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CASE REPORT

Hepatopulmonary syndrome- a case report

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Patients with long-standing pulmonary hypertension and liver disease are prone to the development of hepatopulmonary syndrome. Several diagnostic modalities and treatments have been researched for its management. In this paper, we will discuss the approach to a patient with HPS based on a patient admitted to our facility.

Keywords: hepatopulmonary syndrome, diagnosis, treatment, pulmonary hypertension, liver disease

Case presentation

An 82-year-old woman, from an average socio-economic background, with a more than 10-year history of idiopathic chronic liver disease on diuretic therapy was brought to our facility with a 2 week history of onset of abdominal distension and bilateral leg edema. Other significant history included 25 Kilogram weight loss in the past 7 months.

On clinical examination in the Emergency, the patient was found to have decreased air entry on the right side of the chest and ascites.

Blood work was significant for a low hemoglobin of 10.3 gm/dl, International normalized ratio (INR) of 1.42, serum albumin of 12.3 gm/L and ammonia level of 114 Umol/L.

Blood gases done on room air showed an initial partial pressure of oxygen (pO2) of 53.1, improving on oxygen to >100 mmHg. However, on discontinuing oxygen, pO2 dropped back to <60 mmHg.

Chest x ray (CXR) (**Figure 1**), high resolution computed tomography (HR CT) chest (**Figure 2**), and Ultrasound abdomen (**Figure 3**) confirmed findings of left-sided moderate pleural effusion and moderate ascites, respectively. Other significant findings included a cirrhotic liver.

Ascitic tap and pleural tap were done. Fluid analysis revealed high serum ascetic fluid albumin gradient (SAAG).

On clinical observation, the patient was noted to have clubbing, associated with persistent hypoxia.

Echo (**Figures 4 and 5**) was done with agitated saline, showed a hepatopulmonary shunt. Hence, a diagnosis of hepatopulmonary syndrome was coined for the patient.

The patient's diuretics were optimized. She started on garlic pills and pentoxifylline. Acetylcysteine 600 mg was started as well. The patient was stabilized for discharge on home oxygen therapy @ 1 lt /min.

Definition and diagnostic criteria

Hepatopulmonary syndrome is characterized by a triad of chronic liver disease, low blood oxygen saturation and pulmonary arterio venous shunting, as visualized on a trans thoracic echo done with saline agitation (1).

It is defined as reduced arterial oxygen saturation due to dilated pulmonary vessels in the presence of underlying advanced liver disease or portal hypertension (2).

Criteria for diagnosis are as follows:

1. Presence of underlying chronic liver disease, with or without portal hypertension
2. For patients breathing room air, at rest, in a sitting position a pO2 of <80 mmHg, or alveolar arterial oxygen gradient of >15 mm.

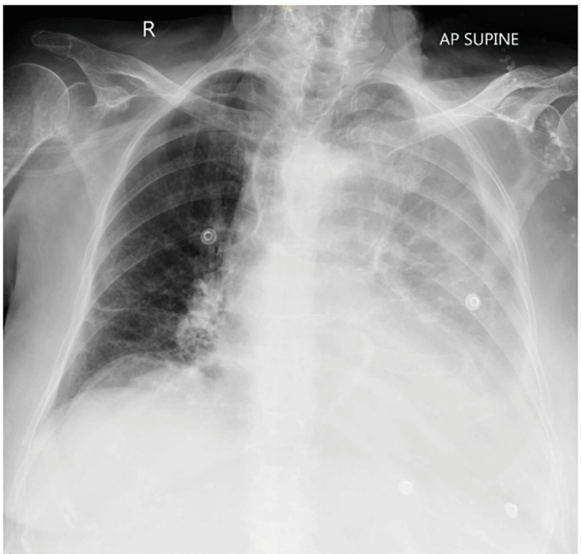

FIGURE 1 | CXR on admission.

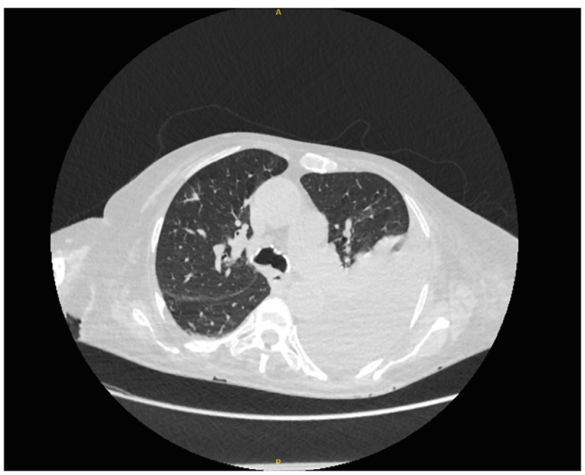

FIGURE 2 | CT on admission.

3. Intrapulmonary dilatation of vasculature, as demonstrated by contrast-enhanced echocardiography or radioactive lung perfusion scanning.

