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Case Report

Pulmonary alveolar proteinosis, unusual infiltrative lung disease, the dilemma for physicians: A case report and literature review

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Abstract

Introduction: Pulmonary alveolar proteinosis (PAP) is a diffuse pulmonary disease characterized by the intra-alveolar accumulation of formless, proteinaceous material. Lipids and proteins materials with specific staining appearance in the alveoli impair pulmonary gas transfer in PAP. The severity of this condition ranges from an asymptomatic clinical presentation to respiratory failure and death. PAP is an extremely rare disorder, occurring worldwide with an estimated prevalence of 0.1 per 100000 individuals. Although the pathogenesis of PAP has remained unknown, most investigators have considered this condition to be caused by the impaired clearance of lipids and surfactant proteins from the airspaces. These functions are known to be performed by alveolar macrophages and type 2 epithelial cells. It is likely that granulocyte macrophage-colony stimulating factor (GM-CSF) dysfunction on macrophages is responsible for PAP. Primarily, in most adult patients with PAP, antibodies against GM-CSF have been observed with dysfunction of macrophages. Secondly, alveolar macrophage dysfunction plays a role in the impaired secretion of surfactant in this disease. It has been noted that both impaired secretion of surfactant and impaired phagocytosis are responsible for disease pathogenesis.

Case Report: A 40-year-old man who had suffered from a cough with sputum for more than 2 years, with no associated fever, referred to our clinic. He had been diagnosed with pneumonia and treated unsuccessfully with antibiotics. His past medical history showed that he had a chronic history of a cough, easy fatigability and shortness of breath upon mild exertion. Computed tomography (CT) imaging of the chest revealed bilateral diffuse reticulonodular opacities and a crazy-paving pattern, which was suggestive of alveolar proteinosis.

Conclusion: PAP is a generalized pulmonary disorder caused by the collection of formless, proteinaceous material with specific staining appearance in the alveolus.

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Introduction

Pulmonary alveolar proteinosis (PAP), also known as pulmonary alveolar phospholipoproteinosis, is a diffuse lung disease with accumulation of formless, periodic acid-Schiff (PAS)-positive material in alveoli with little or no lung inflammation, in which the underlying lung format is saved.[1,2] The lipoproteinaceous material principally consists of the surfactant derivatives including phospholipids and apoproteins. Scientific results have shown that macrophage dysfunction and clearance of surfactant by alveolar macrophages take part in the pathogenesis of PAP.[3] It is clinically diagnosed by pulmonary clinical manifestations of dyspnea and cough. Imaging findings are bilateral symmetric alveolar densities which are located in lower lung areas, like butterfly appearance.[4]

There are two forms of PAP, including primary and secondary, according to etiological and pathogenesis aspects. When patients are presented with similar clinical

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manifestations, the first thing we need is a high-resolution computed tomography (CT) scan of the lungs. If it reveals bilateral symmetric alveolar densities, it is recommended to perform fiberoptic bronchoscopy with bronchoalveolar lavage fluid collection. However, if it is accessible and not contraindicated due to coagulopathy or respiratory distress, transbronchoscopic lung biopsy is recommended. The pathologic findings are positive PAS stain amorphous material from bronchoalveolar lavage fluid or transbronchial biopsy. It is recommended to eliminate the presence of coexisting infective organisms like opportunistic agents such as Nocardia, mycobacteria, fungi. For excluding them, special stains and cultures may be needed. The primary form often presents in the childhood. It is suspected that it is related to mutations in the genes playing role in formation of surfactant structure, the granulocyte macrophage-colony stimulating factor (GM-CSF) receptor or a defect in the plasma membrane carrier of cationic amino acids.

The secondary form of PAP is the prevalent one. It is mostly accompanied by anti-GM-CSF antibodies and may result in macrophage dysfunction and the disturbed production of surfactant. The secondary form develops in adults with high-grade dust exposures like silica, blood-related cancers, with or without bone marrow transplantation. Secondary PAP is likely related to a relative deficiency of GM-CSF and with macrophage dysfunction. It is suggested that certain inhalational exposures may lead to PAP through autoimmune mechanisms, but not due to direct toxic effect on macrophages. It may be considered as a variant type of silicosis that refers to a spectrum of pulmonary diseases caused by inhalation of free crystalline silica dust like silicon dioxide. Pulmonary diseases caused by inhalation of silica must be differentiated from PAP. Silicoproteinosis occurs following massive exposure to respiratory crystalline silica like silicon dioxide within a short period. The most significant finding of imaging data is massive silicon deposition at the chest X-ray and clear airspace filling appearance, with no circular densities or calcifications of lymph nodes. Later, basal alveolar collection changes to greater masses of lung tissue in the lower half of lungs, which are seen symmetrically on both sides of the chest. However, this is not a constant rule.[5]

