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Case Report

Pulmonary alveolar proteinosis: A case report and literature review

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Abstract

Background: Pulmonary alveolar proteinosis (PAP) is a rare disease caused by the accumulation of surfactant in the lung's alveoli, as a result of malfunction in the cleaning function of alveolar macrophages. The major symptoms include cough and dyspnea. Computed tomography scan usually reveals crazy-paving pattern. Lung biopsy confirms the diagnosis by showing accumulations of periodic acid-schiff-positive lipoproteinaceous materials.

Case Presentation: In this report, we present a middle-age man with progressive dyspnea on exertion, and frequent cough with no noteworthy medical history. The results of initial examinations and laboratory tests were non-diagnostic, so imaging studies were requested for the patient. After imaging and suspecting PAP as a differential diagnosis due to results of high resolution computed tomography, a transbronchial biopsy was performed to confirm the diagnosis. Then, according to the histopathology reports, the diagnosis of PAP was made. During the biopsy procedure, the patient developed pneumothorax, and accurate treatment approaches were considered for this complication.

Conclusions: In patients with chronic progressive dyspnea and cough, appropriate and timely imaging and other paraclinic investigations must be considered by the physicians.

Keywords: Pulmonary Alveolar Proteinosis, Biopsy, Surfactant.

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Pulmonary alveolar proteinosis (PAP) is a rare lung disorder characterized by progressive dyspnea and frequent cough as a result of impaired alveolar ventilation. In 1958, Rosen *et al.* first reported 27 patients with an unknown lung disease resulting from accumulation of periodic acid-Schiff (PAS)-positive and lipid-rich protein substance within the alveoli (1). In fact, this accumulation is caused by the defects in the production or clearance of surfactant in the alveolar space (2). Definitive diagnosis of PAP is based on histopathological findings from the sample obtained from surgical or transbronchial biopsy. Bronchoalveolar lavage has clear milky appearance. In the biopsy sample, usually the normal structure of the alveoli is observed without inflammation or with a mild infiltration of mixed inflammatory cells. Alveoli are usually filled with eosinophilic lipoproteinaceous material and are pink in PAS staining (3). To start the proper treatment, it is so important to diagnose the type of PAP, especially to rule out secondary causes. Here, we report a middle-aged male patient complaining of chronic dyspnea and cough who underwent diagnostic procedures and was diagnosed with PAP, but developed one of the dangerous complications of this procedure after transbronchial lung biopsy.

Case Presentation

The patient was a 41-year-old man who was referred to the emergency department affiliated to Babol University of Medical Sciences, Iran complaining of shortness of breath. The patient's dyspnea started seven months ago and has gradually worsened.

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Dyspnea was grade 2 according to the modified Medical Research Council (mMRC) scale, worsening with activity and improving at rest. The patient did not have orthopnea, chest pain, or limb edema. Also, the patient has lost 10 kg of weight four months ago, but he does not mention anorexia. Among other associated symptoms, he mentioned occasional non-productive cough especially during activity, weakness and lethargy. There was no history of fever and chills, night sweats or hemoptysis. No previous disease was reported in the patient's medical history, and he had no allergies to any substances. The patient denied smoking or alcohol consumption and was not in direct contact with toxic vapors in his living and working environment. He had no history of recent travel. During the recent seven months, the patient has been treated with salmeterol/fluticasone spray, montelukast, cetirizine, bromhexine, loratadine, N-acetylcysteine and various antibiotics with numerous visits in different clinics; and did not respond to any of the treatments.

In the physical examinations, he had blood pressure of 120/80 mm/Hg, pulse rate=82/min, respiratory rate=16/min and body temperature=36.5 °c. Peripheral oxygen saturation (spo2) was 90% in room air, and no respiratory distress, pallor or cyanosis was observed. He was alert and aware. No abnormal sound was heard in auscultation of the heart and lungs. The distal pulses of limbs were fully palpable. Laboratory tests showed white blood cells (WBC) 8.800/mm^3 with 74% polymorphonuclear cells and 1% eosinophils, red blood cells (RBC) 6.84 *10^6/mm^3, hemoglobin (Hb) 18.5 g/dL, hematocrit (Hct) 55.2%, mean corpuscular volume (MCV) 80.7 fl, platelets (Plt) 286000/mm^3, C-reactive protein 11 mg/L, lactate dehydrogenase (LDH) 770 IU/L. Other laboratory tests such as renal and liver function tests, showed no abnormality.

