A Case of Pulmonary Histiocytosis X and Diabetes Insipidus

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Abstract

Primary pulmonary histiocytosis X is an uncommon interstitial disorder of unknown etiology characterized by atypical histiocyte infiltration forming nodular lesions. The clinical presentation of PHX is variable. The patient may stay asymptomatic with an abnormal chest radiograph, may experience pneumothorax or advanced lung disorder with respiratory symptoms or nonpulmonary involvement such as central diabetes insipidus. Corticosteroids and cytotoxic agents are of limited value in the treatment of the disorder. In this article we presented a 35-year-old female patient with pulmonary histiocytosis X accompanied by diabetes insipidus.

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Key words: *Histiocytosis X, pulmonary, diabetes insipidus*

Abbreviations: *PHX: Pulmonary histiocytosis X, HRCT: High resolution computerized tomography, CT: Computerized tomography, BAL: Bronchoalveolar lavage, DI: Diabetes insipidus*

Introduction

Primary pulmonary histiocytosis X (PHX) is a rare, smoking related, interstitial lung disorder that primarily affects young adults (1). It is also known as pulmonary eosinophilic granuloma and pulmonary Langerhans cell granulomatosis (2). Like Letterer-Siwe and Hand-Schüller-Christian disease, PHX is characterized by abnormal organ infiltration by Langerhans cells. Lichtenstein introduced the term PHX in 1953 in order to provide a unifying concept for these related disorders, although, they are clinically different (3). Letterer-Siwe disease is characterized by widespread infiltration of the reticuloendothelial system, bones and lungs. Slowly progressive natural history, lytic skull lesions, diabetes insipidus (DI) and exophtalmus affecting young adolescents and children, on the other hand, characterize Hand-Schüller-Christian disease. The true incidence and prevalence of pulmonary PHX are unknown. It is likely that some cases are misdiagnosed as idiopathic pulmonary fibrosis (1,4).

Case Report

A 35-year-old woman was admitted with the complaints of cough, dyspnea, headache, dryness of mouth, nausea and polyuria in 1998. Her dyspnea appeared 5 years ago, after she

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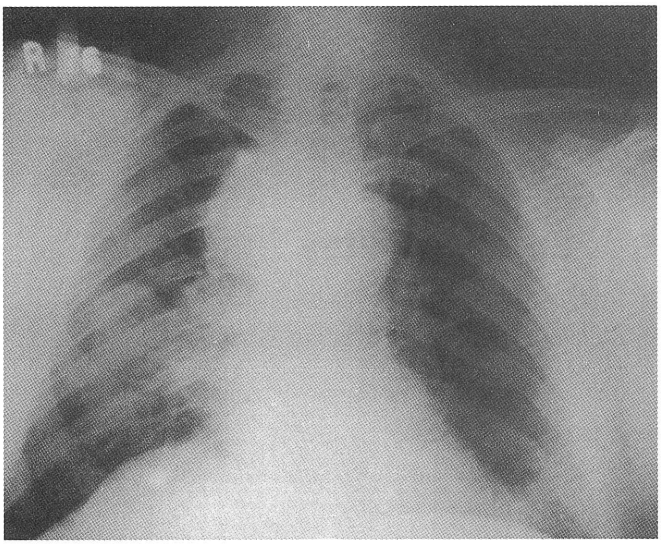

Figure 1. *HRCT scan demonstrating bilateral multiple cystic lesions a few mm in diameter with thin walls that were remarkable at upper lobes.*

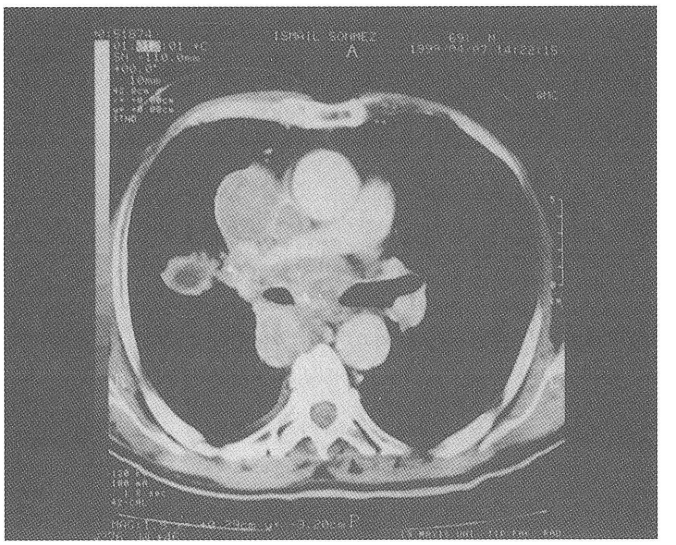

Figure 2. *Bone scintigraphy demonstrating increased inflammatory activity in the 7th left and right ribs and sacroiliac joints.*

had given birth to a child and increased gradually during this 5-year period. She had a dry cough increasing on exertion. She presented to a physician with the complaints of headache, dryness of mouth and polyuria 7 months before the hospitalization. The patient was diagnosed as having DI and minirin treatment was started. She was referred to our clinic for further investigation of the lesions detected on the chest x-rays. The patient was a housewife and had 15 pack-year smoking history.

Physical examination revealed otherwise unremarkable findings except clubbing. Routine biochemical and hematological tests and urinalysis were within normal limits. Pulmonary function tests were consistent with combined obstructive and restrictive lung disease: FEV_1 1.50 L (53%), FVC 2.28 L (69%), FEV_1/FVC 57%. Diffusion capacity was 13.6 (40%) ml/mmHg/min.

