



CASE REPORT

REVISED Case Report: Hepatopulmonary syndrome as the first clinical manifestation of cirrhosis in a patient with underlying chronic lung disease [version 2; peer review: 2 approved, 1 not approved]

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Abstract

An 86 year old woman with multiple chronic lung diseases (including chronic obstructive pulmonary disease, bronchiectasis, and untreated mycobacterium avium-intracellulare) presented with two weeks of increased shortness of breath, notably worse when seated as compared to when lying down. After treatments focused on her known conditions did not resolve her dyspnea, the differential diagnosis was broadened and she was found to have evidence of cirrhosis on imaging. As a result of this new diagnosis, transthoracic echocardiography and arterial blood gas analysis were performed and together yielded the diagnosis of hepatopulmonary syndrome. We describe a rare presentation of hepatopulmonary syndrome manifesting as a patient’s first clinical evidence of suspected cirrhosis, a diagnosis made difficult by this patient’s numerous other lung diseases which muddied the picture.



Keywords

Hepatopulmonary Syndrome, COPD, MAI Infection, Bronchiectasis

Open Peer Review

Reviewer Status

	Invited Reviewers		
	1	2	3
REVISED version 2 published 16 May 2019		 report	 report
version 1 published 02 Aug 2018	 report		

- 1 **Robert Rodríguez-Roisin**, University of Barcelona, Barcelona, Spain
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Any reports and responses or comments on the article can be found at the end of the article.

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REVISED Amendments from Version 1

In this revised version I have attempted to provide further clinical information about the state and nature of the patient's other pulmonary diseases so as to give further evidence as to what role HPS played in her clinical presentation. I have also tried to better characterize the gas-exchange abnormalities caused by HPS which I describe in the discussion.

See referee reports

Introduction

The triad of chronic liver disease, hypoxemia, and microvascular dilatations/malformations in the lungs make up hepatopulmonary syndrome (HPS), a well-known sequela of hepatic cirrhosis¹. These aforementioned vascular abnormalities result in ventilation-perfusion mismatch, which yields the clinical findings of dyspnea (universally) as well as digital clubbing and/or cyanosis (both very common)². We report a case of a patient presenting with HPS as their first clinical manifestation of suspected cirrhosis, and describe how it was distinguishable from other potential causes of her symptoms such as her comorbid chronic obstructive pulmonary disease (COPD), bronchiectasis, and mycobacterium avium-intracellulare (MAI) infection.

Case report

An 86 year old retired latina woman with a past medical history of COPD, bronchiectasis, MAI infection (not previously treated), tobacco dependence (40 pack-years, quit 25 years prior to presentation), diabetes mellitus, hyperlipidemia, and hypertension presented with two weeks of worsened dyspnea and non-productive cough. She reported a baseline of daily shortness of breath with an exercise tolerance of 3 blocks, but over the two weeks prior to her presentation it decreased to the point where she would feel dyspneic when walking around her apartment. Interestingly she stated that she also generally felt more short of breath while seated than when lying down, and also cited a worsening cough over this time course productive of green sputum. Her exam on presentation was significant for an oral temperature of 101.4 degrees Fahrenheit, oxygen saturation of 84% on room air, tachypnea and coarse crackles appreciated diffusely on lung examination. Her blood-work was notable for a white blood cell count of 19.8 k/ μ L, with multiple diffuse small nodular opacities seen on chest x-ray consistent with her known MAI infection. She was started on levofloxacin for treatment of a presumed bronchiectasis flare along with oxygen therapy via nasal cannula in addition to other supportive treatments. Although her fever, leukocytosis, and cough improved with antibiotics (further supporting a diagnosis of bronchiectasis flare), her dyspnea and hypoxemia persisted. Consequently, a chest computerized tomography (CT) scan was ordered which showed the same nodularities seen on chest x-ray, but also elucidated a nodular liver consistent with cirrhosis. While her platelet count, transaminases, bilirubin, and prothrombin time were all normal and she had no ascites or other edema on exam, she did however have spider angiomas. Further chart review done at that time revealed that she had known cirrhotic characteristics on liver imaging as they were incidentally seen almost five years prior, although she had never had any decompensations or serologic evidence of liver dysfunction

since. Work-up back then elucidated no potential cause except for non-alcoholic fatty liver disease, given her histories of hyperlipidemia and diabetes. In light of this knowledge gained from deep chart review, the specter of hepatopulmonary syndrome was raised as a possible explanation for her persistent hypoxemia and dyspnea. In order to investigate this possibility, both seated and supine arterial blood gases were obtained which elucidated orthodeoxia (see Table 1). A transthoracic echocardiogram with bubble study was then performed which suggested an intrapulmonary shunt (see Figure 1), thereby confirming the

Table 1. Patient's orthodeoxia as established via arterial blood gas analysis.