In the chest x-ray, bilateral alveolar opacities were seen (figure 1). Bilateral "crazy-paving" pattern was also evident in high-resolution CT scan (HRCT) (figure 2). Bronchoalveolar lavage (BAL) was performed for the patient, which had a cloudy and milky macroscopic appearance (figure 3). BAL culture was negative for acid-fast bacteria and fungi, and proteinaceous eosinophilic acellular accumulations and mild inflammatory cell infiltration (mostly lymphocytes) were observed, suggesting PAP. To confirm the diagnosis, a transbronchial biopsy was performed for the patient and the histology showed the preserved alveolar structure and PAS-positive accumulations inside alveoli and mild infiltration of mixed inflammatory cells and the final diagnosis of PAP was made (figure 4). During the transbronchial biopsy, the patient developed a pneumothorax in the right lung (figure 5), for which a chest tube was temporarily inserted (Figure 6). Despite the application of appropriate treatment, the patient's condition deteriorated, and the patient was transferred to another hospital with specialized pulmonary disease equipment.

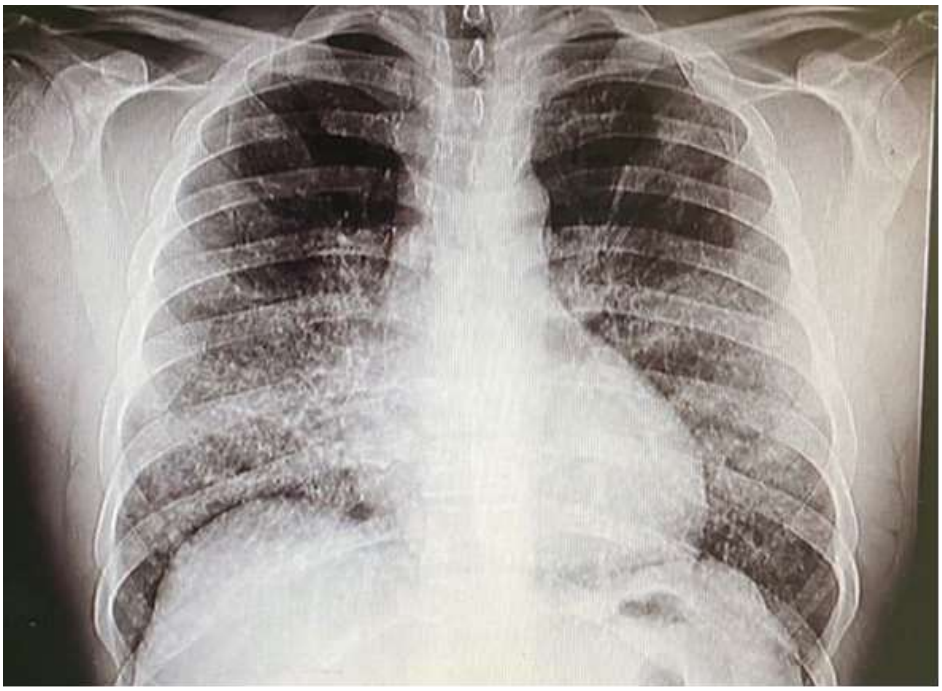

Figure 1. Patient's chest radiograph showing bilateral alveolar opacities

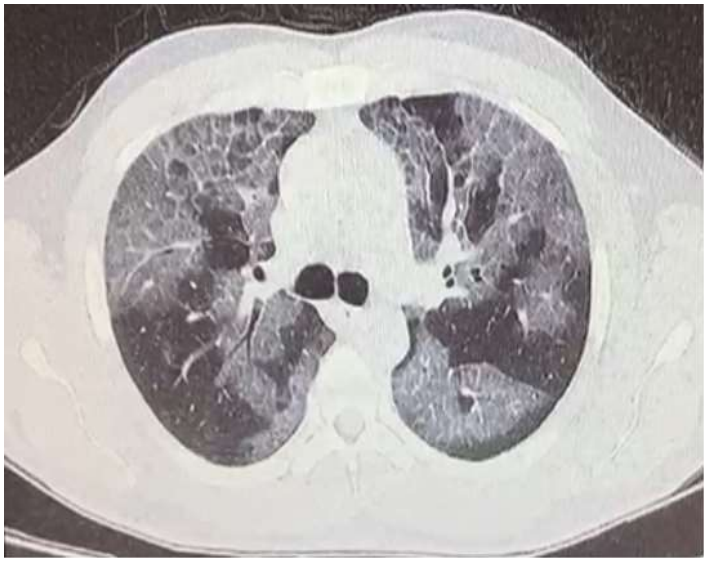

Figure 2. High resolution computed tomography of patient showing crazy-paving pattern

