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Pulmonary Alveolar Proteinosis - A Rare Occurrence

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Abstract

Pulmonary Alveolar Proteinosis (PAP) is a rare syndrome characterised by accumulation of surfactant lipoproteins in the alveoli. This is caused by decreased clearance of surfactant, due to autoimmune, congenital or secondary causes. Patients may be asymptomatic in mild cases, with more severe cases resulting in dyspnoea, cough, sputum production, and systemic features such as weight loss, fever and fatigue. Chest radiographs may show lung opacities, nodules or atelectasis. CT scans may reveal ground glass opacification, and pulmonary function tests may show reduced diffusion capacity. Though histopathological diagnosis is the gold standard investigation, the combination of symptoms, clinical signs, characteristic radiologic findings and diagnostic bronchoscopy lavage findings are all used in clinical practice when diagnosing PAP. Therapies for PAP depend on the severity and etiology. Bronchodilators and chest physiotherapy are used in the treatment of mild PAP. Treatment options for severe cases include whole-lung lavage, GM-CSF protein administration and rituximab therapy, with whole-lung lavage being the standard therapy. This case report follows a 63 year-old-man with shortness of breath caused by PAP.

Keywords: Pulmonary Alveolar Proteinosis; Chest radiographs; Bronchodilators

Introduction

Pulmonary Alveolar Proteinosis (PAP) is a rare pulmonary syndrome caused by accumulation of excess non-secreted surfactant proteins trapped in alveoli and terminal airways [1]. This occurs due to insufficient surfactant protein clearance from alveolar macrophages [2]. Consequently, gas exchange and pulmonary immunity is impaired, resulting in respiratory symptoms ranging from dyspnoea and cough, to respiratory failure [1,2]. In 1958, Rosen and colleagues first described PAP as a disorder with periodic acid-Schiff (PAS) positive proteins filling the alveoli [3]. Epidemiological studies since then have suggested that PAP has a male predilection and typically causes respiratory disease in young to middle aged patients [4].

Case Report

A 63-year-old male presented to our hospital with a 6-month history of worsening shortness of breath. Over this time, the shortness of breath had progressed from occurring on exertion to occurring at rest. Due to this, the patient's exercise tolerance had significantly reduced. The patient did not report cough, sputum production, chest pain, fever, weight loss, night sweats or fatigue. His past medical history included chronic obstructive pulmonary disease, hypertension, gastroesophageal reflux disease and arthritis.

On review, the pulse was 78 beats/min, blood pressure 138/60 mmHg; respiratory rate 18 breaths/min, oxygen saturation of 94% on room air, and the patient was afebrile. Respiratory examination revealed decreased air entry bilaterally, with air entry greater on the right side of the chest compared to the left. No additional sounds were audible. Cardiovascular examination revealed dual heart sounds with an end-systolic murmur radiating to the carotids. Abdominal and neurological exams were unremarkable.

Laboratory tests were undertaken, with the patient's full blood count, electrolyte levels, kidney and liver functions being normal. Additionally, autoimmune and infectious laboratory panels were all negative. An arterial blood gas revealed a pH of 7.45, PCO_2 of

31mmHg, PO_2 of 59mmHg, SaO_2 of 89% on room air and an A-a gradient of 51mmg.

A chest radiograph showed opacities in the middle and lower zones of the lungs with no pleural effusion (Figure 1).

