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Journal

Proceedings of the UCLA Department of Medicine, 17(1)

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Publication Date

2013-07-28

CLINICAL VIGNETTE

Chronic Hepatitis C and Its Double Hit on Lung : A Case of Hepatopulmonary Syndrome

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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[1]. Several studies in the last two decades have identified primary and secondary effects of chronic hepatitis C on pulmonary parenchyma and vasculature[2-4].

Primary pulmonary manifestations of hepatitis C include exacerbation of existing asthma and Chronic Obstructive Pulmonary Disease (COPD) and less frequently interstitial lung disease[4]. The most common secondary effects of chronic hepatitis C on lung 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[4]. 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[4]. The prevalence of hepatopulmonary syndrome has been reported to be as high as 20% in patients awaiting orthotopic liver transplant[5]. Pharmacologic treatments for hepatitis C can also affect pulmonary function. For example, Interferon-α can cause interstitial pneumonia, sarcoidosis and asthma exacerbations[4]. 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[6].

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 afebrile, 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 PaO2 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 4x109/liter, platelets 116x109/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 feto-protein (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

than <50 copies/ml, Hepatitis A antibody positive, Hepatitis B surface antigen negative, Hepatitis B surface antibody negative, HIV 1 & 2 negative and Cytomegalo virus IgG antibody was positive.

Pulmonary function test (PFT) showed mild restriction with a corrected diffusion capacity 27% of predicted. Her FEV1 was 1.78 liter at 86% of predicted without significant change after bronchodilator administration. Her FVC and FEF (25%-75%) were within normal limits. TLC was decreased to 78% of predicted and residual volume was 85% of predicted.

High resolution CT (HRCT) showed diffuse interstitial fibrosis with honey combing and traction bronchiectasis. There was no radiological evidence of pulmonary emboli. Contrast enhanced echo-cardiography (agitated saline contrast) revealed AV shunting within the lungs. Her LVEF was 60%, with no evidence of any valvular heart disease. Bilateral pulmonary arteriogram confirmed AV shunting, right side greater than left. Diagnostic Right heart catheterization revealed right atrial pressure of 8 mmHg and main pulmonary artery pressure of 33/16 mmHg with a mean of 21 mmHg. The patient was managed symptomatically.

Discussion

Hepatitis C virus is a hepatotropic and lymphotropic virus with many systemic manifestations, frequently rheumatologic due to chronic stimulus of the immune system[7]. Over the last two decades studies have shown effects of chronic HCV infection on pulmonary parenchyma and vasculature[4]. The pathogenesis of HCV-related lung disease could be mediated by autoantibodies and/or immune complex production or as an indirect effect of chronic liver disease. A higher prevalence of HCV infection has been documented in idiopathic pulmonary fibrosis (IPF)[8,9], and patients with chronic HCV infection have increased prevalence of idiopathic pulmonary fibrosis[2]. 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[10,11]. Polymyositis, a complication of chronic hepatitis C virus infection can also impair respiration through weakened respiratory muscles[4].

In patients awaiting orthotopic liver transplantation hepatopulmonary syndrome and portopulmonary hypertension have prevalence of up to 20% and 5%[6]. The European Respiratory Society (ERS) task force on hepatic-pulmonary disorder defined hepato-pulmonary syndrome as an "*arterial oxygenation defect induced by intrapulmonary vascular dilatation associated with hepatic disease*"[5]. More commonly it is known as a triad of liver disease, increased arteriolar-alveolar gradient on room air and intrapulmonary vasodilation as described by Kennedy and Knudson in 1977[12]. Diagnostic criteria for hepatopulmonary syndrome is liver disease, PA-a, O2 (Alveolar-arterial oxygen tension difference) ≥ 15 mmHg and positive contrast enhanced echo-cardiography[5]. For patients aged ≥64 years PA-a, O2 ≥20 mmHg is the recommended criteria[5].

This triad of increased PA-a O2, 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[13]. 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[5].

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[14]. 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[5]. 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[5]. 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[5]. Hepatopulmonary syndrome does not correlate with severity of liver disease.

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Submitted on July 28, 2013