Introduction

Since the discovery of Hepatitis C, the virus has been found to not only affect liver but to have many systemic manifestations as well. Several studies in the last two decades have identified primary and secondary effects of chronic hepatitis C on pulmonary parenchyma and vasculature. Primary pulmonary manifestations of hepatitis C include exacerbation of existing asthma and Chronic Obstructive Pulmonary Disease (COPD) and less frequently interstitial lung disease. The most common secondary effects of chronic hepatitis C on lungs are pleural effusions and ascites. Conditions such as cryoglobulinemia, lymphoma and polymyositis have been reported in association with hepatitis C virus infection and may also indirectly affect the lungs. In addition, pulmonary vasculopathies, including hepatopulmonary syndrome (from vasodilation) and portopulmonary hypertension (from vasoconstriction) have been recognized as important secondary effects of chronic hepatitis C. The prevalence of hepatopulmonary syndrome has been reported to be as high as 20% in patients awaiting orthotopic liver transplant. Pharmacologic treatments for hepatitis C can also affect pulmonary function. For example, interferon-a can cause interstitial pneumonia, sarcoidosis and asthma exacerbations. Lack of awareness of pulmonary complication of chronic hepatitis C may contribute to under-diagnosis, despite the increasing worldwide prevalence of chronic hepatitis estimated between 480-520 million.

Case Presentation

A 58-year-female with a history of chronic hepatitis C and idiopathic pulmonary fibrosis, presented with progressively increasing dyspnea and platypnea for one month. She initially developed exertional dyspnea two years ago, which progressed to dyspnea at rest. Other co-morbidities included esophageal varices, pulmonary hypertension, major depression and gastroesophageal reflux disease. She smoked one pack per day for 20 years, but had no known allergies, no exposure to asbestos or industrial fumes or fibrosis inducing treatment. She had a tattoo 25 years ago but never received any blood transfusions or taken intravenous drugs. She had never received treatment for hepatitis C.

At presentation she was febrile, but tachycardic at 110/min., tachypneic at 20/min. with blood pressure of 110/70 mmHg. Her lips and fingertips were cyanotic and she had clubbing in both hands. She had orthodeoxia and platypnea, as well as coarse bilateral rhonchi on chest auscultation. There were spider angiomata over her abdomen, but no palpable purpura. At presentation, her saturation on 12 l/min. oxygen via non-rebreather mask ranged between 50% and 60% with arterial blood gas (ABG): pH 7.47, PacO2 25 and PacO2 34. Her alveolar-arterial oxygen difference (PA-a, O2) was 83.5 mm. When standing, her SaO2 dropped 20%, from recumbent SaO2.

Labs included hemoglobin 15.2 g/dl, hematocrit 44.5, white blood cell count 4x10^9/liter, platelets 116x10^9/liter, Serum bilirubin was 2.5 mg/dl, total protein 8 g/dl, albumin 3.6 g/dl, aspartate aminotransferase 55 U/liter, alanine aminotransferase 22 U/liter, alkaline phosphatase 77. Serum creatinine and BUN were normal. Rheumatoid factor was 23.4 and ANA and ANCA panel were negative. Mitochondrial Ab panel and smooth muscle Ab panel were also negative. Alpha fetoprotein (AFP) and alpha-1 trypsin levels were in normal range. Her activated partial thromboplastin time was 34.9 sec, Prothrombin time was 14.2 sec with an INR of 1.3.

Infectious disease serologies included positive anti-Hepatitis C virus antibody and Hepatitis C RNA less
Hypertension have prevalence of up to 20% and 5% in patients awaiting orthotopic liver transplantation (IPF) and patients with chronic HCV infection respectively. Polymyositis, a complication of chronic HCV infection can cause accelerated decline of lung function in cases with pre-existing asthma or COPD due to chronic immune activation and inflammation induced HCV infection. More commonly it is known as a triad of liver disease, increased arterioalveolar gradient on room air and intrapulmonary vasodilation as described by Kennedy and Knudson in 1977. Diagnostic criteria for hepatopulmonary syndrome is liver disease, PA-aO2 (Alveolar-arterial oxygen tension difference) ≤ 15 mmHg and positive contrast enhanced echocardiography. For patients aged ≥64 years PA-aO2 ≥20 mmHg is the recommended criteria.

