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Case report

Rheumatoid arthritis associated pulmonary hypertension: Clinical challenges reflecting the diversity of pathophysiology

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ABSTRACT

The present article reports three clinical cases in order to elucidate the diversity of the pathophysiological mechanisms that underlie rheumatoid arthritis associated pulmonary hypertension. The condition's three major causes are: interstitial lung disease, vasculitis, and chronic thromboembolic disease, but it should be noted that the multiple pulmonary manifestations of rheumatoid arthritis, can all contribute to chronic lung disease or hypoxia. The first patient in this report suffered from moderate restriction due to fibrosis and was diagnosed with pulmonary hypertension during an episode of life threatening hypoxia. Early upfront combination therapy prevented intubation and reversed hypoxia to adequate levels. The second presented patient was a case of isolated pulmonary hypertension attributable to vasculopathy. The patient maintained normal lung volumes but low diffusion capacity and echocardiography dictated the need for right heart catheterization. Finally, the third patient presented severe functional limitation due to several manifestations of rheumatoid arthritis, but a past episode of acute pulmonary embolism was also reported although it had never been evaluated. Chronic thromboembolic disease was eventually proved to be one major cause of the patient's pulmonary hypertension. The importance of early identification of pulmonary hypertension in patients with rheumatoid arthritis is therefore emphasized, especially since multiple treatment options are available, symptoms can be treated, and right heart failure can be avoided.

1. Introduction

Pulmonary hypertension (PH) is a continuously deteriorating disease of the pulmonary vasculature, directly affecting quality of life and leading to right heart failure. Moreover, PH can appear as a complication of connective tissue diseases [1], resulting from autoimmunity, inflammation, and vascular changes, increasing the morbidity and mortality of the primary illness. In this article, we present three clinical cases in order to discuss the correlation between PH and rheumatoid arthritis (RA), a correlation not so frequent, albeit problematic in its early identification and management. Currently the prevalence of PH in RA can only be grossly estimated by echocardiographic data, and according to several studies, it ranges from 0.8% to 21–27.5% [2,3]. Echocardiography is an important screening tool. However, the gold-standard diagnostic tool of PH remains right heart catheterization. Resting mean pulmonary artery pressure (mPAP) of at least 25 mm Hg and a pulmonary arterial wedge pressure (PAWP) of less than 15 mm Hg determines the diagnosis. We present three cases aimed to illustrate the diversity of the pathophysiological mechanisms that underlie RA associated PH and to emphasize the importance of a thorough evaluation. Early identification is crucial, especially since multiple treatment options are available, symptoms can be treated, and right heart failure can be avoided.

2. Case reports

2.1. Case 1

In September 2015, a 60 year-old woman with known history of rheumatoid arthritis (rheumatoid factor >20, cyclic citrullinated peptide antibodies >300, elevated c-reactive protein and erythrocyte sedimentation rate, synovitis in 8 small joints) and co-existing

Abbreviations: PH, Pulmonary hypertension; RA, rheumatoid arthritis; mPAP, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; RICU, Respiratory Intensive Care Unit; DLCO, diffusing capacity for carbon monoxide; 6MWT, 6-min walking test; RVSP, right ventricular systolic pressure; CTD, connective tissue disease.

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pulmonary fibrosis with chronic type 1 respiratory failure was urgently transferred to the Respiratory Intensive Care Unit (RICU) due to life-threatening hypoxia. Assessment of vital signs revealed a respiratory rate of 35 breaths/min, a heart rate of 110 bpm and a saturation of 85%, receiving maximal flow of oxygen through a non-rebreather mask. Blood gas analysis showed pH of 7.47, pO_2 of 50 mm Hg, and PCO_2 of 36 mm Hg. Physical examination revealed crackles on both lungs, a prominent pulmonic compound of the second heart sound, and leg edema. Electrocardiogram showed right axis deviation, pulmonary P waves, and rSR′ in V1. Hematological and biochemical tests showed: leukocytosis (16.02 k/μL −80% neutro), Hct at 49.9%, Hb of 16.6 g/dL, normal procalcitonin but elevated C-reactive protein of 3.250 mg/dl, normal troponin, and elevated b-type natriuretic peptide levels. Heart echocardiography revealed right heart enlargement, tricuspid valve regurgitation, and an estimated right ventricular systolic pressure (RVSP) of 68 mm Hg. The left heart maintained normal dimensions and systolic function, but the intraventricular septum was flattened forming a D-shaped left ventricle. The patient underwent pulmonary function tests indicating moderate restrictive lung disease with a FVC of 63% pred, TLC of 50.6% pred and a diffusing capacity for carbon monoxide (DLCO) of 19% pred. Thoracic high resolution CT revealed modest honeycombing, ground-glass opacities with fibrotic compound, traction bronchiectasis, and thickening of interlobular septa (illustrated in Image 1). A ventilation perfusion scan was urgently performed and showed normal perfusion. A right heart catheterization confirmed precapillary pulmonary hypertension [PAP (s/d/m):74/35/51 mm Hg, PAWP: 12 mm Hg, Right Atrial Pressure: 11 mm Hg, Cardiac Index: 1.6 L/min/m^2, SvO_2: 64%, PVR: 13 Wood units, SaO^2: 89%]. Early upfront combination therapy was planned for the patient and she was immediately treated with inhaled iloprost six times a day and tb sildenafil 20 mg tqd combined with her previous treatment of iv furosemide and per os methylprednisolone. Her oxygenation status gradually improved. By Day 10, she was able to maintain a pO_2 of 58 mm Hg with 5 lt/min through nasal cannula. She was discharged on Day 15 with further improvement of oxygenation. At the one-year follow up she was stable under oxygen therapy in functional class NYHA III [New York Heart Association class III].

