International Journal of Research in Medical Sciences
Priyadharshini V et al. Int J Res Med Sci. 2026 Oct;14(10):xxx-xxx
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20263279

Original Research Article

A tale of two entities: a rare presentation of hepatopulmonary syndrome associated with non-cirrhotic portal fibrosis

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Received: 25 August 2026
Accepted: 09 September 2026

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ABSTRACT

Hepatopulmonary syndrome (HPS) is traditionally associated with cirrhosis and advanced chronic liver disease, whereas its occurrence in non-cirrhotic portal fibrosis (NCPF) is distinctly uncommon. We report a 21-year-old woman with NCPF, portal hypertension, and autoimmune hemolytic anemia who presented with progressive dyspnea, fatigue, and dry cough. Examination revealed clubbing and marked orthodeoxia, with oxygen saturation decreasing from 89% supine to 81% upright. Room-air arterial blood gas analysis showed a PaO_2 of 71.9 mmHg with hypocapnia. Contrast-enhanced echocardiography demonstrated delayed microbubble transit into the left atrium via the pulmonary veins, confirming an intrapulmonary right-to-left shunt consistent with HPS. Abdominal imaging demonstrated non-cirrhotic portal hypertension (NCPH) with periportal fibrosis, splenomegaly, and extensive portosystemic collaterals, with preserved hepatic function. The patient underwent right-lobe living-donor liver transplantation and subsequently showed marked clinical and respiratory improvement. This case highlights that HPS may develop in NCPF despite preserved hepatic function and underscores the diagnostic importance of orthodeoxia and intrapulmonary shunting in unexplained hypoxemia.

Keywords: Hepatopulmonary syndrome, Non-cirrhotic portal fibrosis, Orthodeoxia, Intrapulmonary shunt, Liver transplantation

INTRODUCTION

Hepatopulmonary syndrome (HPS) is a condition that manifests with hypoxia in the presence of liver disease, which could be of acute or chronic etiologies. The hypoxemia is classically due to dilated pulmonary vasculature, as well as an increased alveolar-arterial gradient.[1] Although erstwhile described with cyanosis, digital clubbing and cirrhosis by Fluckiger in the late 19th century, the description of this entity has evolved into a triad of symptoms that do not limit the liver disease to manifest as cirrhosis alone.[1]

The diagnostic criteria include a partial pressure of less than 80 mm Hg while breathing room air, dilation of pulmonary vessels by a positive contrast-enhanced echocardiography or by radioactive lung-perfusion scanning, and portal hypertension.[1] The severity of disease is based upon the PaO_2 levels: lower levels indicate more severe disease.[1] The vascular abnormalities are predominant in the lower lung fields, since gravity induces increased blood flow to the lower lung fields hypoxemia is increased when changing from supine to upright position.[1] Mild hypoxemia is often multifactorial given that such patients also present with ascites, cardiovascular disease, etc.[1]

NPCF is a disease that has no particular etiology; it is characterised by a so called 'obliterative portovenopathy' leading to PHT, massive splenomegaly and non-severe

episodes of variceal bleeding.[2,3] Such cases do not have cirrhosis and surprisingly retain normal or near-normal hepatic function.[2,3] The disease has higher prevalence in developing nations compared to developed ones, and factors involved in its pathogenesis range from infections to immunological abnormalities.[2,3] Given this variability, NPCF is often grouped by physicians under the umbrella of NCPH or portosinusoidal vascular dieases.[2,4]

The site of anatomical portal vein resistance is found in the pre and perisinusoidal segments in NPCF.[2,3] The pathophysiology involves injury to the portal inflow vasculature, the portal venules, and the sinusoids, leading to occlusion and fibrosis of terminal branches of the portal vein with or without compensatory adjacent hepatocyte regeneration.[2,3] Endothelial injury from the third- and fourth-order portal branches to the portal venules entering in presinusoidal and sinusoidal area triggers stellate cell activation, release of cytokines, and activation of the coagulation cascade.[2,3] This results in altered blood flow, thrombin deposition, and microemboli formation in these portal venules, contributing to the development of NCPF.[2,3]

While HPS has a hepatic component, studies show that chronic disease as well as cirrhosis are the more common forms of liver disease compared to acute conditions such as hepatitis.[1] Even more rare are conditions that impact liver function but are non-cirrhotic liver diseases, such as NPCF, in spite of common mechanisms in both disorders.[2-4] With this backdrop, we herein describe a case of HPS that was associated with NCPF.

