Hypoxaemia – think of the liver! Every internist should be aware of the hepatopulmonary syndrome

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Summary

Hepatopulmonary syndrome is characterised by arterial hypoxaemia, liver disease, and intrapulmonary vascular dilatation. A case is reported in which severe hypoxaemia, detected by chance, led to the diagnosis of liver disease and hepatopulmonary syndrome.

Keywords: hypoxaemia; hepatopulmonary syndrome

When confronted with a severely hypoxic patient, it is unusual for the clinician to make a list of differential diagnoses beyond cardiorespiratory diseases. Hepatopulmonary syndrome (HPS) is characterised by a triad of arterial hypoxaemia, liver disease, and intrapulmonary vascular dilatation.¹ Though the association of chronic liver disease, cyanosis, and digital clubbing was first described over 100 years ago, and the term 'hepatopulmonary syndrome' was suggested in 1977,² this entity has generated interest only recently.³ Literature outlining major recent developments in HPS has appeared mainly in specialist journals, whereas it is likely that internists and emergency room physicians (as in this case) would be the first ones facing the diagnostic dilemma of hypoxaemia of obscure aetiology. I report a case in which severe hypoxaemia, detected by chance, led to the diagnosis of liver disease and HPS.

Case report

A 57-year-old man, not known to have liver disease, felt dizzy while waiting for transportation home after a routine orthopaedic clinic visit. In the emergency room, pulse oximetry recording at room air was alarmingly low at 78% and a simultaneous PaO₂ of 6.26 kPa (normal 11–13 kPa) confirmed the hypoxaemia. With 100% oxygen delivered by a face mask, his oxygen saturation improved to 88%. On inquiry, he reported mildly progressive exertional dyspnoea for 24 months, dizziness for 18 months, weakness and fatigue for 12 months, and minimal lower extremity swelling for the past 2 weeks. He denied any other cardiorespiratory symptoms. He reported a 30-year history of alcohol abuse that had ended 18 months earlier. He was an active smoker with a 60-pack-year history. Examination revealed a middle-aged Caucasian male in no apparent distress. His other vital signs were stable. Positive findings were mild jaundice, digital clubbing, numerous spider naevi on the chest, and

trace ankle oedema. Pulmonary and cardiac examinations were unremarkable. There was no obvious ascites on abdominal examination and the hepatic span was 8 cm. Spleen was not palpable. Laboratory studies showed a haematocrit of 46% (normal 42–52%), haemoglobin of 161 g/l (140–180 g/l) and a mean corpuscular volume of 107.9 fl (86–98 fl). Whole blood count was $10.9 \times 10^9/l$ ($4.3\text{--}10.3 \times 10^9/l$) and the platelet count was $97 \times 10^9/l$ ($130\text{--}400 \times 10^9/l$). Total bilirubin was 53.01 $\mu\text{mol/l}$ ($5.1\text{--}17 \mu\text{mol/l}$) with a direct fraction of 20.52 $\mu\text{mol/l}$ ($1.7\text{--}5.1 \mu\text{mol/l}$). Alkaline phosphatase was 148 IU/l ($30\text{--}120 \text{ IU/l}$), alanine aminotransferase 58 IU/l ($0\text{--}35 \text{ IU/l}$), and aspartate aminotransferase 135 IU/l ($0\text{--}35 \text{ IU/l}$). Serum albumin level was 29 g/l ($35\text{--}55 \text{ g/l}$), total protein 66 g/l ($55\text{--}80 \text{ g/l}$), and INR was 3.0. Serum glucose, electrolytes, creatinine and blood urea nitrogen levels were normal. Serological testing for viral hepatitis was negative. Antinuclear antibody was not detected. Electrocardiogram and chest radiograph were normal. A technetium-99m labelled macroaggregated albumin (^{99m}Tc-MAA) perfusion scan of the lung (figure) showed no perfusion defects suggestive of a pulmonary embolus. However, a significant amount of the radioisotope was taken up by the kidneys and brain indicating an arteriovenous shunt, and the shunt fraction was quantified at 38% (normal < 5%). A contrast echocardiogram using microbubbles generated by agitation of normal saline showed crossover of bubbles from the right ventricle to the left atrium after five ventricular beats, excluding an intracardiac shunt and confirming its intrapulmonary location. Pulmonary function tests showed normal spirometry and lung volumes. The diffusing capacity for carbon monoxide was reduced at 58% of the predicted value. Computed tomography (CT) of the lungs was normal except for minimal pleural thickening at the posterior aspect of the right lung base. A CT scan of the abdomen revealed a small nodular liver, with a preserved caudate lobe. The liver was surrounded by a mild to moderate amount of ascites. Mild enlargement of the spleen with varices in the splenic hilum were noted. These radiological findings were consistent with liver cirrhosis and portal hypertension. Endoscopy showed 2+ oesophageal varices and moderate portal hypertensive gastropathy. A diagnosis of alcohol-related liver disease (probably cirrhosis) and hepatopulmonary syndrome was made.