Parameter	Supine	Seated
FiO ₂	21% (Room Air)	21% (Room Air)
PaO ₂ , Arterial	65.5 mmHg	53.1 mmHg
Direct O2 Saturation	93.3%	88.6%
PaCO ₂ , Arterial	45.0 mmHg	43.1 mmHg
A-a gradient	28.0 mmHg	42.8 mmHg

FiO₂– Fraction of inspired oxygen, PaO₂– Partial pressure arterial oxygen, PaCO₂– Partial pressure arterial carbon dioxide, A-a gradient – Alveolar-arterial gradient.

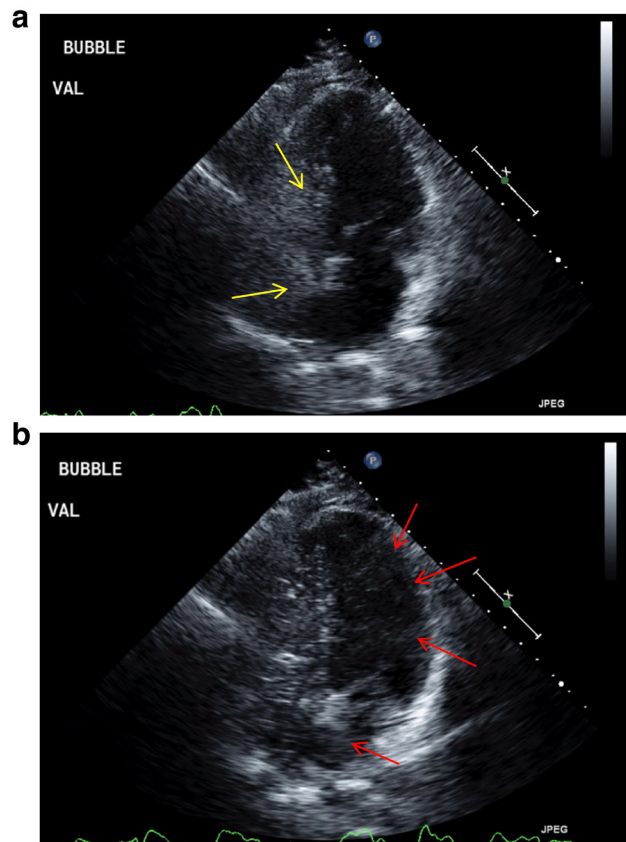


Figure 1. Still images from patient's transthoracic echocardiogram showing (a) no early shunting with saline bubble (identified by yellow arrows) injection, followed by (b) late passage of bubbles (identified by red arrows) into the Left Atrium and Ventricle representing Intrapulmonary Shunting.

diagnosis of HPS. While oxygen supplementation caused her dyspnea to improve and oxygen saturation to rise to a safe level, she interestingly was never able to reach a saturation of 100%. However given this improvement in her dyspnea and oxygenation, as well as the resolution of all signs and manifestations of the bronchiectasis flare that she initially presented with, the patient was discharged home with oxygen. Soon after discharge, she was seen in a pulmonology clinic where she was found to be in stable condition.

Discussion

Our patient possessed all three of the cardinal findings of hepatopulmonary syndrome: chronic liver disease, hypoxemia, and evidence of pulmonary microvascular abnormalities. Her symptom of platypnea (shortness of breath worsened by going from a supine to seated position) and finding of orthodeoxia on arterial blood gas analysis also clearly pointed to HPS. But while most cirrhotic patients with hepatopulmonary syndrome have only mild disease and its severity is often proportional to that of their cirrhosis, she presented with severe disease despite seemingly having compensated cirrhosis³. Moreover, it is very unusual for HPS to be the first symptomatically manifesting sequela of cirrhosis as it was in this patient; there are few other examples of this happening in the literature⁴.

