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Case Report

Hepatopulmonary syndrome: A case report

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Introduction

Hepatopulmonary syndrome is hypoxaemia due to dilated intrapulmonary vasculature in the presence of liver disease or portal hypertension [1]. Intrapulmonary vascular dilatation consists of a dilated precapillary network, direct arterio-venous communication and dilated pleural blood vessels [2]. Deterioration of arterial oxygenation in patients with liver disease indicates poor prognosis. Therefore, there are suggestions to classify hepatopulmonary syndrome as a new indication for liver transplantation. We present a case of a 52-year-old patient with background chronic liver cell disease (CLCD), panhypopituitarism and epilepsy who showed platypnoea and had evidence of orthodeoxia. He was subsequently diagnosed to have hepatopulmonary syndrome and commenced on long-term O_2 therapy. We discuss the evaluation of a patient with hepatopulmonary syndrome and the long-term management of such a patient.

Case presentation

A 52-year-old man presented with shortness of breath, worsening over four weeks. He described symptoms of platypnoea. He was diagnosed to have epilepsy at the age of 36 years and managed on oral phenytoin. He had a prior history of hypogonadotropic hypogonadism, hypocortisolism and pituitary hypothyroidism with a pituitary tumor and evidence of craniopharyngioma at the age of 40 years. He was diagnosed to have CLCD 6 years previously. At the initial diagnosis, he had a high ferritin level (1043) with high transferrin saturation of around 70% and underwent chelation therapy and venesection. The ferritin levels gradually reduced with time and the last ferritin value was 123. Liver biopsy revealed evidence of steatohepatitis with fibrosis. However, the genotype for haemochromatosis was negative. He denied a family history of CLCD or significant intake of alcohol or herbal concoctions. On examination, he was conscious and rational and

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haemodynamically stable but demonstrated evidence of orthodeoxia. He had evidence of clubbing, cyanosis and diffuse telangiectasia, His spO_2 at rest in the erect position was 73% and, when supine was at 83% and improved with oxygen therapy. There was no clinical evidence of murmurs or pulmonary hypertension. The lungs were clear apart from a few basal crepitations. Investigations are shown in Table 1 and in Figures1, 2 and 3.

Table 1: Summary of the investigations carried out in the patient.

Test	Result
WBC	3.03 X 10^3/µL (4-10)
Hemoglobin	13.2 g/dL (11.0-16.0)
Platelet	46 X 10^3/µL (150-450)
Urea	16 mg/dL (17.4-49.2)
S. Cr	0.64 mg/dL (0.73-1.10)
Na	135 mmol/L (136-145)
K	3.2 mmol/L (3.5-5.1)
CRP	6.7 mg/L (<6)
ALT	18.3 U/L (5-34)
AST	37.3 U/L (0-55)
HbA1c	5.3% (<6%)
Hep C	Negative
Hep B	Negative
HIV	Negative
Caeruloplasmin	Negative
Ferritin	471 ng/mL (21.8-274)
Serum Iron	25.9 µ/dL (11.6-31.2)
UIBC	8.9 µg/dL (13.0-56.0)
TIBC	34.8 µg/dL (44-80)
Transferrin saturation	74% (<50%)
FSH	0.7 IU/L (1.42-15.4)
LH	0.04 IU/L (1.24-7.8)
Testosterone	0.02 ng/dL (15-70)
TSH	0.2 µIU/mL (0.27-4.2)
T4	0.1 ng/dL (0.9 – 1.7)
Cortisol	100 µg/dL (5-20)
Liver biopsy	Evidence of steatohepatitis with proof of grade III fibrosis. No evidence of iron deposition.
pH	7.527
pO2	41 mmHg
pCO2	18.3 mmHg
pAO2	58 mmHg
A-a gradient	17 mmHg (8-12)

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Lactate	1.2 mmol/L (<1)