Severity can be determined by the decreasing partial pressure of oxygen in the blood.

- Mild HPS is defined as Po2 > 80 mmHg.
- Moderate HPS is defined as pO2 of 60–79 mmHg.
- Severe HPS is defined as pO2 of 50–59 mmHg.
- Very severe is defined as pO2 of <50 mmHg.

Pathophysiology: (Original table)
Represented in **Table 1**.
Characteristic clinical findings (3):

- Progressively increasing dyspnea in setting of underlying chronic liver disease

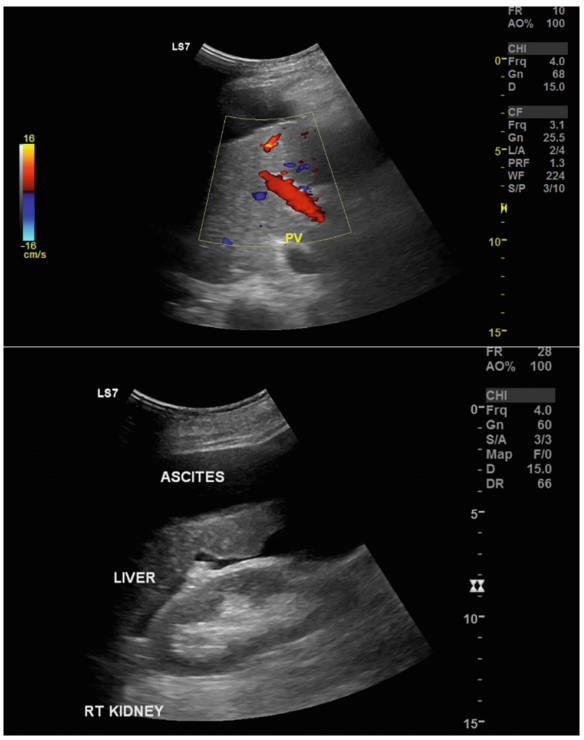

FIGURE 3 | US abdomen images showing ascites, cirrhotic liver, and normal portal vein dimensions (original images).

- Digital cyanosis
- Clubbing
- Spider naevi
- Platypnoea- Increased shortness of breath when moving from supine to sitting position.
- Orthodeoxia- Decrease in partial pressure of oxygen by more than 5% when moving from supine to sitting position.

Additionally, other signs of chronic liver disease may also be seen. In many patients with underlying cardiac comorbidities, findings may be even more pronounced.

Common diagnostic modalities

1. The most important bedside test is an arterial blood gas on room air, at rest, in sitting position. Decrease in partial pressure of oxygen to less than 70 mmHg warrants further investigation. pO2 falls as per the severity of disease.

   Orthodeoxia can be confirmed by performing the ABG in a supine position, followed by sitting position. Although it is not diagnostic, but the greater the difference in pO2, the greater the severity of HPS.

2. Contrast-enhanced echocardiography is the gold standard for confirming pulmonary vasculature dilation. This is performed by injecting agitated saline (saline agitated to produce microbubbles

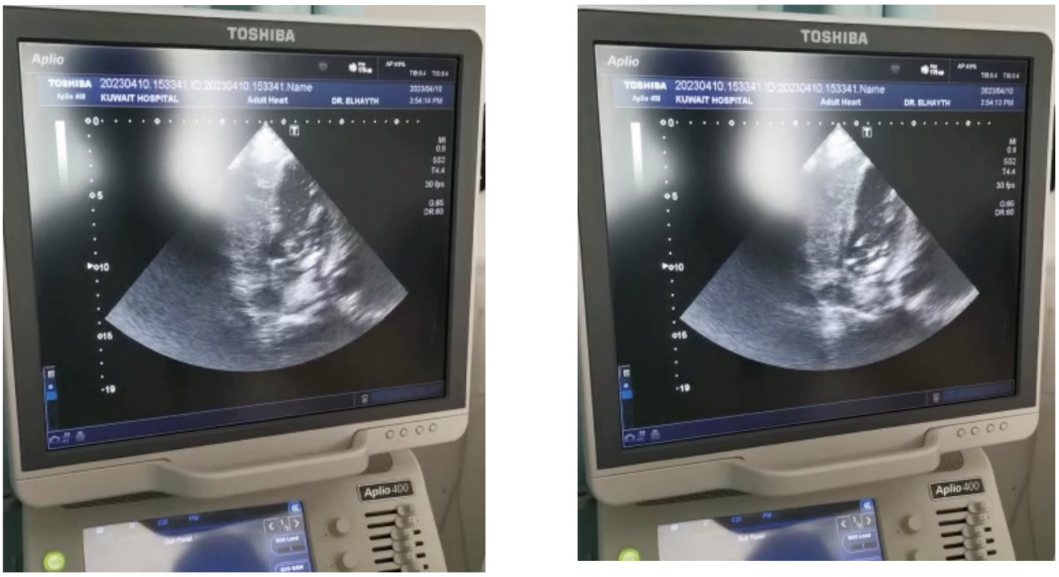

FIGURE 4 and 5 | Echo with contrast (agitated saline) images showing presence of agitated saline in left atrium (original images).