Figure 3. Bronchoalveolar lavage fluid with a cloudy and milky appearance

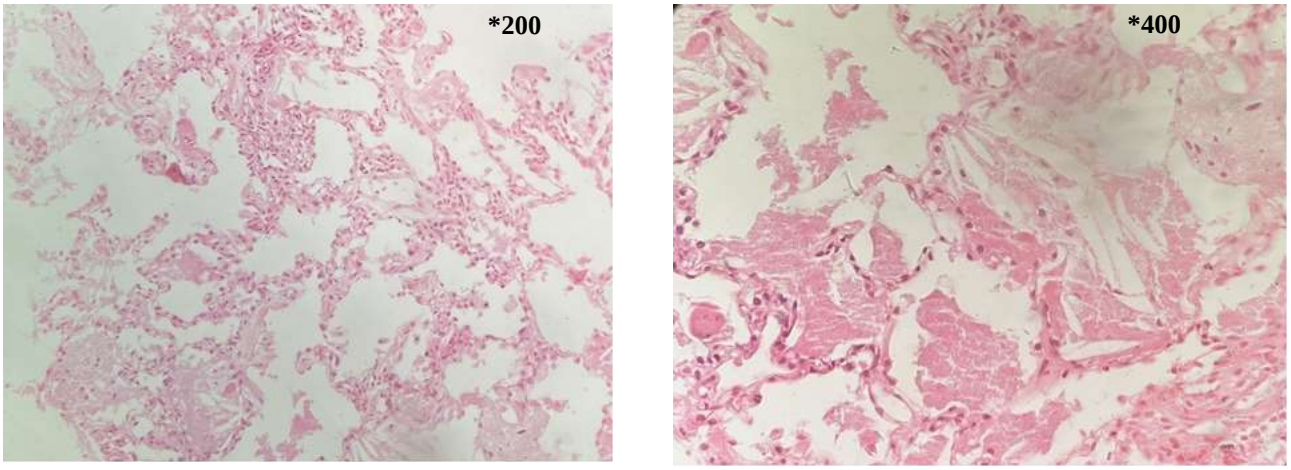

Figure 4. Preserved alveolar structure and PAS-positive accumulations inside alveoli and mild infiltration of mixed inflammatory cells were observed in transbronchial biopsy

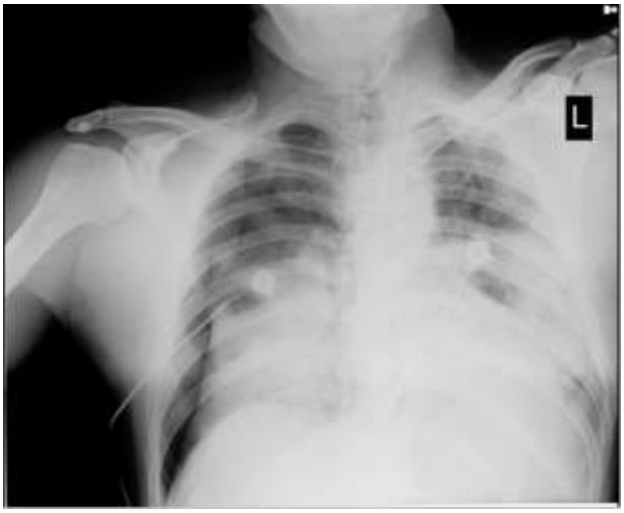

Figure 5. Patient's chest radiograph after transbronchial biopsy showing right pneumothorax