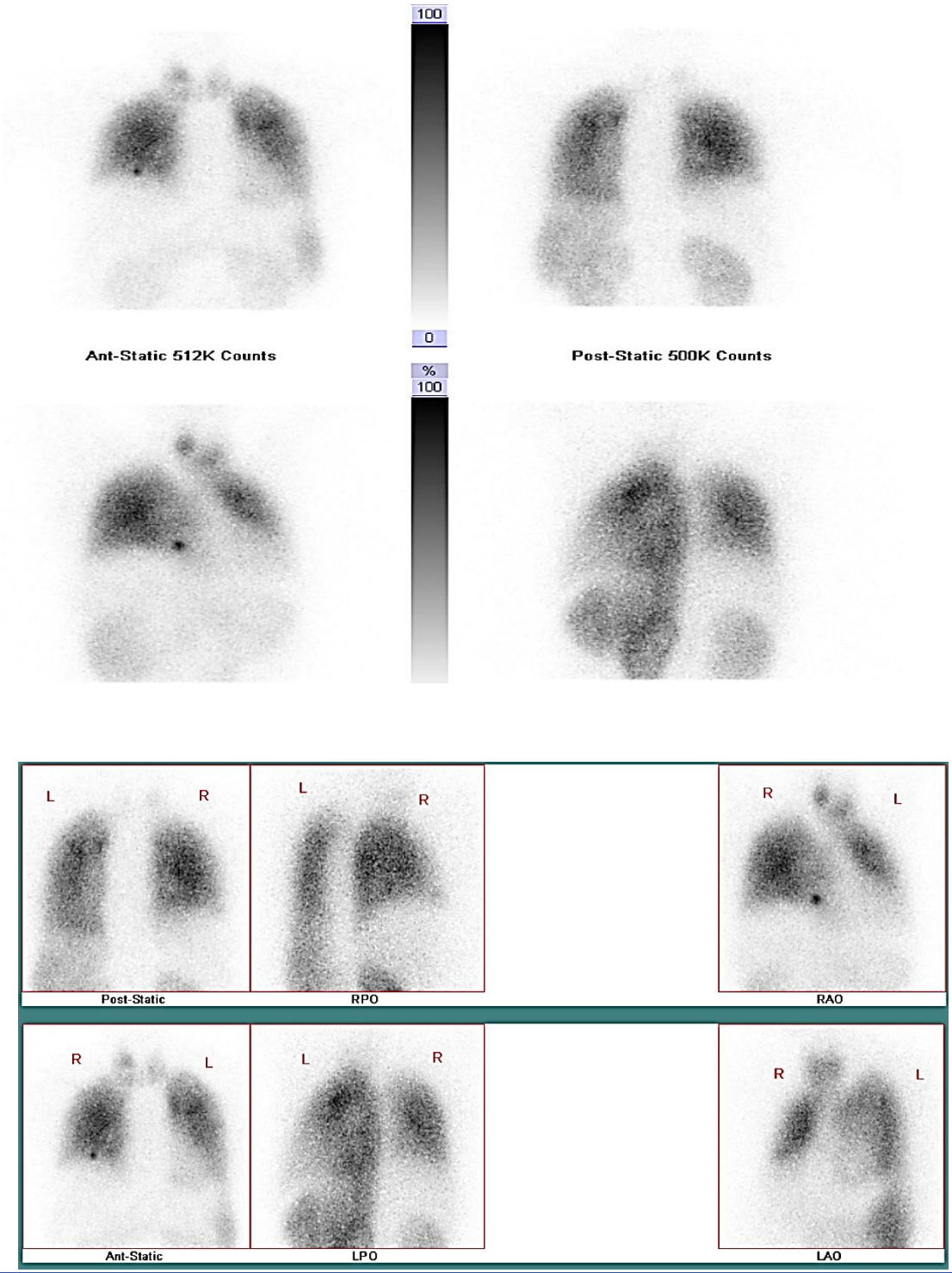

Figure 1:Ventilation perfusion scan

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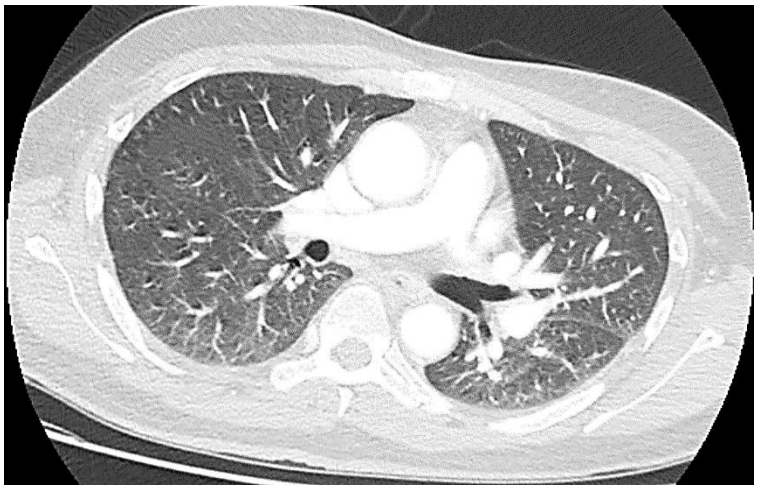