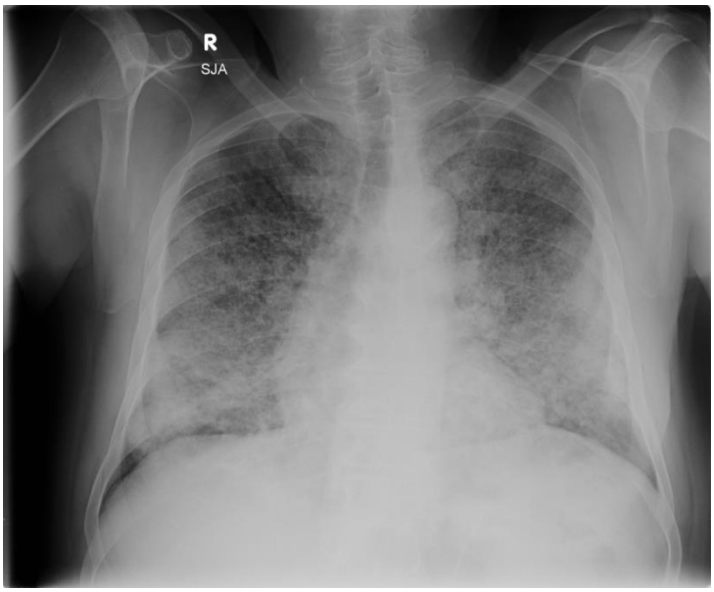

Figure 1: *CXR - Bilateral symmetrical opacities centrally in middle and lower lung zones.*

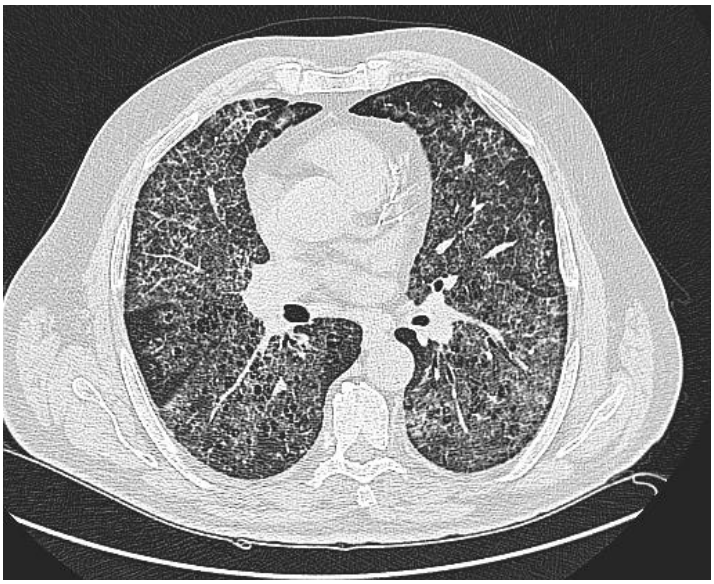

Figure 2: *CT scan - Ground-glass opacities with thickened interlobular septa and intralobular lines bilaterally.*

A CT scan of his chest revealed alveolar opacities in the upper and lower zones with some mediastinal lymph nodes (Figure 2). The patient's pulmonary function test did not indicate airway obstruction or restriction, and the lung volumes were within normal limits. However, a mild impairment in gas exchange was evident. A six-minute walk test was performed, which demonstrated an oxygen saturation drop from 91% to 85% after 3 minutes, a maximum dyspnoea scale of 2, and a walking distance of 200m. An echocardiogram showed normal right and left ventricle sizes and systolic function, with moderate aortic stenosis and a grade 1 mitral regurgitation.

Following this, the patient had a bronchoscopy. This revealed an inflamed left bronchial tree, mostly in the left upper lobe with evidence of a non-specific interstitial fibrosis. His left bronchial alveolar lavage revealed macrophages 33%, lymphocytes 42%, and neutrophils 25% on a background of amorphous globular debris. There were positive foamy bodies on PAS stain, with no malignant cells or acid-fast bacilli. His right bronchial alveolar lavage was unremarkable.

The patient then underwent an elective video assisted thoracoscopic lung biopsy. Intraoperatively it was noted that the left upper and lower lobes had adhesions to the chest wall and the fissure was incomplete. Two biopsies were taken from the upper and lower lobes. His left lower lobe biopsy showed features suggestive of alveolar proteinosis (Figure 3). His left upper lobe biopsy was unremarkable.