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Figure Perfusion scan with ^{99m}Tc -MAA. Uptake over kidneys, liver, spleen and brain suggests abnormal passage through pulmonary vascular bed

Discussion

HPS is characterised by the triad of arterial hypoxaemia, liver disease, and intrapulmonary vascular dilatation. The presence of other concomitant pulmonary disorders such as obstructive airway disease does not exclude the diagnosis of HPS.¹

There are several compelling reasons why internists need to be aware of the HPS:

- the relatively high prevalence of the syndrome: 47% of patients investigated with endstage liver disease,⁴ and 38% with less severe liver disease, were shown to have intrapulmonary shunting⁵
- as in this case, commonly encountered liver diseases can present with HPS. In a review of the aetiologies in 57 patients with HPS, 12 were due to alcoholic cirrhosis and 10 due to chronic active hepatitis⁶
- clinical features of HPS (dyspnoea and clubbing) are non-specific. Although the majority present with hepatic manifestations, up to 18% of patients with HPS have presented with predominantly pulmonary symptoms,⁷ as did this patient
- failure to recognise HPS can be serious. Progressive decline in oxygenation can occur despite stable hepatic function⁸; 41% mortality a mean of 2.5 years after the onset of dyspnoea has been reported⁷
- another reason to recognise HPS early, is that treatment with selective embolization of the dilated pulmonary vasculature⁹ or liver transplantation,¹⁰ offers hope for a cure.

Learning points

- hepatopulmonary syndrome is not rare
- up to 18% of patients present with predominantly pulmonary symptoms
- patients may present in general practice or in an emergency room setting
- failure to recognise the syndrome can be serious
- diagnosis can be made easily
- treatment for this syndrome exists

- diagnosis of HPS is easy and requires no fancy equipment.

^{99m}Tc -MAA perfusion scanning is one of the modalities used to demonstrate intrapulmonary vascular dilatation. Injected peripherally, the majority of the labelled albumin (20–60 μm in diameter) is normally trapped in the pulmonary vasculature and the lungs take up most of the radioisotope. In the presence of intrapulmonary or intracardiac shunting, the albumin is not trapped totally in the pulmonary capillary bed and is taken up in the brain, kidneys, liver and spleen.¹¹ The amount of shunted radioisotope can be quantified. To demonstrate the presence of intrapulmonary vascular dilatation causing an arteriovenous shunt and to localise it anatomically to the lungs, the current gold standard is contrast-enhanced echocardiography.⁸ Agitated saline-generated microbubbles injected intravenously are normally trapped by the pulmonary capillary bed. Should the bubbles appear in the left side of the heart a shunt is implied. Timing of the arrival of the microbubbles in the left atrium helps distinguish intracardiac from intrapulmonary shunting. A 4–6 beat delay after opacification of the right ventricle indicates intrapulmonary shunting.¹² Apart from a reduced diffusing capacity for carbon monoxide, pulmonary function tests are normal, but chest radiographs often show bibasilar nodular or reticulonodular opacities.¹³ Laboratory investigations show evidence of hepatic dysfunction, but there is no correlation between the degree of biochemical abnormalities and the development of HPS.⁶

The dilated pulmonary capillary has an expanded diameter, oxygen molecules from the adjacent alveoli cannot diffuse to the centre of the dilated vessel to oxygenate haemoglobin in erythrocytes at the centre of the venous stream, thus resulting in hypoxaemia.¹¹ The factors causing the dilatation itself have not been established.