Figure 2: CT image of the chest

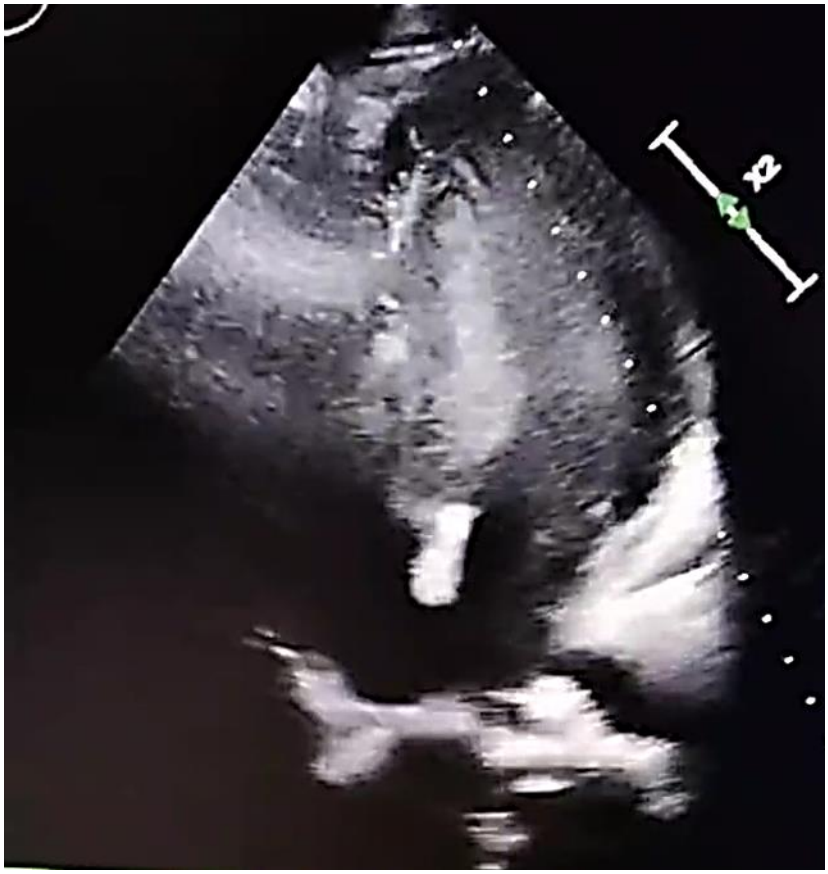

Figure 3: Bubble contrast echo

Mild prominent vessels in the bi-basal periphery of the lungs and significant vessels were noted in the subpleural peripheral region, lower lobes and bilateral lungs on contrat CT od the chest. No pulmonary mass, nodules, consolidation or arteriovenous malformations were seen. Dependent changes were noted. No hilar or mediastinal lymphadenopathy was seen. The trachea and main bronchi were unremarkable. No bronchiectasis or pleural or pericardial effusion were seen. Computed tomography and pulmonary angiogram were negative. The liver showed irregular and nodular changes with splenomegaly and evidence of portal hypertension. Upper gastrointestinal endoscopy showed evidence of mild varices. There was evidence of mild osteopenia. On echocardiogram, the left ventricular ejection fraction was 60%, the tricuspid annular planar regurgitant gradient was 18mmHg, there was mild aortic regurgitation and no patent ductus arteriosus. There was a contrast appearance in the LV after the 4^{th} - 5^{th} cycle in the transthoracic echo but the transoesophageal echogardiogram (TOE) was negative. He had a Child score of A with a Model For End-Stage Liver Disease (MELD) score of 15. His O_2 saturation improved with oxygenation up to 98%, with a partial pressure of O_2 of 84%, and he is currently on LTOT (long-term O_2 therapy). He is also currently under evaluation as a possible candidate for a liver transplant.

Discussion

Hepatopulmonary syndrome is an uncommon condition requiring early suspicion and exclusion of important differential diagnoses.