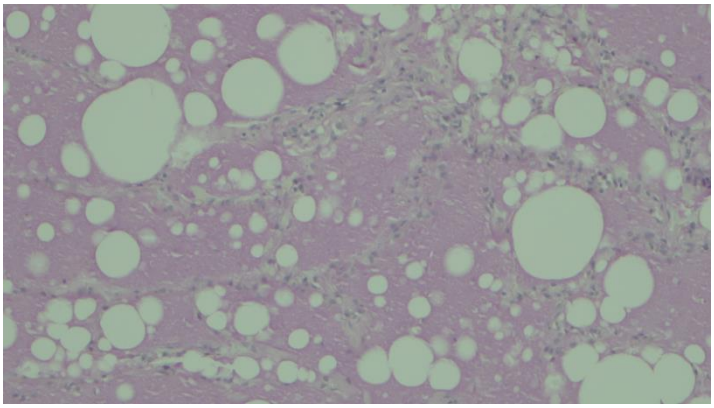

Figure 3: *Histology - Alveolar spaces filled with eosinophilic granular materials (Hematoxylin and eosin stain).*

Following these investigations, the patient was referred to the respiratory outpatient clinic. A GM-CSF antibody test was performed which was positive, and the patient was formally diagnosed with pulmonary alveolar proteinosis. As he was clinically symptomatic with a PO_2 <70 mmHg and $P(A\text{-}a)O_2$ > 40, he was eligible for a whole lung lavage. Following which, he was noted to have symptomatic improvement lasting for more than a year. Over the next 3 years, he was continually reviewed in our outpatient clinic with routine CT scans of his chest to assess for clinical progression (Figure 4) and whole lung lavage was performed when clinically indicated.

Discussion

The estimated prevalence of PAP ranges from 3.7 to 40 cases per million people, varying between countries [2,3,5]. The incidence is reported to be 0.2 cases per million [2]. The rare syndrome

affects all ethnic groups and has a male predisposition [5]. Autoimmune PAP is the most common etiology, making up roughly 90% of cases, followed by secondary PAP (4%) and congenital PAP (1%). The remaining 5% of cases is comprised of undetermined PAP-like diseases [4-6].

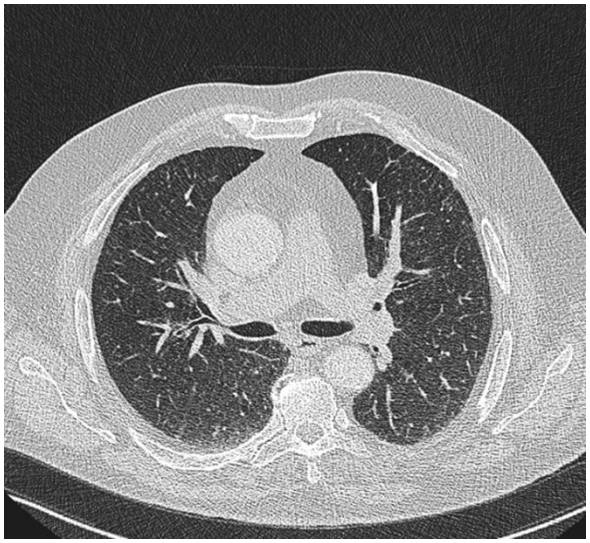

Figure 4: *Post whole lung lavage CT scan- Reduced ground glass opacities.*

Surfactant, a substance comprised of 90% lipids and 10% proteins, is responsible for reducing alveolar surface tension and hence preventing airway collapse during respiration [1]. It is also important for host defence in the lungs [2]. Surfactant is produced and secreted by alveolar type II pneumocytes, with alveolar macrophages playing a role in the breakdown and clearance of surfactant through phagocytosis [1,2]. Granulocyte macrophage colony stimulating factor (GM-CSF) is a cytokine that is relevant to the pathophysiology of PAP. It is responsible for the terminal differentiation of macrophages, which is required for alveolar macrophages to be able to phagocytise surfactant [5,6].