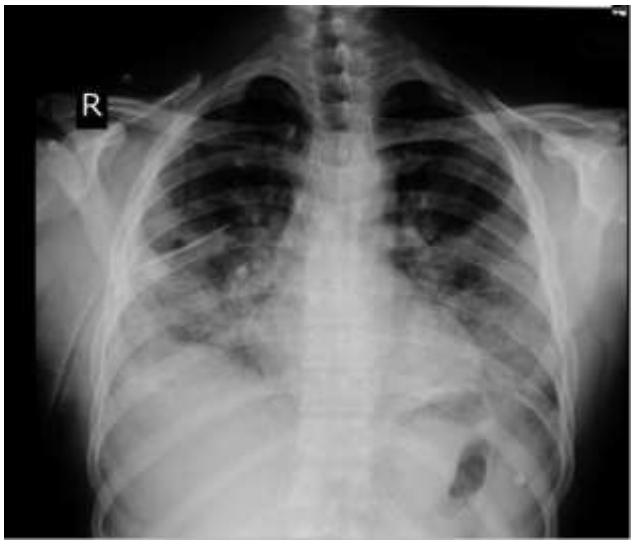

Figure 6. Patient's chest radiograph after chest tube insertion

Discussion

This case report describes a patient with PAP who was referred with complaints of chronic cough and exertional dyspnea. This patient was treated for seven months with various medical diagnoses such as allergic reactions, viral infections and pneumonia, and after not responding to treatment options, and worsening the symptoms, he finally referred to our emergency department. After taking a detailed history and appropriate examination, a chest x-ray was requested. Finally, according to the findings of the paraclinic investigations, the correct diagnosis was made and the appropriate treatment was initiated for the patient. PAP is a rare disease with a reported prevalence of 6.87 per million at least, with an equal ratio between men and women (4). This low prevalence for PAP makes its diagnosis a challenge for physicians. Not taking a detailed history and not considering differential diagnoses in reviewing the paraclinical results such as imaging, can cause a delay in the diagnosis, and treatment of PAP even up to 18 months (3). Due to the chronic and progressive nature of PAP, proper history taking and timely paraclinic request can pave the way for diagnosis and treatment for these patients.

According to the latest classifications, three types of PAP have been reported based on the etiology: primary, congenital and secondary. According to its pathogenesis, primary PAP is classified into two types: autoimmune and hereditary. In the autoimmune type, which includes more than 90% of all PAP cases, anti-granulocyte-macrophage

colony-stimulating factor (GM-CSF) antibodies are seen in the circulation. GM-CSF is a protein, responsible for the final differentiation of alveolar macrophages to perform the effective catabolism of surfactant. In hereditary PAP, receptors on macrophages are defective and binding with GM-CSF does not take place. Congenital PAP is caused as a result of genetic mutations in the surfactant manufacturing pathway, and secondary PAP is caused by a malfunction of macrophages, usually in the context of hematological disorders. Simultaneous occurrence of two types of PAP is also possible and has been reported in the literature (5). PAP usually presents with symptoms of shortness of breath on exertion, frequent cough, sometimes accompanied by sputum and fatigue; In a study on 45 PAP patients conducted in Iran, 4 patients were also presented with non-massive hemoptysis (6). In cases of secondary PAP, symptoms of the underlying disease such as fever and weight loss can also be expected. At the time of history taking, it is important to pay attention to the smoking status, exposure to occupational toxic dusts and vapors, and contact with suspected tuberculosis patient. On examination, no specific finding is usually expected, although sometimes a crackle may be heard or clubbing may be seen due to chronic hypoxia.

Routine laboratory tests are usually within normal range, and no specific test is recommended to diagnose this disease; although, some evidence reported an increase in the level of lactate dehydrogenase and polycythemia. In secondary cases of the disease, hematological involvement might be evident. Recently, the possible role of human leukocyte antibody (HLA) in the pathogenesis of PAP has been discussed. In a study of 198 autoimmune PAP patients and 395 controls, HLA-DRB1*08:03 was found to be associated with high levels of anti-GM-CSF antibodies (7). In another study on 60 PAP patients, it was reported that patients with HLA-DRB1*14:54 have a better response to treatment and are more likely to experience the remission (8). Bilateral hazy opacities are usually seen in x-rays of patients. In HRCT imaging, bilateral and diffuse involvement is seen in the form of increased interlobular septal thickness and ground-glass opacities known as "crazy-paving", which is characteristic of PAP but not specific and is also seen in other conditions such as interstitial pneumonia, sarcoidosis, drug induced pneumonitis, adult respiratory distress syndrome (ARDS) and even in COVID-19 associated pneumonia (9, 10). In addition, localized involvement has also been reported for this disease (11). Finally, definitive diagnosis of PAP is made by surgical or transbronchial biopsy. Transbronchial biopsy is known as a suitable and less risky alternative to surgical biopsy. It has been reported that complications such as pneumothorax occurs in this procedure in up to 5% of cases, which can potentially increase the risk of mortality (12). To conduct this procedure, its indications should be carefully checked and its benefits and risks should be carefully considered by the attending physician. In order to diagnose the type of PAP, a complete paraclinic work-up is necessary to rule out secondary causes such as hematological malignancies. Autoimmune PAP is confirmed by a positive anti-GM-CSF antibody titers. This biomarker can be used to evaluate the response to treatment, and disease prognosis (13).