The triad of liver disease, arterial hypoxaemia and intrapulmonary vascular dilatation is known as hepatopulmonary syndrome (HPS). HPS has two types based on the nature of the pulmonary vascular abnormalities. Type I is characterized by precapillary pulmonary artery dilation and type II by pulmonary arteriovenous fistulas [3]. The definitive diagnostic criteria for HPS include impaired oxygenation (PaO_2 >15 mm Hg or >20 mm Hg if age >64 y) while breathing ambient air, intrapulmonary vasodilatation confirmed by contrast-enhanced echocardiography or lung perfusion scanning (brain shunt fraction >6%) and liver disease, cirrhosis and portal hypertension [4. Pulmonary vascular dilatation can be shown non-invasively by contrast echocardiography or lung perfusion scanning [5,6]. Transoesophageal imaging is much better but less straightforward to perform than transthoracic views. Lung perfusion scanning enables quantification of vascular dilatation and may assist in differentiating vascular from non-vascular reasons for hypoxaemia.

The potential pharmacological treatment for HPS includes inactivation of endothelin-1(ET-1) using pentoxyfylline (PTX), quercetin and mycophenolate mofetil (MMF), inhibition of pulmonary angiogenesis with PTX, methylene blue (MB), MMF or sorafenib, blocking nitric oxide synthesis (NOS) by inhibition of NOS using PTX, MB, N-nitro -L-arginine methyl ester (L-NAME), quercetin, MMF, caffeic acid phenethyl ester (CAPE) or N-acetylcysteine (NAC) and inhibition of bacterial translocation with subsequent decrease in NO and norfloxacin. Despite promising outcomes from treating individuals with HPS with several drugs, the results cannot be generalized to all patients due to the lack of randomized trials with a proper study population. PTX, MB, and MMF, especially, showed promising

results in these studies. The primary disease mechanism involves vasodilation and angiogenesis mediated by NO and carbon monoxide (CO). Treatment studies have targeted this pathway but with disappointing results [7]. Large, randomized, placebo-controlled trials are necessary for the investigation of the efficacy of these agents [8].

The only effective therapy for HPS is liver transplantation (LT), with an improvement in oxygenation seen at one year. After LT in HPS patients, the 5-year survival rate was approximately 76%, similar to patients without HPS. 80% of all HPS patients showed complete resolution after LT and the mortality rate was 16% in the whole group and 30% in the severe HPS group at three months. Some studies showed worse survival in patients with $PaO_2 \leq 50$ mmHg alone or with MAA shunt fraction ≥ 20%. However, some other studies showed no significant differences in survival between HPS and non-HPS patients [7]. Survival post-LT was not dependent on baseline PaO_2 values obtained at the time of HPS diagnosis [9]. Complete resolution of HPS after LT within a year was seen in most HPS patients [7]. The pulmonary vascular changes which occur after LT suggest a slow remodelling process. The resolution requires up to 15 months post-transplant; some may not improve after transplantation [5].

The only other established therapy is the administration of LTOT in patients with severe HPS [10]. Only 2 case studies have been done on the long-term treatment of HPS with mild and severe hypoxemia using oxygen therapy in a home environment. In both cases, an improvement in liver function and oxygenation was observed [11]. Long-term oxygen therapy might offer a new therapeutic approach to improve liver function in patients with cirrhosis with hypoxemia [12]. No data are available, however, regarding the efficacy, compliance, tolerance, and cost-effectiveness of such a therapeutic approach.

Type 2 HPS, as noted previously, is characterized by pulmonary arteriovenous fistulas and does not respond well to oxygen therapy. Transcatheter coil embolization of the arteriovenous pulmonary fistulas in type 2 HPS has reduced the morbidity of HPS before and after liver transplantation. Embolo-therapy may be an excellent first line of bridging therapy in patients with Type 2 HPS before transplantation. Even in Type 1 patients with advanced diffuse pulmonary changes, benefits in reducing morbidity pre-transplantation have been described with coil embolization [3].

The key takeaways include the need for initial suspicion of the possibility of hepatopulmonary syndrome. Diagnosis usually requires a combination of blood gas analysis, CT imaging, pulmonary function, V/Q testing, and bubble contrast echo to exclude other pulmonary parenchymal and vascular causes of cyanosis. Management is usually LTOT, and the definitive management is a liver transplant.

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