This triad of increased PA-aO2, intrapulmonary vasodilation and chronic liver disease is sufficient to diagnosis hepatopulmonary syndrome, even in presence of other pulmonary co-morbidities such as COPD, asthma or IPF. Normal dynamic and static lung volumes and low DLCO values are characteristic in the majority of cases of HPS as in our patient without other co-morbid pulmonary conditions.

In HPS, there are two types of pathologic structural change in pulmonary vasculature. Type I (diffuse pre-capillary and capillary dilatation) and type II (focal arteriovenous communication), allow mixed venous blood to pass either directly or very quickly into pulmonary veins. Type I is further subdivided into –minimal and advanced. Contrast enhanced trans-thoracic echocardiography provides a sensitive, non-invasive and qualitative test for detection of intrapulmonary vasodilation. HPS patients with PaO2 ≤300 mmHg on oxygen supplementation are likely to have “advanced type I” or type II pattern of intrapulmonary vasodilation and could benefit from vascular embolization. These cases should be studied with pulmonary angiography. Based on bilateral pulmonary arteriography and saline agitated echocardiography, our patient had type II pattern of intrapulmonary vasodilation and received embolization.

Orthotopic liver transplantation is the only effective treatment for improving outcome in patients with hepatopulmonary syndrome and resolution of hepatopulmonary has been reported in >80% of cases. Hepatopulmonary syndrome does not correlate with severity of liver disease.

**References**


**Discussion**

Hepatitis C virus is a hepatotropic and lymphotropic virus with many systemic manifestations, frequently rheumatologic due to chronic stimulus of the immune system. The pathogenesis of HCV-related lung disease could be mediated by autoimmune antibodies and/or immune complex deposition in the pulmonary parenchyma and vasculature. The European Respiratory Society (ERS) task force on hepatic-pulmonary disorder defined hepatopulmonary syndrome as an “arterial oxygenation defect induced by intrapulmonary vascular dilatation associated with hepatic disease”.

The prevalence of idiopathic pulmonary fibrosis (IPF) has increased prevalence of idiopathic pulmonary fibrosis. Chronic HCV infection can cause accelerated decline of lung function in cases with pre-existing asthma or COPD due to chronic immune activation and inflammation induced HCV infection. Polyomatositis, a complication of chronic hepatitis C virus infection can also impair respiration through weakened respiratory muscles.

In patients awaiting orthotopic liver transplantation hepatopulmonary syndrome and portopulmonary hypertension have prevalence of up to 20% and 5% respectively. The European Respiratory Society (ERS) task force on hepatic-pulmonary disorder defined hepatopulmonary syndrome as an “arterial oxygenation defect induced by intrapulmonary vascular dilatation associated with hepatic disease”.

Diagnostic criteria for hepatopulmonary syndrome is liver disease, PA-aO2 (Alveolar-arterial oxygen tension difference) ≤ 15 mmHg and positive contrast enhanced echocardiography. For patients aged ≥64 years PA-aO2 ≥20 mmHg is the recommended criteria.

This triad of increased PA-aO2, intrapulmonary vasodilation and chronic liver disease is sufficient to diagnosis hepatopulmonary syndrome, even in presence of other pulmonary co-morbidities such as COPD, asthma or IPF. Normal dynamic and static lung volumes and low DLCO values are characteristic in the majority of cases of HPS as in our patient without other co-morbid pulmonary conditions.

In HPS, there are two types of pathologic structural change in pulmonary vasculature. Type I (diffuse pre-capillary and capillary dilatation) and type II (focal arteriovenous communication), allow mixed venous blood to pass either directly or very quickly into pulmonary veins. Type I is further subdivided into –minimal and advanced. Contrast enhanced trans-thoracic echocardiography provides a sensitive, non-invasive and qualitative test for detection of intrapulmonary vasodilation. HPS patients with PaO2 ≤300 mmHg on oxygen supplementation are likely to have “advanced type I” or type II pattern of intrapulmonary vasodilation and could benefit from vascular embolization. These cases should be studied with pulmonary angiography. Based on bilateral pulmonary arteriography and saline agitated echocardiography, our patient had type II pattern of intrapulmonary vasodilation and received embolization.

Orthotopic liver transplantation is the only effective treatment for improving outcome in patients with hepatopulmonary syndrome and resolution of hepatopulmonary has been reported in >80% of cases. Hepatopulmonary syndrome does not correlate with severity of liver disease.

**References**


