm Hg, and cardiac output of 8.6 L/min.

Her postoperative course was complicated by an episode of rejection and of cholangitis, from which she recovered, and she was discharged to a rehabilitation facility 2 months after LT. In keeping with posttransplantation resolution of HPS, her oxygen requirements progressively lessened, so that she no longer required supplemental oxygen 4 months after LT; at that time, her room air pulse oximetry saturation (Spo_2) was 90-95%.

Thirteen months after her transplantation, she developed acute chest pain, dyspnea, and swelling of her lower extremities. An echocardiogram showed a severely dilated right ventricle with markedly reduced function, right atrial enlargement, and 3+ tricuspid regurgitation. On transfer to the intensive care unit, a bilateral pulmonary angiogram was performed, which showed dilated pulmonary arteries bilaterally but no evidence of pulmonary embolism. At a time when her oxygenation was adequate (Po_2 78 mm Hg, Pco_2 27 mm Hg, pH 7.38 on Fio_2 0.80), Swan-Ganz catheterization

was performed and showed severe pulmonary hypertension with elevated pulmonary vascular resistance (PA pressure 113/46 mm Hg [mean 76 mm Hg], PAOP 17 mm Hg, cardiac output 6.5 L/min, pulmonary vascular resistance 720 dyne-s/cm^5). Laboratory values showed impaired renal function (serum creatinine 2.1 mg/dL), normal liver function and serum chemistries, and normal complete blood count with 151,000 platelets/μL. These measures supported the impression of severe pulmonary hypertension that was otherwise without explanation and consistent with PPHTN. Despite transfer to the intensive care unit and aggressive support, she developed progressive hypotension and refractory hypoperfusion, leading to death 96 hours after admission. No postmortem examination was performed.

DISCUSSION

The current report presents 2 patients who developed both HPS and pulmonary hypertension, possibly related to PPHTN, extending to a total of 8 the number of reported patients in whom these 2 distinct clinical entities coexisted[5-10] (Table 1). In both patients described here, pulmonary hypertension developed after LT, which was undertaken to treat the patient's HPS complicating underlying cirrhosis. In patient 1, restoration of normoxemia within 3 weeks after LT suggested resolution of HPS, followed by the onset of severe pulmonary hypertension 1 month later. In patient 2, the slow but eventual resolution of hypoxemia 4 months after LT is consistent with resolution of HPS, followed by the onset of pulmonary hypertension 9 months later. Intraoperative PA pressure measurements in both patients indicated that pulmonary hypertension newly developed after LT.

As summarized in Table 1, occurrence of HPS and PPHTN within the same patient has been described in 6 earlier reports,[5-10] which we identified in a Medline search (1966 to January 2006) using the search terms "hepatopulmonary syndrome" and "pulmonary hypertension" and by review of references cited in the available reports. Available experience shows that the occurrence of both entities within the same patient has occurred in both adults and children, in both men and women, and in patients with cirrhosis due to several different etiologies, including alcohol consumption, hepatitis C, biliary atresia, alpha-1 antitrypsin deficiency, and autoimmune hepatitis.

In reviewing the experience of the 8 reported patients, 3 possible patterns are evident regarding the development of HPS and PPHTN within the same patient. One pattern is that HPS and PPHTN manifest concurrently.[7] In a second pattern, HPS and PPHTN develop sequentially, most commonly with the onset of HPS preceding that of PPHTN.[5,6,8,9] In the third possible pattern represented by a single patient, Tasaka et al. [10] described pulmonary hypertension in a patient whose cirrhosis and HPS manifested 7 years later. They speculate that the pulmonary hypertension was idiopathic because the evidence supporting liver disease at the time of its onset was scant (i.e., limited to a slightly prolonged prothrombin time and low cholesterol, with otherwise normal liver function tests and no evidence of portal hypertension by ultrasound). Still, because of the possibility that the cirrhosis was subclinical at that time, this report[10] is, to our knowledge, unique in suggesting the development of pulmonary hypertension before the onset of HPS.

In some instances of sequential development of HPS followed by PPHTN, the PPHTN develops after the antecedent HPS resolved—sometimes after LT. In other instances, PPHTN develops in the face of persistent HPS. As in the patients reported by Shah et al.,[5] Martinez-Palli et al.,[6] and Kaspar et al.,[9] in which PPHTN reportedly developed after LT, pulmonary hypertension developed after LT in both currently reported patients.

That the pathogenesis of HPS and of PPHTN remains uncertain currently precludes certain explanation of events in the 8 patients described, or clear attribution of the pulmonary hypertension to PPHTN in our 2 patients. Still, Martinez-Palli et al.[6] have speculated about 2 potential mechanisms by which antecedent HPS could lead to PPHTN after LT. First, because HPS is characterized by abnormal pulmonary vasodilation (presumably mediated by nitric oxide[1]), removal of the diseased liver lessens pulmonary vasodilation, allowing pulmonary hypertension to be unmasked. A second potential mechanism is that the increased pulmonary blood flow characteristic of HPS leads to remodeling of the pulmonary arteries in a manner resembling that seen after congenital left-to-right intracardiac shunt.[6]

Whether the pulmonary hypertension that developed after LT can be confidently ascribed to PPHTN in the 2 patients we describe is speculative. On the one hand, it is reasonable to imagine that the portal hypertension that characterized the patients' cirrhosis before LT had resolved after LT. Indeed, objective evidence of portal hypertension after LT is not available in these patients. On the other hand, careful patient assessment after LT fails to indicate an alternative explanation for pulmonary hypertension (e.g., pulmonary embolism, HIV infection, new obstructive sleep apnea), leaving open the possibility that the pulmonary hypertension developing after LT was either idiopathic or due to PPHTN with subclinical portal hypertension.

