CASE REPORTS FROM THE UNIVERSITY OF PUERTO RICO
SCHOOL OF MEDICINE HOSPITALS

Hepatopulmonary syndrome

GEORGE P. FAHED-INIGO, MD; ALFONSO TORRES-PALACIOS, MD;
WILLIAM RODRÍGUEZ-CINTRÓN, MD*

This is a report of a 56-year-old male who was admitted to the Intensive Care Unit of the San Juan V.A. Medical Center with altered mental status and severe hypoxemia. He was diagnosed with severe hyponatremia and hepatopulmonary syndrome.

Key words: Hepatopulmonary syndrome, Hypoxemia.

In view of the elevated incidence of hepatic disease in Western society, chest physicians should screen for hepatopulmonary sydnrome (HPS). Estimates of HPS prevalence among patients with chronic liver disease (CLD) vary, but usually range between 15-20% in patients with liver cirrhosis (1,2). Mild hypoxemia in cirrhotic patients is common and is presumably caused by ascites, with resulting diaphragmatic elevation and ventilation/perfusion (V/Q) mismatch. Moreover, it is estimated that approximately half of all patients with cirrhosis have at least mild hypoxemia. Severe hypoxemia (Pa <60 mmHg) is less common and, in the absence of associated cardiopulmonary disease, should strongly suggest HPS (3). This syndrome is characterized by progressive hypoxemia, which leads to deleterious physiologic effects, which may worsen the prognosis of chronic liver disease patients.

Case Report

A 56-year-old veteran who had been well until day of admission, was seen at the emergency room for complaints of sudden onset of bilateral tonic-clonic movements, loss of sphincter tone, and unresponsiveness. The events were witnessed and were attested by reliable informants who were playing dominoes with the patient at that moment. The episodes occurred twice, lasting 10 minutes each, and were followed by transient quadri-paralysis and visible respiratory distress as described by witnesses. There was interval somnolence between the episodes. The medical history in our records was notable for schizophrenia, active smoking, untreated hepatitis-C, and previous alcohol, tobacco & cocaine abuse currently on remission. His only current medication was olanzapine. He underwent liver biopsy in January 2002, which revealed minimal fibrosis. History failed to reveal any pulmonary disease, recent trauma, fever, liver biopsy, sickened close contacts, chills, or recent drug or alcohol use. A 911 call was placed by witnesses and upon arrival paramedics found patient in a stuporous state, with stable vital signs, adequate glucose levels, and with evidence of enuresis and generalized diaphoresis. He was brought promptly to our Emergency Room Department in the VA Medical Center. There the patient was intubated, and treated with intravenous lorazepam and phenytoin as for new onset seizures.

Physical examination was notable for lethargy, stable vital signs, well nourished, looked stated age, clubbing of the fingers (Figure-1,2), isolated left anterior thoracic wall spider nevi (Figure-3), and rigid extremities. There

