

# A rare case of common variable immunodeficiency and hepatopulmonary syndrome

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## Abstract

Hepatopulmonary syndrome (HPS) is the triad of liver disease, hypoxia and intrapulmonary shunt. In this case report, we describe an immunocompromised female with a background of common variable immunodeficiency (CVID) who presented with haemoptysis and dyspnoea. Investigations demonstrated significant hypoxaemia and intrapulmonary right-to-left shunting. Further evidence revealed advanced liver cirrhosis, and a diagnosis of HPS was made. This extremely rare association of CVID and HPS is one of the few cases reported in the literature.

## KEYWORDS

chronic bronchiectasis, clinical allergy and immunology, immunodeficiency, pulmonary circulation and pulmonary hypertension, rare lung diseases

## INTRODUCTION

Common variable immunodeficiency (CVID) is a primary immunodeficiency syndrome, usually presenting in childhood with recurrent infections. Liver disease occurs in approximately 10% of patients. Hepatopulmonary syndrome (HPS) is a rare complication of cirrhosis, resulting in intrapulmonary shunt and hypoxia. HPS due to CVID-related cirrhosis is extremely rare and poses difficult management decisions.

## CASE REPORT

A 46-year-old female with a history of CVID presented with 2 weeks of nocturnal frank haemoptysis on a 6-month background of progressive dyspnoea, exacerbated when standing, fevers and tender digital clubbing.

The patient was diagnosed with CVID at age 32 with bronchiectasis and recurrent pneumonia, autoimmune cytopenias and splenomegaly, managed with splenectomy. She received monthly intravenous immunoglobulin (IVIg) with improved immunoglobulin levels. Additionally, she had poorly controlled type 2 diabetes mellitus (HBA1c 10%), requiring insulin. She was a reformed smoker with a 15-pack-year history and consumed no alcohol, with no relevant environmental or occupational exposures and no

significant family history. She had been lost to respiratory follow-up 3 years previously.

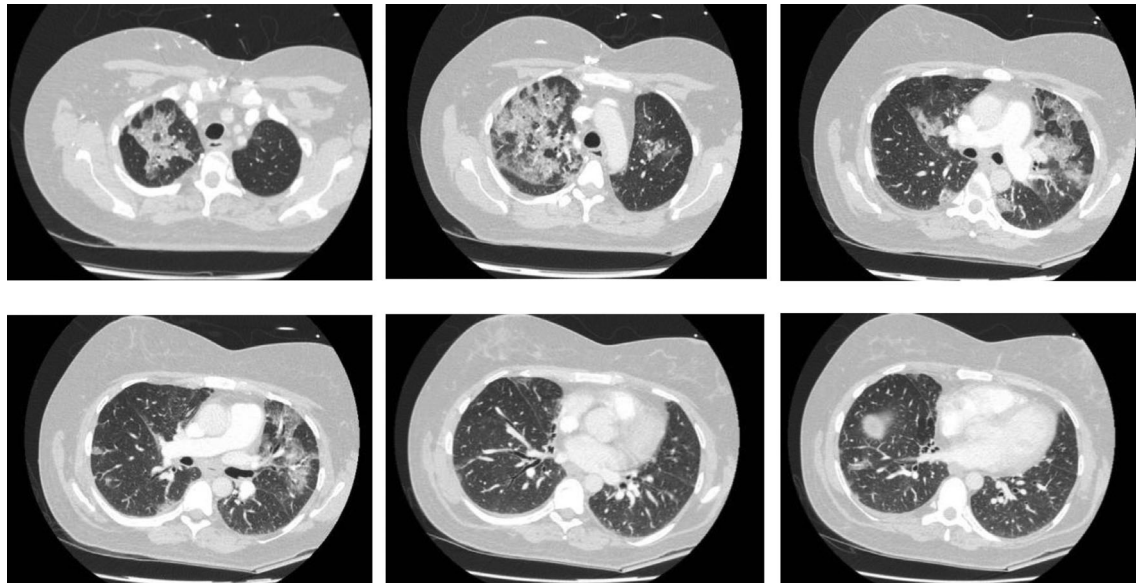
Examination revealed a respiratory rate of 28 breaths-per-minute; oxygen saturations 93% on 4 L/min oxygen via nasal cannula when supine, 87% sitting; palmar erythema; and digital clubbing. On chest examination, spider naevi were seen and coarse bi-basal crepitations auscultated. Abdominal examination revealed tender hepatomegaly, with no ascites. Cardiac examination was unremarkable.