CASE REPORT

A 21-year-old female presented with dry cough and fatigue for the past one year. She also complained of shortness of breath for same period of time, which has progressed from grade 1 to 3 based on the mMRC score. There was a history of postural variation whereby the dyspnea improved on lying down. There was no history of hemoptysis.

The patient also complained of an evening rise in temperature for one week and a significant loss of weight in the last six months, accompanied by epigastric tenderness. However, she denied any contact with known cases of tuberculosis. She was a known case of autoimmune hemolytic anemia, NPCF and portal hypertension for the last five years.

General examination elicited no significant pallor, icterus or cyanosis; clubbing was found. The patient was tachypneic, with a respiratory rate of 28 per minute and an elevated pulse rate of 124 per minute.

With regards to the respiratory system in particular, she had an SpO_2 in upright position was 81% and improved in supine position to 89% suggestive of orthodeoxia. On auscultation, crackles were heard in the right suprascapular region. Apart from these findings there were no visible deformities visualised over the thorax. On examination of the abdomen, the spleen was found to be palpable. There were no other significant findings pertaining to pathologies of the other systems.

Based on the above findings, further investigations were performed. Arterial blood gas analysis performed on room air revealed a pH of 7.43, PaO_2 of 71.9 mmHg, $PaCO_2$ of 31 mmHg, and HCO_3^- of 20 mmol/l, suggestive of mild hypoxemia with hypocapnia. Mild pulmonary hypertension was also noted. All the above findings put together were suggestive of a possible bronchopneumonia or type 1 respiratory failure, for which she was given continuous positive airway pressure therapy (CPAP).

Blood counts were indicative of a pancytopenic picture; thrombocytopenia was one of the most significant decreased counts observed (Table 1). The combination of AIHA, thrombocytopenia and suggested Evans' syndrome; however, immune thrombocytopenic purpura was excluded. A computed tomography (CT) chest report indicated active pulmonary infection, which was managed with and subsequently resolved by antibiotic use. Following this, persistent hypoxia and presence of orthodeoxia raised suspicion for HPS, for which bubble echocardiography was indicated.

Two-dimensional echocardiography showed no regional wall motion abnormality, with a preserved left ventricular ejection fraction of 62% and normal left ventricular systolic function. Bubble echocardiography demonstrated delayed appearance of microbubbles in the left atrium, occurring after four cardiac cycles. The bubbles were seen entering the left atrium via the pulmonary veins, confirming the presence of an extracardiac right-to-left shunt, consistent with an intrapulmonary vascular shunt. The echocardiographic findings of pulmonary vascular abnormalities (likely to be pulmonary hypertension), resulting in vessel dilatation, combined with low O_2 saturation and portal hypertension strengthened the diagnosis of HPS in this patient.

Ultrasonography of the abdomen with portal venous Doppler demonstrated periportal fibrosis, and portal hypertension, findings suggestive of NCPF. FibroScan revealed a liver stiffness measurement of 11.8 kPa. Contrast-enhanced computed tomography (CECT) of the abdomen showed massive splenomegaly with multiple portosystemic collateral vessels. The presence of an eccentric thrombus in the main portal vein was observed, probably due to long standing portal hypertension. Splenic findings on Doppler showcased moderate splenomegaly, splenic vein thrombosis and multiple collaterals in the region. For this condition and in view of AIHA, she was initially treated with prednisolone; which was gradually weaned off of. The etiological workup was negative for autoimmune.

After receiving advice from the hepatology and surgical gastroenterology departments, it was advised that the patient undergoes a permanent cure of liver

transplantation, with removal of the portal and splenic veins as well. A right lobe liver transplant was done. The explanted liver histologically showed portal fibrosis with septae and occasional bridging fibrosis and mild lymphoid cell infiltrate of portal tracts and focal macrovesicular fattty changes. Symptoms of breathlessness and fatigue were reported to have reduced in the following months post-op.

Table 1: Complete baseline parameters.

Parameters	Value	Reference range/impression
Complete blood count parameters		
White blood cell count (10^3/µl)	6.7	4-11
Hemoglobin (g/dl)	10.9	13-17
Platelet count (10^3/µl)	300	165-415
MCV (fl)	89	80-100
MCH (pg/cell)	26	27-33
Arterial blood gas parameters		
pH	7.45	7.35-7.45
pO2 (mmHg)	61	75-100
pCO2 (mmHg)	25	35-45
HCO3 (mmol/l)	17	22-26
Coagulation profile		
PT (seconds)	15.2	11-13
APTT (seconds)	28.2	25-35
INR	1.2	0.8-1.2

*MCV-Mean corpuscular volume, MCH-Mean corpuscular hemoglobin, PT-Prothrombin time, APTT-Activated partial thromboplastin time, INR-International normalized ratio.