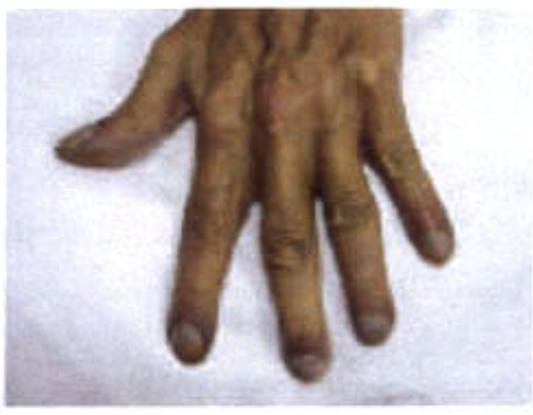


Figure 1

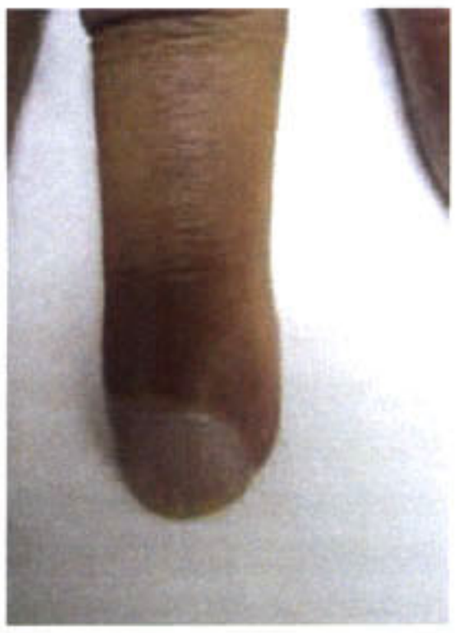


Figure 2

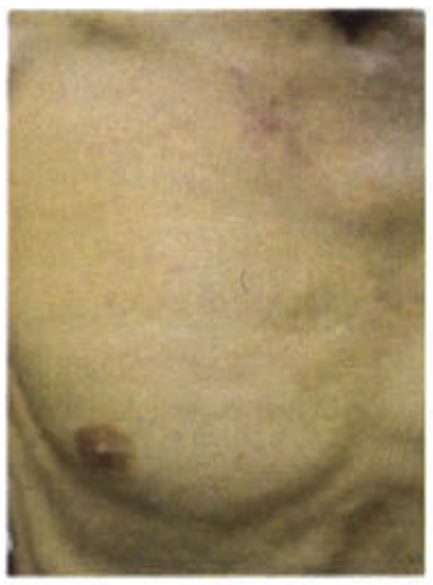


Figure 3

*From the VA Medical Center, San Juan, Puerto Rico.

Address correspondence to: William Rodriguez, MD, Pulm/CCM (11-E) Section, VA Caribbean Health Care System One Veterans Plaza, 10 Casia St. San Juan, Puerto Rico 00921-3201

was no evidence of increased abdominal girth, shifting dullness to suggest ascites, nor dependant zone edema. No evidence of focalizing neurological deficits.

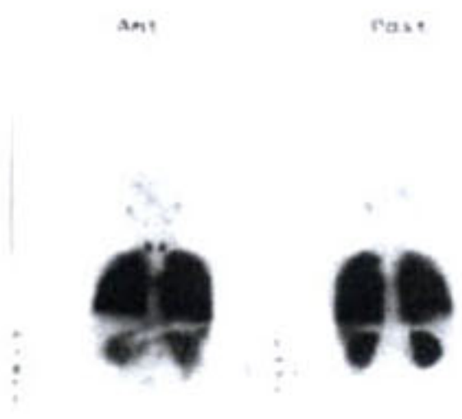
The patient was connected to a mechanical ventilator, coupling with ease and baseline pulse oxymetry was 89%. While breathing 100% FiO_2 on the ventilator, the SpO2 failed to rise above 96%. Chest x-ray showed mildly increased symmetrical vascular markings yet failed to show the presence of infiltrates, consolidates, pneumothorax; the pleural and mediastinal structure were unremarkable.

Upon admission the serum sodium was 118 mmol/dL, and there was a high-anion-gap metabolic acidosis 9AG=26); the white blood cell was 19.5 x 10x3 cells/cubic mm, and the total CPA was 13,000 U/L. Liver function tests, hemoglobin, platelet count, glucose, and coagulation times were normal. After correction of serum electrolytes the patient regained consciousness, remained free of seizures and was subsequently extubated on the seventh day of ICU stay after full recovery of baselin neurological state. The diagnosis of psychogenic polydipsia with severe hyponatremia casing new onset seizures was made.

Several days after extubation, hypoxemia with wide A-a gradient (622 mmHg while receiving 100% FiO2 via non-rebreathing mask) and orthodeoxia (SpO2 88% while in the supine position, decreasing to 79% upon assuming and upright posture) were notable. Patient was otherwise asymptomatic, and completely self-sufficient. HPS was considered to be the cause of hypoxemia in this patient. An agitated saline contrast enhanced 2D echocardiogram and a tagged-albumin V/Q scan were done (Figure-3), all showing intrapulmonary shunting with intrapulmonary vascular dilations, which confirmed the diagnosis of HPS.

The patient was subsequently discharged home with supplemental oxygen use, in fair condition. Currently he is undergoing evaluation by for Hepatitis-C treatment.