Laboratory investigations revealed: haemoglobin 129 g/L; white cell count  $20 \times 10^9/L$ ; absolute neutrophil count  $19 \times 10^9/L$ ; platelet count  $213 \times 10^9/L$ ; creatinine elevated at 128  $\mu\text{mol/L}$ , estimated glomerular filtration rate (eGFR) 43; C-reactive protein 63 mg/L; liver function test derangement: alkaline phosphatase 154  $\mu\text{mol/L}$ , alanine aminotransferase 78  $\mu\text{mol/L}$ , aspartate aminotransferase 76  $\mu\text{mol/L}$ , lactate dehydrogenase 425  $\mu\text{mol/L}$ . Coagulation studies were unremarkable. Immunoglobulin G was normal (10.6 g/L), with low immunoglobulin M (<0.05 g/L) and immunoglobulin A levels (0.16 g/L).

No pathogens were isolated on extended sputum cultures, peripheral blood cultures or viral respiratory polymerase chain reaction. Hepatitis and HIV serology were negative, and liver immunoblot, autoimmune and connective tissue screens were within the normal range. Bronchoscopy revealed extensive blood clots throughout the airways and active contact bleeding. Bronchoalveolar lavage detected

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**FIGURE 1** Computed tomography of the chest and lung windows, showing crazy-paving inflammatory changes

only herpes simplex virus (HSV). Arterial blood gas on room air demonstrated pH of 7.46, partial pressure of carbon dioxide ( $p\text{CO}_2$ ) 28 mmHg, partial pressure of oxygen ( $p\text{O}_2$ ) 48 mmHg, bicarbonate 20 mmol/L and lactate of 4.2 mmol/L.

Pulmonary function tests (PFTs) were not performed due to haemoptysis, however, PFTs 3 years prior showed mildly reduced forced expiratory volume in 1 s (FEV1) (2.41 L/76%) and forced vital capacity (FVC) (3.08 L/79%), no bronchodilator response and normal FEV1/FVC ratio; static lung volumes were within normal range; and severely reduced diffusing capacity for carbon monoxide (DLCO) corrected for Hb 6.3 ml/min/mmHg/ 24%. The 6-min walk distance was 200 m with oxygen desaturation nadir 69%. Following these PFTs, the patient had been 'lost to follow-up'.

Computed tomography (CT) pulmonary angiogram excluded pulmonary emboli and demonstrated bilateral crazy-paving changes with upper lobe predominance, ground-glass opacities and interlobular septal thickening with chronic bronchiectasis (Figure 1). Ventilation–perfusion scan showed multiple bilateral mismatched perfusion defects. Given the clinical picture, further investigations focused on a possible right-to-left shunt. Transthoracic contrast echocardiogram demonstrated bubbles entering left atrium via pulmonary veins indicating an extra-cardiac right-to-left shunt. This was confirmed with macroaggregated albumin technician shunt study showing a shunt fraction of 32% (Figure 2).

Considering the aetiology of the intrapulmonary shunt, the hereditary haemorrhagic telangiectasia gene testing was negative. CT of the brain revealed no intracranial arteriovenous malformations. Liver ultrasound revealed nodular liver surface, coarse parenchymal echotexture and echogenicity. Fibroscan pressure was 43 kPa and hepatic biopsy confirmed cirrhosis.