The aetiology of PAP can be categorised into primary and secondary causes. The most common primary cause is autoimmune PAP, where patients develop IgG antibodies against GM-CSF. This results in impairment of alveolar macrophages, leading to accumulation of surfactant in alveoli [2,5]. The other primary cause is congenital, whereby there are genetic mutations implicating GM-CSF receptor proteins or surfactant proteins [2]. Secondary causes of PAP occur due to decreased functional macrophages. These secondary causes include infections (e.g. nocardia, cytomegalovirus, mycotuberculosis bacterium), environmental irritants (e.g. silica, cotton, cement, titanium, and nitrogen dioxide) and, haematological disorders (e.g. myelodysplastic syndrome, leukemia, and multiple myeloma) [4].

The clinical presentation of PAP is vague and most often presents as dyspnoea. Occasionally, it can also present with a cough and gummy white sputum [1]. Systemic features such as weight loss, fever and fatigue may also be present [7]. On clinical examination, mild PAP presents asymptomatically. Severe PAP may present with crackles on auscultation of lungs, clubbing, hypoxemia or cyanosis [6].

Laboratory studies including serum lactate dehydrogenase (LDH), partial pressure of oxygen (PaO_2) and arterial-alveolar oxygen ratio (A-aPO_2) have the utility of assessing the disease severity of PAP [7]. The sensitivity and specificity of anti-GM-CSF IgG antibody in the diagnosis of PAP is 92% and 100% respectively [8]. Chest radiographs may show perihilar alveolar opacities, nodules or atelectasis, while a CT scan of the chest may reveal ground-glass opacification in middle or lower lung fields with thickened interlobular septa [6]. Pulmonary function tests may show reduced diffusion capacity which correlates with the disease severity of PAP [6-7]. A histopathological diagnosis is the gold-standard investigation tool in the diagnosis of PAP, with eosinophilic, granular material and foamy alveolar macrophages in alveoli spaces being characteristic findings [7].

The management of PAP is dependent on the severity of the disease. In the mild form of PAP, physiotherapy and bronchodilators can be used [1,6]. In severe forms of PAP, patients can undergo whole lung lavage, GM-CSF protein administration or rituximab therapy as directed by a respiratory physician [1,2,4,5,7]. All patients with PAP should have regular follow up in the outpatient setting with pulmonary function tests and chest CT scans [6,7].

Whole lung lavage is the gold standard treatment for primary and some secondary causes of PAP [4,5]. The invasive procedure is done under general anaesthesia and the patient is intubated with a double lumen endotracheal tube [1,2]. Whilst one lung remains ventilated, the other undergoes lavage, with 1-1.5 litres of warmed normal saline repeatedly introduced to mechanically remove surfactant from the lungs [1,2,4]. In our respiratory department, patients become eligible for whole lung lavage if they are symptomatic and hypoxic with an ABG showing PO_2<70mmHg or P(A-a)O_2>40mmHg.

GM-CSF therapy is an alternative treatment strategy for autoimmune PAP which is well tolerated compared to whole lung lavage, but results in a slower response [1]. The therapy involves exogenous GM-CSF proteins being inhaled or subcutaneously administered. Inhaled GM-CSF therapy is an emerging field, which has shown positive results in early trials with minimal adverse effects. Finally, immunosuppressive therapy with Rituximab (an anti-B cell monoclonal antibody) is another potential alternative to whole lung lavage for patients with autoimmune PAP [2]. Theoretically, the therapy would reduce levels of GM-CSF autoantibodies. However, more research is required before the effectiveness of this therapy can be concluded on [5].

Conclusion

PAP is a rare, complicated disease caused by the failure to degrade surfactant proteins in alveoli, causing dyspnoea, and in severe cases, respiratory distress. To date, the most effective therapy is whole lung lavage therapies in combination with chest physiotherapy, resulting in the mechanical removal of surfactant products from the alveoli, which provides symptomatic relief for patients.

Declaration of Interest

The author has no relevant affiliations or financial involvement with a financial interest in or financial with the subject matter or materials discussed in the manuscript.

Conflict of Interest

Authors declare no conflict of interest.

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