Pulmonary function tests are usually in the normal range; however, in severe cases of the disease, a restrictive lung disease is observed, which indicates the beginning of the fibrotic processes. Several scoring systems have been introduced to determine the severity of PAP, including disease severity scores (DSS) and severity and prognosis score of pulmonary alveolar proteinosis (SPSP). Recently, the SPSPII scoring system has been introduced, which is evaluated based on symptoms, smoking status, % predicted carbon monoxide diffusing capacity of the lung (DLCO), PaO2, and HRCT findings, and its efficiency in predicting prognosis has been reported much better than other scoring systems (14). Treatment of PAP should be managed according to the severity of disease and symptoms; from watch-full waiting in mild and asymptomatic cases to lung transplantation in severe cases that lead to pulmonary fibrosis and respiratory failure. Treatment choice for most cases of PAP is whole lung lavage (WLL). The WLL technique was first described in 1963 by Ramirez *et al*. (15). WLL is an invasive and specialized procedure that has become the gold-standard treatment of PAP, and makes a dramatic response to treatment by physically removing lipoprotein accumulations. WLL should be performed by a skilled physician in a specialized center to reduce its unwanted complications, such as hypoxia, bleeding, pleural effusion, pneumothorax, etc. (16).

Initially, due to the autoimmune nature of the disease, corticosteroids were suggested for medical therapy (15); however, today the inefficiency and even their role in increasing the mortality rate of these patients have been reported (2). Inhaled GM-CSF is also discussed and interested in many studies as a new treatment approach that seems to have good efficacy and safety in the treatment of mild cases of the disease (17). Rituximab, an anti-CD20 monoclonal antibody, is also recommended for the treatment of refractory cases (18). Considering the role of

genetics and the discovery of several genes involved in the occurrence of hereditary PAP, gene therapy is a new treatment that needs more research (18). In severe cases where fibrosis and respiratory failure occurs, there is no other way rather than lung transplantation (19); although, the recurrence of PAP in the transplanted lung has been reported in literature (20). Opportunistic infections are common in these patients, especially in autoimmune PAP. Microorganisms such as nocardia, mycobacteria and fungal infections such as Aspergillus have been reported as disseminated and systemic involvement, especially in the central nervous system (21, 22). This can be due to defect in the function of alveolar macrophages and GM-CSF signaling in the lungs, or due to immunosuppression with drugs used in these patients. It also seems that the infection of COVID-19 in these patients might be related to the occurrence of more post-COVID complications, especially hypoxia (23).

Over the years since PAP was first defined as an independent disease entity, the survival of the disease has significantly improved due to the development of new therapeutical methods. 5-year survival of patients in new studies has been reported up to 90% (24), which requires more studies due to the development of new treatments. The outcome of the patients can be different from a spontaneous improvement to fibrosis and respiratory failure and subsequent death. Spontaneous improvement has been reported in 25-50% of patients in 18-60 months follow-up. In the study of Campo *et al*. (25), which was conducted on 81 patients with PAP, it was observed that 34 patients did not perform WLL due to mild symptoms. Also, out of 47 other patients, 32 cases received a good therapeutic response with one WLL and 15 cases required multiple WLLs. In a study of 26 patients with PAP, it was observed that without WLL treatment, 50% of patients experience spontaneous improvement; 31% have progressive deterioration and the other 19% have stable persistent symptoms (1). A limitation of this case report is the absence of the patient's outcome, which may restrict the ability to fully assess the effectiveness of the treatment and the overall prognosis. Future reports should aim to include this information to provide a more comprehensive analysis. The diagnosis of PAP is difficult due to its rarity. However, the diagnosis should be considered in patients with progressive dyspnea, non-productive cough, and characteristic imaging findings, especially the crazy-paving pattern on HRCT. Confirmation typically involves bronchoalveolar lavage, which shows milky fluid with characteristic cytologic findings, and may be supported by identifying anti-GM-CSF autoantibodies in cases of autoimmune PAP.

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Conflict of interests: The authors declare that they have no conflict of interest.

Authors' contribution: Yasaman Sajadi: Contributed to patient care and manuscript preparation. Sussan Moudi: Assisted with the manuscript editing. Ehsan Chogan: Contributed to the design and implementation of the research, and to the writing of the manuscript. Mahmood Monadi: Provided overall supervision, contributed to patient care, and was responsible for critical revisions of the manuscript.

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