This finding mimics many imaging and clinicopathological aspects of many respiratory diseases with proteinosis. Differential diagnosis of the basilar alveolar collection with masses of lung tissue includes chronic infections like the miliary spreading of mycobacterial or fungal agents, pulmonary malignancy, multiple rheumatoid nodules, sarcoidosis, some kinds of pneumoconiosis, and finally, PAP. Literature review has shown that decreased GM-CSF protein or function causes PAP and is responsible for the dysfunction of surfactant physiology. GM-CSF binds to cells through its receptor. Some congenital and rare acquired forms of PAP are associated with decreased or absent function of the GM-CSF receptor that results in functionally-defective GM-CSF receptors. As a result, greatly diminished binding of GM-CSF to the related receptor occurs which reduces the receptor function. Lack of GM-CSF production does not appear to play a major role in adult PAP (secondary or acquired type), but Instead, autoimmunity process may explain the functional deficiency of GM-CSF in adult patients with acquired PAP.[6] Serum autoantibodies against GM-CSF protein have been found in these patients that classified PAP as autoimmune phenomena.[7]

GM-CSF can affect surfactant clearance by the mediation of alveolar macrophages. Alveolar macrophages from patients with PAP have demonstrated decreased levels of clearance of surfactant, as compared to normal controls. However, the levels can be returned to the normal status with an injection of GM-CSF transcutaneously. This observation may explain how a deficiency of this factor can induce airspaces collection of surfactant lipoprotein.

The co-existence of PAP with hematologic

malignancies and bone marrow transplantation may be indicative of the generalized pattern of autoantibodies against GM-CSF or its relative deficiency. These results suggest that impaired macrophage dysfunction and clearance of surfactant by alveolar macrophages takes part in the pathogenesis of PAP.

Clearance function of alveolar macrophage is increasingly disturbed with the collection of the surfactant lipoprotein, causing diseased phagocytosis and consequently phagolysosome fusion. Death of alveolar macrophages may take part in the formless material collection.[8,9] Secondary macrophage dysfunction, due to immunosuppressive drugs or hematologic malignancies, can explain some cases of PAP. Typical age of presentation of patients with PAP is the fourth decade among adults. Being man is dominated by a woman with a ratio of 2:1. The clinical manifestations and symptoms are the innocent beginning of respiratory distress with a non-productive cough and occasionally some mucoid sputum, dyspnea on exertion, fatigue, weight loss, and low-grade fever. However, one-third of cases are not symptomatic despite filling of the lumen of airspaces.

Dyspnea is the most common presenting symptom. Physical examination is usually nonsignificant, but occasionally may observe clubbing and cyanosis in some patients. Pulmonary auscultation may be normal and inspiratory crackles may be absent despite obvious airspaces filling on chest X-ray, presumably due to absent air movement in the totally occupied distal alveoli. Patients with PAP may have associated infections with opportunistic agents like Nocardia, mycobacteria, and opportunistic fungi, due to alveolar macrophage malfunction. Cardinal paraclinic finding includes increased hematocrit, gamma-globulins, and lactic dehydrogenase values.

Diagnostic utility of increased value of pulmonary surfactant proteins and tumor markers like carcinoembryonic antigen, carbohydrate antigens 19-9 in bronchoalveolar lavage and serum from patients with PAP is not specific. Some serum biomarkers may correlate with disease activity, including lactic dehydrogenase, and the carcinoembryonic antigen. Sputum examination may suggest PAP in the consistent clinical finding, with documenting of the Papanicolaou-stained smears-positive compound in alveoli. Radiographic findings include bilateral symmetric alveolar opacities located centrally in mid and lower lung zones, rarely air bronchograms, the interstitial pattern at chest X-ray similar to batwing distribution.

Additional findings include the high-resolution computerized tomography scanning showing ground-glass densities, largely in a continuous pattern with some thickened interstitial structures like polygonal forms, named as crazy-paving. This is more common among patients with secondary PAP. Pulmonary function tests have shown a restrictive pattern, but are often discordant to the degree of decreased pulmonary capacity and are concordant with disease activity, and decrease in pulmonary artery oxygen. Some degrees of hypoxemia and respiratory alkalosis with compensation may be seen and is deteriorated exertionally.[10,11]

At echocardiography of PAP patients, the high right-to-left functional pulmonary-cardiac shunt may be observed. Characteristic bronchoalveolar lavage findings of PAP include an opaque or milky appearance due to the abundant lipoproteinaceous material, which may settle upon standing, alveolar macrophages that are engorged with the PAS-positive material large acellular eosinophilic bodies in a background of eosinophilic, globules in Papanicolaou-stained smears of bronchoalveolar lavage fluid are suggestive of the diagnosis, histopathologic evaluation of trans bronchoscopy lung biopsy. It has been seen that the normal alveolar architecture is generally not disturbed, although the interstitial septa may slightly widen due to high epithelial cell generation, with little inflammation. The airspaces are occupied with lipoproteins which are stained

pink with PAS stain sometimes in histiocytic giant-cell observation.[12,13]

