

Pulmonary Hypertension in a Patient with Non-cirrhotic Portal Hypertension and Scleroderma Sine Scleroderma: A Case Report

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Abstract Porto-pulmonary hypertension is a known complication of liver cirrhosis but its association with non-cirrhotic portal hypertension patients is rare. We report a case of pulmonary hypertension in a patient with non-cirrhotic portal hypertension and scleroderma sine scleroderma. The two latter conditions have been shown to be independently associated with pulmonary arterial hypertension. DLCO is expected to decrease in scleroderma patients due to pulmonary vascular disease, which will result in an increased FVC/DLCO ratio. The low FVC/DLCO ratio in our patient suggests that pulmonary arterial hypertension was more likely to have been due to non-cirrhotic portal hypertension than scleroderma sine scleroderma.

Keywords: *scleroderma, pulmonary hypertension, non-cirrhotic portal hypertension*

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1. Introduction

Portal hypertension is an independent risk factor for the development of pulmonary hypertension [1], and is associated with a worse prognosis in patients with pulmonary hypertension [2]. Non-cirrhotic portal hypertension consists of signs of portal hypertension without the evidence of cirrhosis [3]. It has a wide variety of causes, including hepatoportal sclerosis, schistosomiasis, portal vein thrombosis, and nodular regenerative hyperplasia (NRH) [4]. Some of these underlying factors have also been associated with pulmonary arterial hypertension (PAH).

NRH, accounting for approximately 25% of cases of non-cirrhotic portal hypertension [3], was first described by Steiner in 1959 [5], and is characterized by regenerative nodules that are 1-3 mm in diameter, and is distinguished from cirrhosis by absence of bands of fibrosis around the hepatic nodules [6]. NRH often leads to portal hypertension and has the same hemodynamic state as compensated cirrhosis [7]. A large number of underlying diseases have been associated with NRH, including autoimmune diseases such as rheumatoid arthritis, myeloproliferative conditions and medications such as azathioprine [6].

2. Case Report

A 57 year old Caucasian woman presented with progressively worsening shortness of breath over several months. Initially this was manifested by mild shortness of breath on exertion, and a dry cough at night. Within 3 months, her symptoms had worsened enough that dyspnea on exertion became a limiting factor for her job as a nurse. She developed orthopnea, worsening cough, lower extremity edema and generalized fatigue. Physical exam on presentation was significant for 3/6 systolic murmur, JVD and lower extremity edema. Echocardiography showed severe pulmonary hypertension, with a right ventricular systolic pressure (RVSP) of 80 mmHg. A ventilation-perfusion scan was negative for thromboembolism, and a computed tomographic scan of the chest showed an enlarged pulmonary artery (Figure 1) and gastroesophageal varices.

A complete connective tissue diseases workup suggested scleroderma with the presence of anti-centromere and anti-polymerase III antibodies (Table 1). Esophagogastroduodenoscopy revealed small esophageal varices and mild portal hypertensive gastropathy. Percutaneous liver biopsy showed hepatoportal sclerosis and NRH, without evidence of autoimmune hepatitis or cirrhosis (Figure 2).

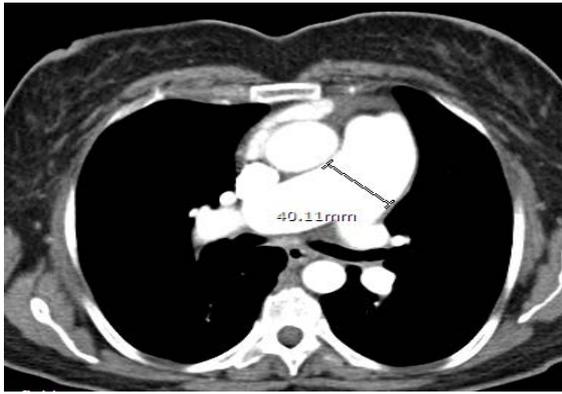


Figure 1. CT scan of the chest with IV contrast: The main pulmonary artery is enlarged measuring 4.11 cm. The left and right pulmonary arteries are also enlarged

Table 1. Results for rheumatologic and liver disease work-up in our patient

Test	Result	Value
Anti-ds DNA	Positive	> 1000 IU/ml
ANA	Positive	1:320 (centromere pattern)
Anti-centromere antibodies	Positive	6.8 AI
CH 50	Normal	50 U/ml
C3	Normal	86 mg/dl
C4	Low	14 mg/dl
Ferritin	Normal	123 ng/ml
C-ANCA/P-ANCA	Negative	< 1:20
Hep C AB	Negative	--
Hep C sAg	Negative	--