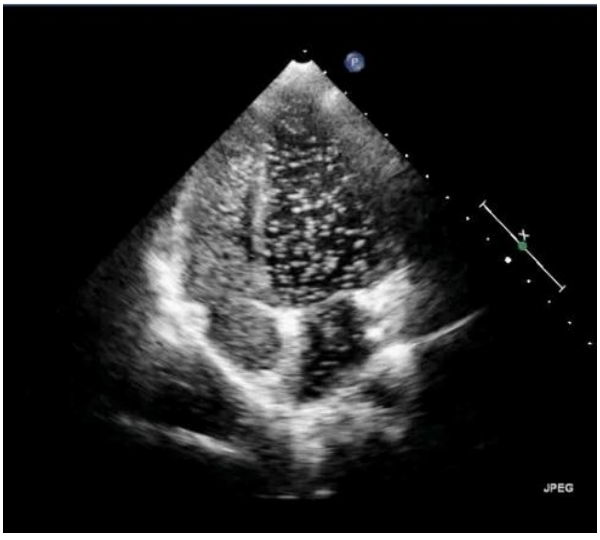

Figure 1: Delayed appearance of bubbles in the left atrium, which confirms the presence of an extracardiac right-to-left shunt as seen in hepatopulmonary syndrome.

DISCUSSION

HPS is traditionally regarded as a pulmonary complication of advanced chronic liver disease, particularly cirrhosis.[1] However, its occurrence in NCPH challenges the concept that cirrhosis or impaired hepatic synthetic function is required for the development of pulmonary vascular abnormalities.[1-3] NCPF, characterized by presinusoidal portal hypertension with preserved hepatic architecture and synthetic function, provides a useful clinical model in which the contribution of portal hypertension can be considered independently of cirrhosis.[2-4] The present case adds to the limited literature on NCPF-associated HPS and is notable for the combination of preserved hepatic function, moderate resting hypoxemia, marked orthodeoxia, and objectively demonstrated intrapulmonary shunting; it has been estimated that there are about only 20 to 30 cases of such an association in published literature.[2,4]

Intrapulmonary vascular dilatation (IPVD) appears to be substantially more frequent in NCPH than clinically overt HPS.[5] In a study by Anand et al IPVD was identified in 26.6% of patients with NCPF, whereas only 13.3% fulfilled criteria for HPS; these proportions were comparable to those observed in cirrhosis, in which IPVD and HPS were present in 27% and 17.5% of patients, respectively.[5] Patients with HPS were more likely to have dyspnea, platypnea, clubbing, and spider nevi.[5] Similarly, Kaymakoglu et al reported HPS in 9.7% of patients with NCPH compared with 10.8% of those with cirrhosis, with increased shunt fractions and impaired diffusing capacity among affected patients.[6] These findings suggest that IPVD represents a relatively common pulmonary vascular phenotype of portal hypertension, whereas HPS reflects the subset in whom these vascular abnormalities become sufficiently extensive to produce clinically relevant gas-exchange impairment.[5,6] Our patient demonstrated the latter of the two phenotypes.

The clinical spectrum of NCPF-associated HPS is heterogeneous.[5,6] At one extreme, Sood et al. reported a 17-year-old boy with NCPF and severe HPS, characterized by cyanosis, clubbing, a room-air oxygen saturation of

70%, a PaO_2 of 49 mmHg, and an alveolar-arterial oxygen gradient of 60 mmHg.[7] In contrast, our patient had no peripheral cyanosis and a resting PaO_2 of 71.9 mmHg, indicating only moderate resting hypoxemia. Nevertheless, the physiological impairment was clinically significant, with profound positional desaturation and an upright SpO_2 of 81% that improved to 89% in the supine position.[1-7] This marked orthodeoxia highlights an important point: the clinical burden of HPS cannot necessarily be inferred from the resting PaO_2 alone.[1-7] In patients with NCPF, substantial functional impairment and positional hypoxemia may occur before severe resting hypoxemia develops.[5-7]

Pediatric studies further support the concept of a continuum between IPVD and clinically overt HPS.[5,6] Sari et al found that a child fulfilling criteria for HPS among 16 patients with NCPH did not exist, despite evidence of IPVD, suggesting that pulmonary vascular abnormalities may remain subclinical in a proportion of younger patients.[8] Conversely, Borkar et al. identified HPS in 13% of children with NCPH and noted that the phenotype was generally milder than that observed in cirrhosis, with clubbing frequently occurring in the absence of respiratory symptoms.[9] The determinants of progression along this spectrum remain poorly understood.