In the context that idiopathic pulmonary arterial hypertension may be familial and associated with heterozygous mutation in the bone morphogenetic protein receptor type II and activin receptor-like kinase 1 genes,[11-14] genetic predisposition to PPHTN must be considered. Although these genetic abnormalities have not, to our knowledge, been described in individuals with PPHTN to date,[1] none of the 6 previously described patients with both HPS and PPHTN or the 2 currently reported patients was tested for these genetic predispositions. In most instances, the reports preceded recognition that these genetic variants are associated with pulmonary hypertension.

The dire prognostic impact of developing PPHTN[1] invites better understanding of how to predict its development. Although data from our 2 patients and those

TABLE 1. Summary of Available Reports in Which Pulmonary Hypertension and Hepatopulmonary Syndrome Occurred in the Same Patient

Reference	Year	No. of patients	Occurrence of pulmonary hypertension and HPS	Age/ gender	Cause of liver disease	Features	Outcome
Jones et al.[7]	1999	1	Concurrent	46/F	Cirrhosis due to hepatitis C and alcohol	PA 43/25 mm Hg and right-to-left shunt by bubble echo	LT 3 times, death with third graft failure
Tasaka et al.[10]	1995	1	Sequential (pulmonary hypertension preceding by 7 years the development of the HPS)	57/M	Cirrhosis due to hepatitis C	PA 72/12 mm Hg and then developed HPS 7 years later; HPS diagnosed by ^{99m}Tc-macroaggregated albumin scan and evidence of "abnormal dilatation of the precapillary pulmonary arterioles on postmortem examination)	Died of "pulmonary infection" and heart failure 7 years after initial onset of pulmonary hypertension that progressed to HPS
Shah et al.[5]	2005	1	Sequential (HPS first, then PPHTN 4 years after LT)	15/F	Cirrhosis due to biliary atresia	HPS by bubble echo before LT; PPHTN developed 4 years after LT (RVSP 72 mm Hg on echo	HPS resolved ~3 weeks after LT; died 55 months after second LT
Mal et al.[8]	1999	1	Sequential (HPS first, then PPHTN without LT)	46/M		HPS by ^{99m}Tc scan and RA PaO_2 51 mm Hg; PPHTN by RVSP 85 mm Hg on echo and 93/33 mm Hg by right heart catheterization	HPS resolved spontaneously; PPHTN developed 32 months after onset of HPS
Martinez-Palli et al.[6]	1999	1	Sequential (HPS resolved after LT; PPHTN developed after LT)	53/M	Cirrhosis due to alcohol	HPS by positive bubble echo; PPHTN by catheterization (PA 62/35 mm Hg) after a second LT	Second LT for cholangitis after first LT; intra-operative death during second LT
Kaspar et al.[9]	1998	1	Sequential (HPS resolved after LT; PPHTN developed after LT)	33/M	Cirrhosis due to alpha-1 antitrypsin deficiency	HPS present before LT; by 14 months after LT, oxygenation had improved (room air Spo_2 90%) but PPHTN developed (PA 76/29 mm Hg [mean 45 mm Hg], PVR 332 dynes-s/cm^5)	HPS resolved 14 months after LT when PPHTN became evident; alive 6 years after LT (when PA 109/26 mm Hg, PVR 688 dynes-s/cm^5)
Current report	2006	1 (Patient 1)	Sequential	31/F	Cirrhosis due to autoimmune hepatitis	HPS by positive bubble echo; PPHTN by cath (PA 75/34 mm Hg) developed 2 months after LT	HPS resolved 3 weeks after LT; died 2 months after LT
Current report	2006	1 (Patient 2)	Sequential	43/F	Cirrhosis due to hepatitis C	HPS by positive echo; PPH by catheterization (mean PA pressure 76 mm Hg) developed 13 months after LT	HPS resolved 4 months after LT; died 13 months after LT

Abbreviations: HPS, hepatopulmonary syndrome; LT, liver transplantation; PA, pulmonary artery pressure; PPHTN, portopulmonary hypertension; RVSP, right ventricular systolic pressure; RA, room air; ^{99m}TC, technetium 99m macroaggregated albumin lung scan.

previously described regrettably provides little insight into predictors, we might speculate that a hemodynamic profile in which the pulmonary vascular resistance is normal (i.e., not low) at a time when HPS is present might suggest concurrent PPHTN, such that resolution of HPS after LT might allow unmasking of the PPHTN. More specifically, one might expect HPS to decompress the pulmonary circulation, causing decreased pulmonary vascular resistance. We speculate that finding a normal pulmonary vascular resistance in a patient with HPS might predict subsequent development of PPHTN, perhaps especially if HPS resolves. This hypothesis provides an opportunity for prospective study.

The unusual occurrence of PPHTN after antecedent HPS in these patients also invites the question about routine posttransplantation "surveillance" echocardiography to assess right ventricular function and PA pressures when LT is undertaken for HPS or PPHTN. Although the infrequency of these events and the paucity of data on the issue preclude a firm conclusion, our emerging view favors follow-up posttransplantation echocardiography with contrast enhancement and estimation of right ventricular systolic pressure whenever PPHTN or HPS are present before LT.

In summary, we describe 2 patients in whom pulmonary hypertension developed after LT that was undertaken for antecedent HPS. This experience extends the number of patients with pulmonary hypertension and HPS to 8 and invites future study of strategies to better understand the pathogenesis of these pulmonary vascular disorders as well as predictors of their development.

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