Case Report

A 40-year-old man who had suffered from a cough with sputum for more than 2 years, with no associated fever, referred to our center. He had previously been seen at another hospital, where he had been diagnosed with pneumonia, and treated unsuccessfully with antibiotics. Upon presentation to our hospital, the patient complained of trouble breathing, thus viral infection was suspected. However, the results of laboratory testing were negative. His past medical history showed that he had a chronic history of a cough, easy fatigability and shortness of breath upon mild exertion. There was no history of drug intake or exposure to toxic fumes or inorganic dust. The patient had smoked for 15 years, 20 cigarettes per day. He had no particular family history. Further investigations were performed including CT imaging of the chest, which revealed bilateral diffuse reticulonodular opacities and a crazy-paving pattern which was suggestive of alveolar proteinosis. After the patient was admitted, an open-lung biopsy was performed to confirm the diagnosis. The histopathologic examination revealed eosinophilic secretions with a granular appearance suggestive of PAP (Figure 1, A and B).

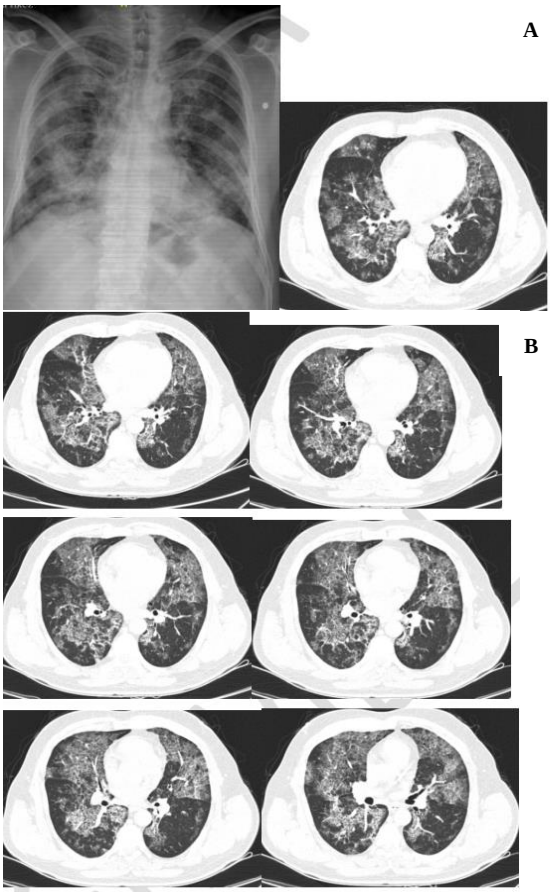

Figure 1. Chest X-ray and computed tomography (CT) scan shows ground-glass densities, largely in a continuous pattern with some thickened interstitial structures like polygonal forms, named as crazy-paving (A, B)

Discussion

PAP is a generalized pulmonary disorder caused by the collection of formless, proteinaceous material with specific staining appearance in the alveoli. GM-CSF dysfunction on macrophages is likely responsible for PAP. Primarily in most adult patients with PAP, antibodies against GM-CSF are observed with dysfunction of the GM-CSF receptor on macrophages. Secondly, alveolar macrophage dysfunction plays a role in PAP. Finally, both impaired secretion of surfactant and impaired phagocytosis are responsible for disease pathogenesis.

Chest radiographs have shown bilateral symmetric alveolar opacities located centrally in mid and lower lung zones, sometimes resulting in a batwing distribution. High-resolution CT scanning reveals ground-glass opacification that typically spares the periphery and may have a crazy-paving appearance. Typical bronchoalveolar lavage fluid has an opaque or milky appearance due to the abundant lipoproteinaceous material. Cytological examination of bronchoalveolar lavage reveals alveolar macrophages engorged with the PAS-positive material. Transbronchial lung biopsy reveals filling of the terminal bronchioles and alveoli with flocculent and granular lipoproteinaceous material that stains pink with PAS stain.

Conclusion

PAP is a generalized pulmonary disorder

caused by the collection of formless, proteinaceous material with specific staining appearance in the alveoli. Our case was a 40-year man who had suffered from a cough with sputum for more than 2 years, with no associated fever. He had been diagnosed with pneumonia and treated unsuccessfully with antibiotics. His past medical history showed that he had a chronic history of a cough, easy fatigability and shortness of breath upon mild exertion. CT imaging of the chest revealed bilateral diffuse reticulonodular opacities and a crazy-paving pattern suggestive of alveolar proteinosis.

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Authors' Contribution

Collection of data and analysis and management, follow up of the case.

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Conflict of Interest

Authors have no conflict of interest.

Ethical Approval

This study was approved by the Medical Ethics Committee of Tabriz University of Medical Sciences.

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