This case also broadens the clinical phenotype previously described in NCPF-associated HPS.[7-9] Maganty et al reported a 26-year-old woman with NCPH-associated HPS who had severe hypoxemia, platypnea, and a requirement for supplemental oxygen at home.[10] Although our patient had less severe resting hypoxemia and predominantly exertional rather than resting respiratory symptoms, both patients demonstrated orthodeoxia and intrapulmonary shunting on contrast echocardiography and ultimately underwent liver transplantation.[10] These cases underscore that the physiological diagnosis of HPS, rather than the severity of conventional hepatic dysfunction, may be clinically decisive in selected patients with NCPH.[5,6,10] Importantly, preserved synthetic function and relatively modest hepatic disease should not preclude consideration of HPS when unexplained hypoxemia, orthodeoxia, clubbing, or exertional dyspnea is present.[8-10]

The development of HPS in NCPF supports a model in which portal hypertension and altered portal-systemic hemodynamics (rather than hepatic failure per se) can drive pulmonary vascular remodeling.[1,11,12] Extensive portosystemic collateralization, as present in our patient, may further facilitate the systemic delivery of vasoactive mediators originating from the splanchnic circulation that would otherwise undergo hepatic metabolism.[11,12] Although this mechanism remains hypothetical, the occurrence of HPS in a setting of preserved hepatic function provides important clinical support for a portal hypertension-driven pathway.[11,12]

The postoperative improvement in oxygenation and respiratory status further supports the reversibility of the pulmonary vascular phenotype following correction of the underlying hepatic–portal disorder.[10,14] Although the number of reported NCPF-associated HPS cases remains small, the consistency of improvement following transplantation is clinically important.[10,14] It also suggests that the pulmonary vascular abnormalities associated with portal hypertension may remain at least partially reversible, even when clinically significant hypoxemia has developed.[10,14]

This report has a few limitations. Firstly, although contrast-enhanced echocardiography demonstrated delayed appearance of microbubbles in the left atrium, consistent with an intrapulmonary vascular shunt, a quantitative shunt fraction by technetium-99m macroaggregated albumin lung perfusion scanning was not performed.[1] Secondly, the physiological characterization of HPS could have been strengthened by serial arterial blood-gas measurements in the supine and upright positions and by reporting the alveolar–arterial oxygen gradient.[1] The presence of cough, fever, weight loss, and focal crackles also introduces potential pulmonary confounders, although the demonstration of orthodeoxia and an intrapulmonary shunt strongly supports HPS as an important contributor to the patient's hypoxemia.[1,10] In addition, the coexistence of autoimmune hemolytic anemia and pancytopenia may have contributed to exertional symptoms.

CONCLUSION

HPS can occur in NCPF despite preserved hepatic architecture and synthetic function, supporting the concept that portal hypertension itself may contribute to the development of pulmonary vascular abnormalities. This case highlights an important clinical phenotype characterized by moderate resting hypoxemia but marked orthodeoxia and objectively demonstrated intrapulmonary shunting. Accordingly, HPS should be considered in patients with NCPF who develop unexplained dyspnea, exertional limitation, clubbing, or positional desaturation, even in the absence of advanced liver dysfunction or severe resting hypoxemia.

Recognition of HPS in this setting has important therapeutic implications. The marked improvement following living-donor liver transplantation in our patient supports the potential reversibility of the pulmonary vascular abnormalities after correction of the underlying hepatic–portal disorder. Thus, physiological assessment for HPS, rather than liver dysfunction alone, may be important when evaluating patients with NCPF for definitive therapy. This case further expands the spectrum of HPS beyond cirrhosis and emphasizes the need for heightened clinical suspicion in NCPH.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Priyadharshini V, Syed MHS, Chengalwarayulu PN, Murugan KR, Shiva MS, Paul AJ, et al. A tale of two entities: a rare presentation of hepatopulmonary syndrome associated with non-cirrhotic portal fibrosis. Int J Res Med Sci 2026;14:xxx-xx.