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Case report

Possible role of anti-SSA/Ro antibodies in the pathogenesis of pulmonary hypertension

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ABSTRACT

Introduction: There are many different causes of pulmonary hypertension and the pathogenesis of the disease is still being elucidated. Although they are not the most common, autoimmunity and inflammation have been identified as possible causes. No one autoantibody has been identified as the definite cause of pulmonary hypertension. We present a rare association of anti-SSA/Ro antibodies and isolated pulmonary hypertension.

Case presentation: A 53 year old African American female presented with abdominal pain, nausea, weight loss, dyspnea and fatigue. Upon further exam she was found to have high titers of antinuclear antibodies and anti-SSA/Ro antibodies. This antibody profile would typically be suggestive of Sjögren's Syndrome, which is characterized by dry eyes and poor salivary gland function. However, since this patient did not have any symptoms consistent with the disease a diagnosis of Sjögren's Syndrome could not be made. A combination of laboratory, imaging and diagnostic studies were done that revealed a final diagnosis of pulmonary hypertension.

Conclusion: It is known that pulmonary hypertension has association with autoimmune diseases, however no clear markers yet exist. Anti-SSA/Ro antibodies have been rarely described in cases of pulmonary disease, and less so in pulmonary hypertension. This case describes a unique association between isolated pulmonary hypertension and anti-SSA/Ro antibody, thereby illustrating the need to investigate this autoantibody and others in the pathogenesis of autoimmune pulmonary hypertension.

1. Introduction

Pulmonary hypertension (PH) is a rare disease and its cause has yet to be elucidated. However, multiple studies have suggested an autoimmune component to the development of PH. Here is described a case of a patient with PH and positive antinuclear antibodies (ANA) and anti-SSA/Ro titers without associated Sjögren's Syndrome (SS). Anti-SSA/Ro antibodies have been described in pulmonary disease in the literature, but rarely in pulmonary hypertension. This case is a rare presentation of PH in conjunction with otherwise asymptomatic elevated ANA and anti-SSA/Ro antibodies.

2. Case report

A 53 year old African American female presented to the emergency center complaining of a two day history of nausea and right upper quadrant pain. She stated that she experienced weight loss in the last year and a three year history of dyspnea with increasing fatigue. She attributed her weight loss to the difficulty of simultaneous eating and breathing. She denied dry mouth, dry eyes, hemoptysis, and epistaxis. She denied current and past tobacco, alcohol and illicit drug use. She had not seen a primary care physician regularly due to financial circumstances.

The physical exam was significant for a cachectic appearance, temporal wasting, digital clubbing in all fingers on the left hand and fifth finger on the right, and xerosis on her lower extremities. Labs revealed hyponatremia, leukopenia, thrombocytopenia, macrocytic anemia, elevated liver enzymes, hyperproteinemia and hypoalbuminemia. Hepatitis B, C, and HIV tests were negative, B12, folate and TSH levels were within normal limits. ESR and CRP were elevated. An autoantibody panel was strongly positive for ANA and

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anti-SSA/Ro IgG autoantibody.

Protein levels were elevated and a serum protein electrophoresis showed hypoalbuminemia and diffuse polyclonal hypergammaglobulinemia suggestive of chronic inflammation or autoimmune disease. Urine protein electrophoresis was insignificant. AP chest x-ray showed suspicion of emphysematous change in the upper lungs without infiltrates or effusions and cardiac enlargement. A thorax CT with contrast showed a faint right upper lobe subpleural peripheral groundglass opacification measuring 11 × 6.5 mm, and a soft tissue density left lung base likely atelectasis and/or partial consolidation Fig. 1.

An echocardiogram showed the right ventricle (RV) and right atrium (RA) both to be mildly dilated, RV systolic pressure estimated to be 60–65 mmHg, moderate tricuspid regurgitation, mild to moderate pulmonic valvular regurgitation, and no definite evidence of ASD or PFO. A right heart catheterization showed primary pulmonary hypertension. Pulmonary artery (PA) pressure was 50/25 with a mean of 36. RV pressure was 50/9 with an EDP of 10. RA pressure mean of 9. RA saturation 73%, PA sat 70% and aortic saturation 90%. Pulmonary vascular resistance: 5.81 Woods. Fick cardiac output: 4.13 with a cardiac index of 2.91.

3. Discussion

This case uniquely describes a patient with an antibody profile consistent with SS, yet devoid of a clinical picture that would complete the diagnosis. This patient was also found to have primary pulmonary hypertension with resulting right heart disease. This case represents a need to identify the anti-SSA/Ro IgG antibody as a possible pathogenic autoantibody in lung disease, and more specifically PH. There have been other associations of lung disease and PH with this autoantibody and will be further discussed here.

PH is defined as pulmonary artery pressure ≥25 mmHg in the setting of normal or reduced cardiac output with a normal capillary wedge pressure [1]. Many mechanisms of injury are described, each with the end result of elevated pressures in the pulmonary vasculature. Some mechanisms, such as the BMPR2 mutation, cause proliferation of the pulmonary vascular smooth muscle cells [1]. Others affect the endothelial cells of the vasculature or the autoregulation of the pulmonary vasculature [1]. Other causes include proinflammatory and procoaguable states [1].