Figure 3- Perfusion lung scan of the reported case, performed with the intravenous administration of Technecium-99m labeled albumin (microalbumin aggregates). Whole body images show faint deposition of the tracer in the brain, salivary glands, spleen and small small-bowel. In addition, there is significant deposition of the tracer in the kidneys and thyroid-gland. Under normal condition there should be minimal or no uptake of tracer in extra-thoracic structures. This study evidences right –to-left shunting although it cannot differentiate between intrapulmonary or intra-cardiac shunting.



Discussion

Patients with liver disease frequently encounter respiratory problems. Hepatopulmonary syndrome occurs when intrapulmonary vasodilation impairs arterial gas exchange (4). Another frequently encountered respiratory problem found in patients with CLD complaining of respiratory problems is portopulmonary hypertension (POPH) (5). This entity is caused when pulmonary arterial constriction and remodeling lead to increased pulmonary arterial pressure. HPS is clinically noted to be more common than POPH, and the presence of these syndromes increases mortality and morbidity in patients with liver disease.

HPS is related to any type of chronic liver disease. There has been no consistent relationship between biochemical indicators for hepatic dysfunction or Child-Pugh classification on either the severity of hypoxemia or shunt (6). Impaired arterial oxygenation is the hallmark for HPS, with the presence of hepatic dysfunction or portal hypertension , and in specially with the absence of parenchymal pulmonary disease. The etiology for the hypoxemia is secondary to ventilation-perfusion mismatching with overlying intrapulmonary shunting caused by areas of pulmonary vasculture dilations. This causes a widened age-corrected alveolar-arterial oxygen gradient. The vascular anomalies are caused by failure of the damaged liver to clear circulating vasodilators and impaired production of vaso-active enzymes, which predominate in hepatopulmoanry hypertension (7,8).

In a study by Rolla G. et.al. (9) the role of nitric oxide was analyzed and has been implicated as a major vasodilator product that causes the areas of intrapulmonary shunting. This group documented a decrease in the exhaled nitric oxide concentration post liver transplant which significantly correlated with the decrease in the alveolar-arterial oxygen gradient. An animal model using rats with surgically induced chronic common bile duct ligation is used in medical research to simulate human HPS (10). In these studies there has been evidence of increased vaso-constrictive substances such as endothelin and angiotensin, and eicosanoids produced by intravascular macrophages. Other studies using this animal model have revealed an increased hepatic production of endothelin-1, which is known to increase NO from intravascular macrophages, which counteracts the effects of any vasoconstrictor produced under normal condition in the liver.

Intrapulmonary vasodilation is common in chronic liver disease and may be detected in over 40% of patients being

evaluated for liver transplantation (12). Further diagnostic procedures include the contrast-enhanced echocardiography with the use of the agitated saline test. Via this technique there is visible filling of the right heart chambers with micro bubbles. The contrast-bubbles normally are filtered by the pulmonary capillary bed. Patient with right-to-left shunts, whether intrapulmonary or intra-cardiac, the microbuses will fill the left heart chambers. In intra-cardiac shunting these bubbles enter the left-heart chambers within 2-3 heartbeats. In contrast, in intrapulmonary shunting anomalies the contrast bubbles will be visible in the left atrium after 6-10 cardiac cycles.

Technetium-labeled albumin macro aggregates usually are trapped in the pulmonary capillary bed, and is used for Ventilation-Perfusion (V/Q) scanning procedures. In patients with intrapulmonary or intra-cardiac shunts these scans (13) may demonstrate radionuclide uptake in the kidneys and brain as was seen in this case (Figure-3). Conventional pulmonary angiography is another diagnostic alternative and possible therapeutic method albeit more invasive [14,15]. By means of this method we may distinguish between different patterns of vascular anomalies. Type-I pattern is characterized by fine and diffuse abnormalities and are associated with a good response to 100% inspired oxygen. Type-II pattern is characterized by localized arteriovenous communications. This abnormality typical responds poorly to supplemental oxygen; such a lesion we suspect was present in the reported patient. Thorax HRCT may be helpful in the diagnosis of HPS as well, using newer technology which may demonstrate dilated peripheral pulmonary vessels or increased pulmonary artery to bronchus ratios in patients with liver disease and hypoxemia (16).