As it is classically described, our patient's hypoxemia likely resulted from intrapulmonary vascular abnormalities causing ventilation-perfusion mismatch (primarily) and direct arteriovenous communications (to a lesser degree), which yielded her dyspnea^{5,6}. More specifically this shunting caused her to have platypnea, which is the symptomatic manifestation of orthodeoxia, and has been shown to be very closely tied with HPS. In one prospective study comparing cirrhotics with HPS vs. those without the complication, platypnea was endorsed by 65.5% of the HPS group vs 6.2% of the non-HPS cirrhotic group⁷.

Given that they are also manifestations of cirrhosis-related vascular malformations, spider angiomas are also commonly seen in HPS as they were with our patient⁸. The intrapulmonary anomalies can be reliably detected via saline-enhanced transthoracic echocardiography, as well as with more advanced confirmatory tests such as technetium-99m macroaggregated albumin (MAA) nuclear scanning or pulmonary angiography^{3,5,9}. Given the clear presence of lately-transmitted bubbles seen on her transthoracic echocardiogram though, these more advanced and expensive tests were not pursued in our patient's case.

Once the diagnosis is made with the aforementioned triad, disease severity is assessed via PaO₂. Patients with mild disease have a PaO₂ ≥ 80mmHg, those with moderate have PaO₂ ≥ 60 < 80 mmHg, severe have PaO₂ ≥ 50 < 60 mmHg, and those with very severe disease have a PaO₂ of < 50 mmHg¹⁰. Our patient was found to have severe disease based upon her PaO₂ although much of her arterial hypoxemia was likely related to her other pulmonary diseases. The pathogenesis

of HPS is thought to involve increased serum levels of nitric oxide (although correlations with elevated carbon monoxide and tumor necrosis factor α have also been seen) resulting from cirrhosis, which is postulated to cause pulmonary vascular dilatation, and to a lesser degree arteriovenous malformations (AVMs)^{5,11}. Autopsy studies have shown that the number of dilated precapillary and capillary vessels in the lungs far outnumbers the number of pulmonary AVMs in these patients, but the end result of each is the same: passage of mixed-venous blood into the pulmonary veins, resulting in V/Q mismatch and hypoxemia⁵. Where those vessels dilated as a result of HPS are concerned, the hypoxemia is a result of diffusion-limited gas exchange. Cirrhosis itself (independent of HPS) is associated with impaired autoregulation of pulmonary vascular tone in a heterogeneous distribution throughout the lung, which in HPS results in orthodeoxia as alveoli in dependent areas see alterations in ventilation for which blood flow cannot be adequately accommodated for with respect to gravitational changes when patient position is adjusted^{5,6,12}.

The only definitive treatment for HPS is liver transplantation¹³. While those with this condition are more prone to post-operative complications than other patients post-liver transplant, ultimately those who survive have resolution of the hypoxemia caused by their pre-transplant HPS¹⁴. Given her age, comorbidities, and otherwise well-compensated liver disease, liver transplant was not considered in our patient.

In addition to HPS, there are other similar clinical entities which are worth discussing as part of the differential diagnosis for patients who present like ours. Similar to HPS, portopulmonary hypertension (PPH) is also a sequela of cirrhosis which is characterized by pulmonary hypertension (as defined by elevated mean arterial pressure of >25mmHg at rest, and pulmonary vascular resistance greater than 240 dynes/sec/cm⁵) in the setting of portal hypertension and/or cirrhosis with other causes of PH having been excluded¹⁰. Patients with PPH typically present with clinical findings consistent with other causes of pulmonary hypertension, namely external dyspnea, fatigue, chest pain, and/or syncope, with progression to *cor pulmonale* in severe cases¹⁵. PPH was excluded in our patient by the fact that her transthoracic echocardiogram showed no evidence of pulmonary hypertension.

Hereditary hemorrhagic telangiectasia (HHT) is a genetic (autosomal dominant) disease in which arteriovenous malformations (AVMs) and mucocutaneous telangiectasis form throughout the body¹⁶. The predominant symptom with which people present is paroxysmal epistaxis related to AVMs in the nasal mucosa, although 15–35% of patients with HHT have pulmonary AVMs which cause dyspnea in a manner analogous to those with HPS¹⁷.