The diagnosis of SS is made when certain laboratory and clinical criteria are met. Positive laboratory findings include: antibodies to SSA/Ro and/or SSB/La antigens and salivary gland histopathology consistent with focal lymphocytic sialoadenitis [2]. Clinical criteria include xerostomia and/or xeropthalmia in the absence of another possible cause, or diagnostic studies such as parotid sialography and salivary sctinography that display subfunctional glandular structures [2]. This patient had an antibody panel that would be consistent with SS, however she lacked any glandular symptoms, thus making this diagnosis incomplete. It is possible to primarily display extraglandular symptoms with SS [2], however PH has only rarely been described in SS [3].

The relationship between PH and autoimmune diseases has long been recognized, frequently described in systemic scleroderma and SLE [4], but the pathogenesis is unknown. It is not known whether the inflammation present in PH is a cause or consequence of PH [4]. A relationship between dysregulation of CD4+ T cells and CD4+25 + Treg cells has been identified[4]. There have been cases of PH citing the pathogenic activation of autoreactive B and T cells in the face of this dysfunction [3,4].

No single autoantibody has been identified as the cause of the damage in PH, but many have been associated with the disease. A review of a small number of cases of primary SS patients with PH showed that antinuclear, anti-SSA/Ro, anti-RNP, positive rheumatoid factor and hypergammaglobinemia were more common in these patients than in primary SS patients without PH [3]. Although many patients with autoimmune diseases have a positive ANA titer, studies have shown that the prevalence of positive ANA titers in PH patients is equal to that of the population without PH, thus making ANA a less likely candidate for a cause of PH. A 1989 study in India of clinical correlations with antibodies to extractable nuclear antigens was the first to find an association between anti-SSA/Ro antibodies and PH [5]. Another study looked at the prevalence of a variety of autoantibodies in the blood of patients with primary PH (PPH) and found anti-Ku antibodies to be most significantly a suggestive of a marker for PH, although they also saw anti-CENP-B, anti-topoisomerase I, anti-SSA/Ro and anti-SSB/La autoantibodies in PPH patients [6]. A study of cardiac involvement in SLE patients determined that 18.2% of patients with anti-SSA/Ro antibodies had PH [7].

Anti-SSA/Ro antibodies have been seen in patients with lung disease. A case report demonstrated a patient with toxic epidermal necrolysis (TEN) who unusually suffered from chronic pulmonary complications after the resolution of his disease and was also found to be asymptomatically positive for anti-SSA/Ro antibody at the onset of TEN [8]. Another researcher discovered that in patients with antisynetase syndrome, the presence of anti-SSA/Ro

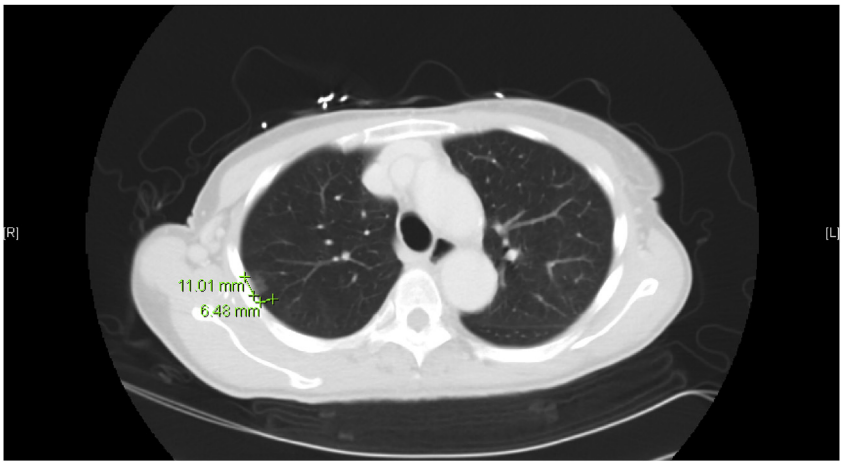

Fig. 1. Faint right upper lobe subpleural peripheral groundglass opacification 11 × 6.5 mm and soft tissue density in the left lung base likely atelectasis and/or partial consolidation.

antibodies was associated with more severe interstitial lung disease [9]. A case was reported in Japan of pulmonary fibrosis in a anti-SSA/Ro positive and ANA negative patient without lupus [10]. The relationship between these cases and our own shows a relationship between anti-SSA/Ro antibodies and chronic inflammation and destruction of pulmonary structures, thus making a case for a target of these antibodies in the lungs.

4. Conclusion

This is a unique case of PH associated with anti−SS−A/Ro antibodies in the absence of clinical signs of SS. Although there is an association between autoimmunity and inflammation with PH, the association with anti-SSA/Ro autoantibodies and PH is quite rare. Since this is only a single case a definite association cannot yet be established to support the involvement of anti-SSA/Ro antibodies in the pathogenesis of lung disease and PH. However, this case highlights the potential for further evaluation of anti-SSA/Ro antibodies as a possible PH marker.

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