Gas diffusion in impaired as well and diminished DLCO clearance may be the only anomaly in pulmonary function test (17). In our patient the hypoxemia could be additionally related to obstructive pulmonary disease in view of tobacco smoking for which complete pulmonary function test would aid in further diagnosis. Yet the objective evidence gathered in this case is indicative of HPS as the primary cause of hypoxemia in this patient. This syndrome should be suspected in any patient with underlying liver disease presenting with platypnea and orthodeoxia.

No clearly effective medical therapy for HPS is available. Hypoxemia in these patients can be life threatening and can progress without an associated decline in liver function. Medical therapy for this condition has been the subject of intense research. Trials have tested indomethacin ethelene blue, sandostatin, among others (18,19). Plasma exchange, transjugular intrahepatic portosystemic shunt (TIPS) have also been reported as successful treatments modalities, yet clinical trials to support their use are lacking and cannot be clearly recommended for use at present. Pentoifyline with its effect or inhibiting nitrc oxide-synthase has showed promising results in early animal trials (20). Case reports using agents such as aspirin, norfloxacin, garlic powder, and methylene blue are documented.

Liver transplantation is the only established effective therapy for HPS. No large multi-center, randomized trials have been performed to assess the role of liver transplantation in the management of HPS. Hypoxemia used to be a contraindication to liver transplant in earlier years. Subsequent experience has documented striking improvements in oxygenation and reversal of shunting following liver transplantation in some patients (21,22). Liver transplantation has emerged as the only proven treatment based on many reports demonstrating total resolution or significant improvement in gas exchange postoperatively (23,24).

Other authors have looked at the outcomes of patients who underwent liver transplant due to cirrhosis and had underlying HPS (25). The post operative mortality at one year survival of these patients was lower than expected. In contrast, in a recent report by Krowka et al, (15) showed that the hospitalization mortality after liver transplant for HPS was still elevated (16%), yet this mortality was half of that associated to liver transplant in patients with portopulmonary hypertension. Over time, spontaneous resolution is rare. In a recent publication by Schenk P. et al a total of 27 of 111 patients with cirrhosis had HPS without transplant and were followed from time of diagnosis until death and there was no spontaneous resolution (27). This study also showed that HPS was independently associated with worsened prognosis after adjustments for degrees of severity of liver cirrhosis were done (median survival 4.8 vs. 35.2 months, P = 0.005). In essence, early liver transplant is the only clearly effective therapy for these patients, yet the decision must be weighted carefully in each case in view of the complications posed by such a procedure.

Conclussion

HPS is an increasingly common and well-recognized complication of chronic liver disease and portal hypertension that can cause significant hypoxemia. Its recognition is important because its presence increases mortality in cirrhotic patients The diagnosis can be made early in liver disease with well-standardized diagnostic tests which are available to detect intrapulmonary vasodilation.. These tests are simple and require only minimally invasive procedures. Newer, high-resolution radiologic techniques may simplify diagnostic strategies

in the future. The pathogenesis of intrapulmonary vasodilation may involve mediators released from the liver that influence the pulmonary vasculature and will likely be the target of effective medical therapies. Therapeutic alternatives are limited. At present, liver transplantation is the only beneficial therapy, but unique postoperative complications may occur and should be anticipated when a transplant is undertaken.

Key Points

1. HPS is a frequent cause of hypoxemia and orhtodeoxia in patients with underlying liver cirrhosis
2. Diagnosis is simple and requires minimally invasive procedures.
3. Treatment alternatives are limited and progressive hypoxemia my be considered an indication for liver transplant

Search Terms

Hepatopulmonary Syndrome, orthodeoxia, ventilation perfusion scan, agitated saline, liver transplant