While it was tempting at first to presume that our patient's untreated MAI (and/or her other lung diseases, see [Table 2](#) below) could be causing her symptoms, the clinical presentations

Table 2. Comparing notable clinical and diagnostic characteristics of her different lung disorders.

Parameter	COPD	Bronchiectasis	MAI	HPS	PPH	HHT
Productive Cough	Yes	Yes	Yes	No	No	No
Shortness of Breath with Exertion	Yes	Yes	Yes	Yes	Yes	Sometimes (if pulmonary involvement)
Shortness of Breath at Rest	Yes	Yes	Yes	Yes	Yes	Sometimes (if pulmonary involvement)
Platypnea/Orthodeoxia	No	Sometimes (if basilar predominant)	Sometimes (if basilar predominant)	Yes	No	Sometimes (if pulmonary involvement)
Pulmonary Hypertension	Sometimes (WHO Group 3)	Sometimes (WHO Group 3)	Sometimes (WHO Group 3)	No	Yes	Sometimes (Usually WHO Group 2)

COPD- Chronic obstructive pulmonary disease, MAI - mycobacterium avium-intracellulare infection, HPS – Hepatopulmonary syndrome, PPH – Portopulmonary hypertension, HHT - Hereditary hemorrhagic telangiectasia, WHO - World Health Organization.

which result from this infection are not typically mimickers of HPS. Those with symptomatic pulmonary MAI infection typically present in one of two ways, depending on whether they have underlying lung disease or not. Those with underlying lung disease (most commonly COPD or bronchiectasis) typically have a tuberculosis-like (albeit milder) presentation: chronic cough, weakness, malaise, weight loss, dyspnea, and upper-lobe predominant infiltrates and/or cavitation on chest imaging¹⁸. Patients with underlying bronchiectasis will usually have their MAI infection develop in bronchiectatic areas, not necessarily in the upper lobes¹⁹. Those without underlying lung disease tend to present with months of productive cough, without the other “tuberculosis-like” constitutional symptoms²⁰. A subset of these patients classically present with “Lady Windermere syndrome:” lingular/right-middle lobe infiltrates in elderly women without predisposing lung disease who suppress their cough²¹. Regardless of which way a patient presents, diagnosis is made via the combination of radiographic findings indicative of pulmonary disease along with either MAI-positive sputum or an MAI-positive bronchial wash in a patient with respiratory symptoms, according to the Infectious Disease Society of America and the American Thoracic Society²².

The patient’s lack of basilar-predominant nodularities on CT scan made MAI the unlikely cause of her platypnea and/or orthodeoxia. As Table 2 also illustrates though, many of her signs and symptoms could be ascribed to her COPD and/or bronchiectasis. Obstructive airway diseases such as these are a known cause of ventilation-perfusion defects similar to those seen in HPS, as the distribution of alveolar ventilation is increased whereas that of pulmonary blood flow is not, with this effect positively correlated with disease severity but significantly

hastened during acute exacerbations²³. However neither of these conditions are known to cause orthodeoxia, and her COPD was stable (FEV₁ was 0.61 liters on recent spirometry) at the time of her hospitalization. In the end, the clinical and diagnostic characteristics of HPS are so specific as a result of its entirely unique gas-exchange pattern that it can be reliably diagnosed even in the setting of other diseases that cause arterial hypoxemia, as it was in our patient²⁴.

Hepatopulmonary syndrome belongs on the differential diagnosis for dyspnea in any patient with chronic liver disease, even those like our patient without any previous decompensations of cirrhosis. While it can present in a way which is symptomatically similar to that of other chronic lung diseases, it can be definitively diagnosed via a relatively simple work-up which should be performed in any dyspneic patient with evidence of liver disease. While the only definitive cure is liver transplant, it can be conservatively managed via oxygen therapy when transplant is contraindicated, as it was in our patient’s interesting case.

Consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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Version 2

Reviewer Report 15 July 2019

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Elias Kouroumalis 

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This is a case report of a complicated situation. An old lady with many chronic pulmonary problems was presented with what was considered at first as an ordinary lung infection complicating her COPD and/or bronchiectasis. Despite antibiotic treatment her dyspnea was not improved despite improvement of inflammatory indices. This led to an additional work up, revealing the existence of an unsuspected cirrhosis with HPS.