2.2. Case 2

In 2008, a 68-year old patient was presented with dyspnea on exertion and type 1 respiratory failure. The patient had seropositive rheumatoid arthritis (rheumatoid factor: 787, cyclic citrullinated peptide antibodies > 300, elevated c-reactive protein and erythrocyte sedimentation rate) with erosive arthritis in both upper (metacarpophalangeal joints, wrists, elbows) and lower extremities (metatarsophalangeal joints) and pulmonary fibrosis. The patient had received previous treatment with methotrexate plus methylprednisolone, leflunamide, cyclosporine, and abadacept, all unable to control his arthritis (DAS28 score = 5.92, high disease activity) and was treated with azathioprine and methylprednisolone at the time of presentation. He underwent chest X-ray showed enlargement of proximal pulmonary arteries. Lung function tests revealed slightly diminished total lung capacity (5.8 lt, 82.3% pred) and a greatly impaired DLCO (55%). The patient could only walk 150 m with desaturation of 10% in a 6-min walking test (6MWT). Chest CT revealed a reticulonodular pattern with honeycombing and mild lymphadenopathy. On echocardiography, the estimated RVSP was 105 mm Hg and there were also signs of left ventricular diastolic dysfunction. Right heart catheterization was performed after excluding acute pulmonary embolism and chronic thromboembolic disease. The measured mPAP was 63 mm Hg and the PAWP was 10 mm Hg. The patient started treatment with oxygen, ambrisentan, furosemide, and spironolactone, resulting in the improvement of symptoms, and exercise capacity. Seven years later he complained about deterioration in dyspnea on exertion. A chest CT scan revealed similar fibrotic lesions with preserved pulmonary volumes (TLC = 5.4 lt, 78.3% pred), while DLCO was further diminished (34.2% pred). He could only walk 70 m due to severe hypoxia. Echocardiography revealed an estimated RVSP of 120 mm Hg and a CT angiography was negative for pulmonary embolism. Deterioration was attributed to the progression of vasculopathy and therapy was intensified, by adding tadalafil and inhaled iloprost to the previous ambrisentan monotherapy. The patient was gradually stabilized with less dyspnea on exertion, smaller degree of desaturation, and improved functional capacity.

2.3. Case 3

The third case involves an 80-year old woman, ex-smoker, with seronegative rheumatoid arthritis (negative rheumatoid factor and cyclic citrullinated peptide antibodies, elevated c-reactive protein, synovitis in 10 small joints and 6 large joints) treated with azathioprine, and prednisolone, presented with dyspnea on exertion, and severe functional limitation. The patient has previously received various disease modifying antirheumatic drugs such as methotrexate, leflunomide and infliximab, which did not control effectively joint disease. The patient also reported treatment with acenocoumarol and long term oxygen therapy for five years after an episode of pulmonary embolism that was not further evaluated. On clinical examination, crackles in basal lung fields, leg edema, and kyphoscoliosis were identified. Blood gas analysis on 5 lt O_2/min revealed a pO_2 of 54 mm Hg. She could not walk more than 25 m in a 6MWT due to extreme dyspnea. Lung function tests revealed a mild obstructive-restrictive impairment and a moderately diminished DLCO. An echocardiogram was next performed, revealing

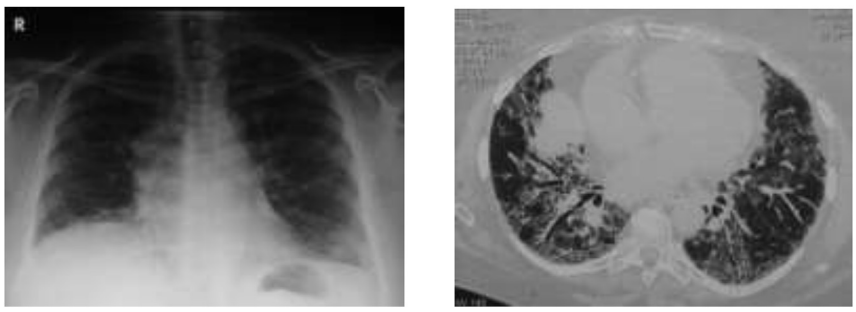

Image 1. Chest X-ray (right) showing right atrium enlargement and chest CT-scan (left) showing modest honeycombing, ground-glass opacities with fibrotic compound, traction bronchiectasis, and thickening of interlobular septa.