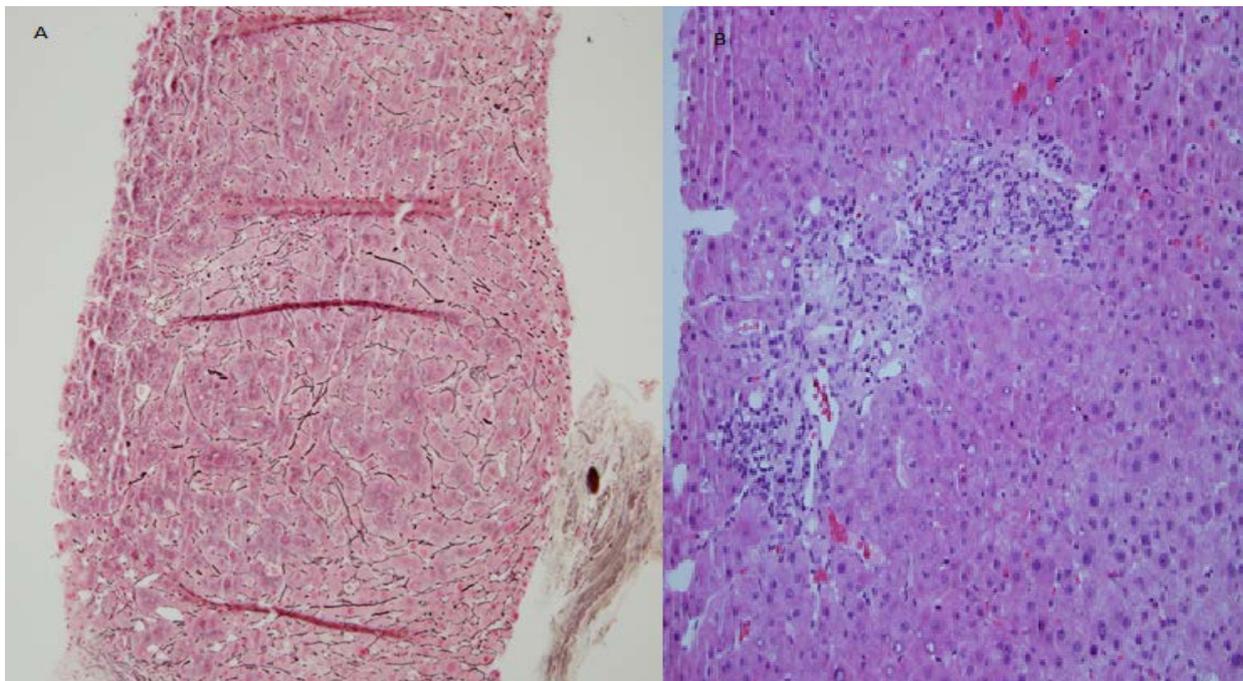


Figure 2. Slides showing results of the liver biopsy performed on the patient: (A). **Reticulin stain** (100x) This slide shows a regenerative nodule of hyperplastic hepatocytes rimmed by cords of atrophic hepatocytes at periphery is evident. In contrast to cirrhotic nodule, there is no fibrosis surrounding the nodule. This is consistent with nodular regenerative hyperplasia. (B). **H&E** (200x): The portal veins are characteristically absent in this portal tract with numerous irregular small vascular channels. Some are herniated into the surrounding liver parenchyma forming ectopic veins. These findings are consistent with Hepatoportal sclerosis (obliterative portal venopathy).

Right heart catheterization revealed wide transpulmonary gradient (TPG), elevated pulmonary vascular resistance (PVR), and relatively normal left-sided filling pressures consistent with severe pulmonary hypertension [mean pulmonary artery pressure (PA mean) =63 mmHg, pulmonary artery occlusive pressure (PAOP) =16 mmHg, TPG=47 mmHg, PVR=6.6 Woods units (529 dynes/sec/cm), cardiac index=3.7 L/min/m²]. Polysomnography showed sleep-related hypoxemia (time spent with oxygen saturation below 90% was 32 consecutive minutes) and mild obstructive sleep apnea (the overall apnea-hypopnea index (AHI) was 13.9/hour). The sleep related breathing abnormalities were adequately controlled with continuous positive airway pressure set at 18 cmH₂O. A diagnosis of pulmonary arterial hypertension due to non-cirrhotic portal hypertension was made. Vasodilator regimen for pulmonary hypertension included ambrisentan 10 mg daily and sildenafil 20 mg three times daily. She was also started on Furosemide twice daily, the dose of which was

increased later to 120 mg in the morning and 80 mg in the evening. She also required oxygen supplementation at rest and with exertion to keep her oxygen saturation around 92. Hydroxychloroquine 200 mg twice daily was started to treat scleroderma since scleroderma. At 5-month follow-up, she had improved dyspnea, increased 6 minute walk distance from 360 to 400 meters, and a decreased RVSP at 59 mmHg. Six months later, her 6 minute walk distance decreased from 400 meters to 240 meters (lower limit of normal for the patient was 363 meters). Almost a year after her initial presentation, she experienced cardiac arrest and died shortly after withdrawal of life support. An autopsy was not performed.

3. Discussion

Pulmonary arterial hypertension, a well-known complication of scleroderma, is associated with increased

mortality compared to other rheumatologic diseases-associated conditions [8]. Scleroderma sine scleroderma lacks the skin manifestations of systemic sclerosis but presents with pulmonary manifestations in around two-third of the cases [9]. NRH has been described in association with many rheumatologic diseases including scleroderma [5,6,10,11]. In addition to causing portal hypertension, NRH itself is an independent risk factor for porto-pulmonary hypertension [2].

Pulmonary function testing and echocardiography are the main tools used for screening for PAH in scleroderma patients [2,12]. Anti-centromere antibodies along with anti-nucleolar antibodies have been associated with severe pulmonary hypertension [8]. Our patient had 2 conditions that have been independently associated with the development of pulmonary hypertension: portal hypertension and systemic sclerosis. Thus, it is very important to screen for pulmonary hypertension in patients with scleroderma or portal hypertension, irrespective of the cause.

We assessed that our patient's pulmonary hypertension was secondary to portal hypertension and not scleroderma based on the low FVC%/DLCO% ratio (0.9) and normal DLCO (81%). We postulate that the increased pulmonary blood flow due to the generalized vasodilatation associated with cirrhosis and portal hypertension results in a normal DLCO. On the other hand, in PAH secondary to scleroderma in the absence of extensive parenchymal lung disease, the DLCO is reduced due to pulmonary vascular disease while the lung volumes are preserved, resulting in an increased FVC%/DLCO% ratio (> 1.6) [12].

In summary, we reported on a patient with a complex interaction of diseases, specifically, non-cirrhotic portal hypertension, scleroderma, and porto-pulmonary hypertension, and described the utility of the FVC%/DLCO% ratio in determining the mechanism of pulmonary hypertension.

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