The presentation is informative, well written, the diagnosis of HPS is fairly well documented and the discussion is very informative on the differential diagnosis of HPS. My reservation is that the authors classify their patient as having severe HPS based on PaO₂ measurements. Although they accept that the other confounding comorbidities may influence the results, the subsequent progress of the patient seem to contradict their conclusion. Severe HPS is not expected to lead to an uneventful course after treatment of the other comorbidities. I feel that this should be commented in the discussion.

Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Liver Diseases including cirrhosis and its complications

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 10 July 2019

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Mohan Rudrappa 

Department of Pulmonary and Critical Care Medicine, Mercy Hospital, Joplin, MO, USA

Well written article.

The case presentation is good with attention to the relevant symptoms.

The management strategies are also excellent.

The discussion part is well written and the authors have considered all the potential causes and have systematically and reasonably rule out other causes.

It would be ideal if the authors upload the video of the bubble study and specify after how many cycles they saw the shunt just to rule out intracardiac shunt. Any intracardiac shunt can produce the triad of hypoxia, orthodeoxia and platypnea

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: pulmonary and critical care medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 29 August 2018

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**Robert Rodríguez-Roisin**

Pneumology Service, Thorax Institute, Hospital Clinic-The August Pi i Sunyer Biomedical Research Institute (IDIBAPS)-Networked Centre for Biomedical Research on Respiratory Diseases (CIBERES) (Hospital Clínic-IDIBAPS-CIBERES), University of Barcelona, Barcelona, Spain

This is another case report of an interesting and complex HPS in the context of several comorbidities, such as COPD and bronchiectasis, let alone the coexistence of MAI infection, that each, all in combination or even one more than another entity, can cause arterial hypoxaemia, along with an incomplete differential diagnosis approach. All in all both the discussion and presentation are weak and modest which detract from the potential clinical interest of the case report. Behind this negative short review lie three major caveats.

First, the lack of a better knowledge on gas exchange abnormalities in HPS is overwhelming despite that some of the quoted references (i.e., ref 7) masterly describe the pathophysiology of gas exchange alterations in HPS. Yet, the Authors miss a succinct good description. One of the reasons of this is that the Author is confounded by the use of the broad term of 'shunting' to encompass the three well established intrapulmonary determinants of arterial hypoxaemia in HPS (ventilation-perfusion imbalance, increased intrapulmonary shunt, and diffusion limitation to O₂ transfer) quite thoroughly reported in a recent publication of the Amer Physiol Soc (Rodríguez-Roisin R, et al.¹). May I therefore suggest to the Author to take a look at this publication and make the appropriate changes in your paper. HPS is not a problem of 'intrapulmonary shunting', as it is repeatedly quoted, but a predominant ventilation-perfusion mismatching along with other additional altered pulmonary and non-pulmonary determinants of gas exchange (see also, Rodríguez-Roisin²).

Second, the Author does not afford the lung function testing of this lady, including the most likely smoking habits of his old patient which are completely ignored. As a result, we are in the middle of nowhere to grasp the comprehensive nature of her gas exchange abnormalities. Are these due to her severe chronic pulmonary problems (COPD with bronchiectasis), to HPS as the author is inclined to, without providing any rationale, or to a combination of both pulmonary and liver disorders (most likely). The lack of a proper differential diagnosis is another of the main gaps. I, for me, suggest to also read a very interesting paper focusing on cardiopulmonary comorbidities and HPS (Martinez GP, et al.³) that may help the Author to improve his differential diagnosis. Moreover, the Author has completely neglected the relevant role of the alveolar-arterial oxygen partial pressure difference. With due respect, I suggest you read again ref 7, now more critically and more in detail!

Third, I have to admit that although it is most likely that the arterial hypoxaemia of this old lady is due to a combination of lung and hepatic problems, there is a sentence in the Case Report that worries me. It says: 'Soon after discharge, she was seen in a pulmonology clinic where treatment for MAI was commenced.'

When last seen a month afterward, the patient reported that she was tolerating her treatments well and felt improved since her hospital discharge'. This sentence makes me suspicious and questions me if the hypoxaemia is due to HPS for there are no pharmacological options for HPS so far.

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Is the background of the case's history and progression described in sufficient detail?

No

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

No

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

No

Is the case presented with sufficient detail to be useful for other practitioners?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: COPD and hepatic vascular disorders

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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