References

1. Prognostic significance of the hepataopulmonary syndrome in patients with cirrhosis. Schenk P, et al. Gastroenterology 2003Oct;125(4):1042-52.
2. Hepatopulmonary Syndrome: Current concepts in diagnostic and therapeutic considerations. Krowka MJ, et al. Chest 1994 May;105(5):1252-37).
3. Mechanisms of pulmonary vascular complications of liver disease: Hepatopulmonary Syndrome. Fallon MB, et al. J Clin Gastroenterology 2005 Apr;39(4):S138-423.
4. Effect of transjugular intrahepatic portosystemic shunt on pulmonary gas exchange in patients with portal hypertension and hepatopulmonary syndrome. Martinez-Palli G World J Gastroenterol 2005 Nov 21;11(43):6858-62.
5. Portopulmonary hypertension: a tale of two circulations. Budhiraja R, Hassoun PM. Chest. 2003 Feb;123(2):562-76.
6. Hepatopulmonary Syndrome: Current concepts in diagnostic and therapeutic considerations. Krowka MJ, et al Chest 1994 May;105(5):1252-37.
7. Hepatopulmonary syndrome: a prospective relationship between severity of liver disease, PaO2 response to 100% oxygen, and brain uptake after (99m) Tx MAA lung scanning. Krowka MJ, et al Chest 2000 Sep;118(3):615.
8. Pulmonary-Hepatic vascular disorders Roriguez-Roisin R Eur Respi J 2004;24:861.
9. Exhaled nitric oxide and impaired oxygenation in cirrhotic patients before and after liver transplantation Rolla G, et al Ann Intern Med 1998 Sep 1;129(5):375-88.
10. Lung capillary changes in hepatic cirrhosis in rats Chang SW, Am J Physiol 1997 Jan;272(1 Pt 1):L139-47)
11. Role of nitric oxide in hepatopulmonary syndrome in cirrhotic rats. Nunes H, et al Am J Respir Crit Care Med. 2001 Sep 1;164(5):879-85.
12. Frequency, Clinical Characteristics, and Respiratory Parameters of Hepatopulmonary Syndrome Beatriz G, et al Mayo Clin Proc. 2004;79:42-48.
13. An intravenous radionuclide method to evaluate hypoxemia caused by abnormal alveolar vesselsl Genovesi MG, et al. Am J Respir Crit Care Med 2001;164:879.
14. Gas exchange detection of right-to-left shunt in dyspneic patients: Report of three cases Chuang ML, Int J Cardiol. 2006 Mar 22;108(1):117-9.
15. Hepatopulmonary syndrome: angiography and therapeutic embolization Ryu JK Clin Imaging. 2003 Mar-Apr;27(2):97-100.
16. Evaluation of intrapulmonary vascular dilatations with high-resolution computed thorax tomography in patients with hepatopulmonary syndrome Koksal D . J Clin Gastroenterol. 2006 Jan;40(1):77-83.
17. Frequency, clinical characteristics, and respiratory parameters of hepatopulmonary syndrome Lima BL Mayo Clin Proc. 2004 Jan;79(1):42-8.
18. Mechanism of impaired arterial oxygenation in patients with liver cirrhosis and severe respiratory insufficiency: effect of inomethacin. Andrivet P, et al. Chest 1993;103:500.
19. Hepatopulmonary syndrome. Clinical observations and lack of therapeutic response to somatostatin analogue. Krowka MJ, et al. Chest 1993;104(2):515.
20. Prevention of hepatopulmonary hyperdynamic state by pentoxiflline in cirrhotic rats. Sztrymf B, et al. Eur Respir J 2004;23:752.
21. Retrospective analysis of the results of liver transplantation for adult with severe hepatopulmoanry syndrome. Collisson EA, et al Liver Transpl 2002 Oct, 8(10):925-31.
22. Liver transplantation for hepatopulmonary syndrome; a ten-year experiency in Paris, France. Taille C, et al. Transplantation 2003 May 15;75(9):1482-9.
23. Resolution of gas exchange abnomalities an intrapulmonary shunting following liver transplantation in patients with liver cirrhosis Battaglia SE, et al Hepatology 1997 May;25(5):1228-32.
24. The hepatopulmonary syndrome: effect of liver transplantation. Lange PA, Clin Chest Med 1996, 17:115-123
25. Outcomes in patients with hepatopulmonary syndrome undergoing liver transplantation Kim HY Transplant Proc. 2004 Nov;36(9):2762-3.
26. Hepatopulmonary syndrome and portopulmonary hypertension: a report of the multicenter liver transplant database. Krowka MJ Liver Transpl. 2004 Feb;10(2):174-82.
27. Prognostic significance of the hepatopulmonary syndrome in patients with cirrhosis Schenk P. et.al Gastroenterology 2003;125:1042-52).