The patient was diagnosed with cirrhosis secondary to CVID, complicated by HPS with multiple intrapulmonary

arteriovenous malformations. Regarding management, the only pathogen found on extensive testing was HSV, which was treated with intravenous acyclovir. The patient continued IVIg and supplemental oxygen and was referred for consideration of liver transplant.

## DISCUSSION

This case demonstrates a patient diagnosed with cirrhosis, an uncommon manifestation in CVID, and HPS, a rare complication of cirrhosis, in the context of multiple potential alternative contributors to her hepatic and pulmonary presentation. It highlights the importance of considering these entities in a patient with CVID and respiratory failure and raises complexities in the long-term management.

Chronic liver disease develops in approximately 10% of patients with CVID due to nodular regenerative hyperplasia (NRH).<sup>1</sup> In some patients, NRH leads a benign course; however, a subgroup of patients progress to cirrhosis with portal hypertension, splenomegaly and ascites. Progression to HPS is rare and poorly understood. HPS is a triad of liver disease, impaired oxygenation and intrapulmonary shunting or vascular abnormalities. The pathogenesis is not fully understood. It is thought to be related to pulmonary angiogenesis and vasodilation resulting in intrapulmonary vascular dilations (IVPDs). Hypoxia occurs via ventilation–perfusion mismatch due to increased blood flow through IVPDs, alveolar–capillary disequilibrium due to increased IVPD diameter and direct anatomic shunting between pulmonary and arterial venous capillary beds.<sup>2</sup> Clinical manifestations include signs of chronic liver disease; orthopnoea and platypnoea are more specific features, due to the preferential perfusion of the predominantly basally located IVPDs when the patient is upright.<sup>3,4</sup>

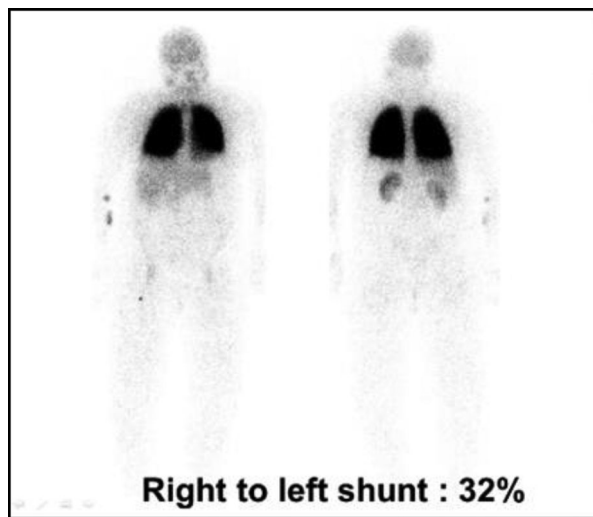


FIGURE 2 Macroaggregated albumin technician scan showing symmetrical tracer activity in the lungs, kidneys and brain

The only definitive management of HPS is liver transplant. Patients with severe HPS, categorized as partial pressure of oxygen ( $\text{PaO}_2$ ) < 60 mmHg, should have expedited referral for transplant evaluation.<sup>5</sup> In the literature, there are few reported cases of liver transplant for HPS secondary to CVID. This is likely due to the high risk of infection and graft rejection in solid organ transplant in the CVID patient cohort. There are only two reported cases of improved respiratory failure post liver transplant in this group.

In summary, HPS is a rare cause of hypoxia and should be considered in any patient with signs of chronic liver disease. The more specific symptoms of orthopnoea and platypnoea should prompt investigation. Our patient is one of the few cases of HPS associated with CVID in the literature. It poses a difficult decision regarding management due to the rarity of the association and the poor outcomes in this small cohort of patients.

#### CONFLICT OF INTEREST

None declared.

#### AUTHOR CONTRIBUTION

Emily Lawton: Primary author of the manuscript. Drafted and revised the paper. Conducted literature review and background research.

Chien-Li Holmes-Liew: Secondary author of the manuscript. Reviewed and revised the paper.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

#### ETHICS STATEMENT

The authors declared that appropriate written informed consent was obtained for the publication of this case report and accompanying images.

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