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Massive pleural effusions in cryptococcal meningitis

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Summary

Cryptococcal infection uncommonly presents with pulmonary manifestations and even more rarely so as massive bilateral effusions. Pleural involvement is usually associated with underlying pulmonary parenchymal lesions and is unusual while on antifungal therapy. We report a patient with cryptococcal meningitis who, while on intravenous 5-flucytosine and amphotericin B, developed life-threatening bilateral massive pleural effusions with evidence of spontaneous resolution, consistent with prior hypothesis of antigenic stimulation as the cause of pleural involvement.

Keywords: cryptococcosis; pleural effusions

Cryptococcus neoformans infection usually presents as chronic meningitis and is increasingly recognised in immunocompromised patients.¹ Serious underlying illnesses or treatment with corticosteroids and/or immunosuppressants predispose to disseminated cryptococcosis. Pleural effusions are unusual and may be diagnosed with a positive cryptococcal antigen test.¹ We report a case of massive bilateral pleural effusions occurring in an apparently immune-competent woman with cryptococcal meningitis.

Case report

A 30-year-old previously well woman presented with severe persistent bitemporal and occipital headaches of six weeks duration. There were associated symptoms of night sweats and vomiting but no other constitutional symptoms. She was a non-smoker and had had no prior illness. Medical examination and magnetic resonance imaging of the brain performed at the beginning of the illness at another hospital were unremarkable. On the day of admission to our hospital, she developed diplopia and had a generalised tonic-clonic seizure. She was drowsy but afebrile and had bilateral papilloedema and lateral rectus palsies. Computed tomography (CT) of her brain

was normal. Her cerebrospinal fluid (CSF) showed lymphocytosis (240 cells/dl), high protein level (59 mg/dl), normal glucose and chloride levels, elevated pressure of 37.8 cmH₂O and was positive for cryptococcal antigen (titre 1:256) and culture-positive for *Cryptococcus neoformans*. Her chest X-ray was normal. She tested negative for HIV I and HIV II antibodies.

She was commenced on intravenous amphotericin B (0.5 mg/kg/day) and 5-flucytosine (180 mg/kg/day) for cryptococcal meningitis. On day 8 of therapy, a ventriculoperitoneal shunt was inserted to relieve the increasing CSF pressure (>60 cmH₂O) which was associated with worsening papilloedema and visual loss. On day 10, she was still febrile and had become extremely dyspnoeic overnight; unable to recline from a sitting position. The chest radiograph at this stage revealed bilateral massive pleural effusions, greater on the right side. Thoracentesis was performed and an intercostal chest tube was left in-situ on the right. Clear pleural fluid amounting to over 3.5 litres was drained over the next three days. Pleural fluid analysis revealed a protein concentration of 2.5 g/dl (serum protein 78 g/dl), lactate dehydrogenase (LDH) 23 IU/l (serum LDH was 218 IU/l), white cell count 230 cells/dl with 91% polymorphs. The pleural fluid was culture and smear negative for pyogenic micro-organisms, mycobacterium and fungus but was positive for cryptococcal antigen. Blood cultures were also negative.

The massive left effusion resolved spontaneously and the right chest drain was removed after 8 days with no further recurrence of the effusion. A repeat chest radiograph while on antifungal therapy was clear but the CT scan of the thorax showed a cavitating infiltrate in the left lower lobe.

The patient made an uneventful recovery after 11 weeks of amphotericin and 5-flucytosine therapy and was functionally normal when last seen. Further questioning revealed she had been living two doors away from a pigeon breeder for the last 3 years. She was discharged on oral fluconazole 400 mg daily but was lost to follow-up.

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