TABLE 1 | Pathophysiology.

Underlying chronic liver disease	•Endotoxemia (TNF-α, endothelin-1) •Translocation of intestinal bacteria
Increased macrophages and monocytes in lung	•Production of inducible nitric oxide synthase (iNOS) •Increased level of nitric oxide and heme oxygenase •Heme oxygenase leading to increased production of carbon monoxide
Increased NO and CO	•Pulmonary vasodilation •Poor oxygen exchange, leading to low pO2
Increased TNF α and VEGF	•Increased TNF α induces inflammatory response •In combination with vascular endothelial growth factor (VEGF), increase in pulmonary angiogenesis is seen
Vasodilation and angiogenesis	•Shunt formation in pulmonary vasculature •Ventilation perfusion mis match

of >10 mm in diameter) into a peripheral vein, while simultaneously performing a transthoracic or transesophageal echo. In a normal person, the bubbles cannot be seen in the heart as these are absorbed in the alveoli. However, in case of a pulmonary shunt, the bubbles reach the left atria between the 3rd and 6th cardiac cycles after injection (4).

3. A technetium-99 m labeled scan with micro aggregated albumin is a useful method to demonstrate pulmonary shunting. If radionuclide uptake is demonstrated in kidney or brain or both, it confirms intrapulmonary shunting. Limitations to doing this test include absence of nuclear testing facility at general hospital. Specific referral requiring transport of patient to a faraway facility may be needed, which was a practical challenge we faced in our case (5).
4. Other modalities like CXR, CT scan, and pulmonary function tests are used to provide supportive evidence and to rule out other differentials.

Prognosis and management

Patients with hepatopulmonary syndrome present a poor prognosis with mortality increasing two-fold as compared to patients with chronic liver disease without hepatopulmonary

syndrome (6). The following modalities of treatment are advised (7):

1. Oxygen therapy, usually life long, and titrated as per the patient's needs.
2. Liver transplant is the only definitive management of HPS. The challenges associated with that are well known to us. In our case, the patient needed a referral to one of the very few tertiary care units in the country offering transplants. However, unfortunately, it could not be arranged.

   Liver transplant helps by improving hypoxemia, improving diffusion capacity of lungs for carbon monoxide (DLCO) on pulmonary function tests, and even leads to shunt reversal in some cases.
3. Multiple medical modalities are available to help achieve symptomatic relief in HPS. Some of the more commonly used drugs are as follows:

   – Pentoxifylline:

     Mechanism of action: Phosphodiesterase 2 inhibitor. It helps by negating the effect of TNF α, thus reducing pulmonary angiogenesis.

     Dose: 400 mg once daily for 7 days, followed by 400mg twice daily for 7 days, and then 400 mg TID after that.

     Serious Side effects: Agitation, angina, angioedema, arrhythmias, bronchospasm.

   – Garlic:

     Mechanism of action: Unknown. However, improvement in oxygen saturation has been seen in various previous studies.

     Dose: 1 capsule daily

     Serious side effects: None

   – Methylene blue:

     Mechanism of action: Nitic oxide inhibitor

     Dose: 3 mg/kg Iv infusion

     Serious side effects: Arrhythmia, aphasia, confusion, hemolytic anemia

   – Mycophenolate mofetil:

     Mechanism of action: Immunosuppressive agent; inhibits nitric oxide production by blocking TNF α

     Dose: 500 mg twice daily, oral

     Serious side effects: Neutropenia, endocarditis, pure red cell aplasia

   – N acetyl cysteine:

     Mechanism of action: Inhibitor of reactive oxygen species

     Dose: 600 mg twice daily, oral

     Serious side effects: Anaphylaxis, Arrhythmia, Seizures

Many more medications are used without success, and many are undergoing trials.

Conclusion

Hepatopulmonary syndrome has been known to be a difficult-to-recognize entity in the past. With everchanging times and massive improvements in diagnostic modalities, it has become easier than ever to diagnose the condition now. Easy and effective treatment and cure remains a challenge. The drugs used till now have been unable to provide lasting benefit or improve the mortality significantly. Large trials are still ongoing, keeping alive the hopes for a brighter future for patients with hepatopulmonary syndrome.

Author contributions

SM: Specialist physician. Handled inpatient care of the patient. Did the writeup and compilation of article, including case presentation, discussion, pathophysiology, and treatment. AO: Specialist Internal Medicine. Conducted echocardiography and provided Echocardiography images. NT: Consultant Gastroenterologist, the most responsible physician of the patient, decided initial line of management and handled inpatient care. RG: Consultant Pulmonologist. Diagnosed hepatopulmonary syndrome and added specific treatment for it.

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