Chest x-ray revealed bilateral reticulonoduler opacities at the upper zones consistent with an interstitial lung disease. High resolution computerized tomography (HRCT) scans demonstrated bilateral multiple cystic lesions a few mm in diameter with thin walls that were remarkable in the upper lobes and two small nodules in the subpleural area and one in the at left upper lobe anterior segment (Figure 1). Costophrenic sinuses were not involved. Bone radiographs did not reveal cystic lesions, but bone scintigraphy demonstrated increased inflammatory activity at 7th left and right ribs and sacroiliac joints (Figure 2).

The patient underwent fiberoptic bronchoscopic examination that revealed normal endobronchial system and transbronchial biopsy was performed. Pathological examination of the transbronchial biopsy material was nondiagnostic. Open lung biopsy was decided and wedge biopsy from right upper lobe apical segment was performed. The biopsy specimen demonstrated cellular nodules that centers on bronchioles, in association with increased alveolar macrophages, lymphocytes, eosinophils and occasional neutrophils (Figure 3). Although S-100 staining was not performed, the patient was diagnosed as having PHX and prednisolone (1 mg/kg) treatment was initiated. She was advised to give up smoking. There was no improvement on the chest x-ray and spirometric parameters after 6 months of prednisolone treatment, therefore, prednisolone treatment was discontinued. The patient is still under follow up and no change on the chest x-ray and pulmonary function tests were detected.

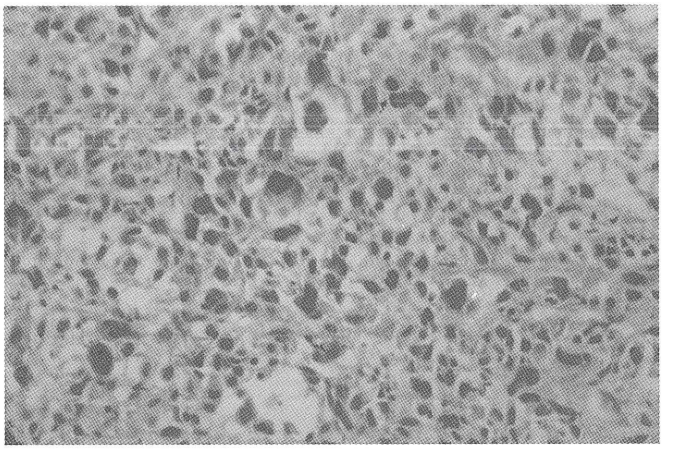

Figure 3. *The biopsy specimen demonstrated cellular nodules that centers on bronchioles, in association with increased alveolar macrophages, lymphocytes, eosinophils and occasional neutrophils.*

Discussion

PHX is a rarely encountered interstitial lung disorder. It is also called pulmonary eosinophilic granuloma and pulmonary Langerhans cell granulomatosis, and most commonly affects the people at 20 to 40 years of age. Previous literature suggested a male preponderance; however recent studies suggested equal sex distribution. (1,4)

Pathogenesis of the disorder is unknown. Presence of invariable smoking history suggests a link between cigarette smoking and PHX, possibly as a triggering factor (5). It is considered that bombesin-like peptide, changes in adhesion molecules, abnormalities in immune system, increased IgG in bronchoalveolar lavage (BAL) fluid, T cell function abnormalities and circulating tissue specific immune complexes seen in PHX is thought to have a role in the pathogenesis (1,4). Our case was a middle aged female with a smoking history of 15 pack-year.

The clinical picture of PHX is variable. The patient may stay asymptomatic or may experience pneumothorax or advanced lung disorder with respiratory symptoms. The most frequently encountered complaints are cough, dyspnea, chest pain, weight loss and rise in body temperature (1,3,4,6). Pleuritic chest pain and acute dyspnea can be seen. Hemoptysis is uncommon and should prompt a superimposed infection or a tumor. Cystic bone lesions are present in %4-20 of the cases and may produce localised pain or a pathological bone fracture. Central nervous system involvement with DI is also seen in 15% of PHX cases and is thought to portend a worse prognosis (7,8). Our case presented with the complaints of dyspnea and cough, and diagnosis of the DI had been made.

Physical examination is usually unremarkable. Crackles and digital clubbing are not commonly found (1,4). Clubbing was present in our case.

Characteristic chest x-ray findings in PHX are combination of ill defined or stellate nodules, reticulonodular infiltrates and upper zone cysts or honeycombing. Nodular lesions are more apparent in the early stages of the disorder, while cystic lesions appear later during the course of the disorder. In contrast to other interstitial lung disorders, reticulonodular opacities are seen in the middle and upper zones. Sparing of the costophrenic angles and preservation of lung volumes are highly specific for the disorder. The cases with involvement of the costophrenic angles have poor prognosis (9,10). Pneumothorax was reported in 20-25 % of the cases (10). Pleural thickening is most often due to treated pneumothorax. Hilar and mediastinal lymphadenopathies are infrequent findings and should prompt consideration of malignancy. Computerized tomography (CT) of the thorax is superior to chest x-ray in the evaluation of nodules and cysts. The most important advantage is the detection of cystic structures that are assessed as reticular or emphysematous lesions in chest x-ray (3,9). In our case, though the chest x-ray showed reticulonodular lesions, the HRCT scans revealed only a few nodular lesions, and mostly diffuse cystic lesions which are a sign of late-stage disease.

Spirometry may reveal obstructive, restrictive or combined pattern of pulmonary function abnormality. Total lung capacity is usually normal (1,3,4). Decrease of diffusion capacity nonproportional to spirometric measurements suggests pulmonary vascular involvement by the disorder process. In advanced PHX cases, secondary pulmonary hypertension can develop (11). In our case spirometry revealed pulmonary function abnormality of combined pattern. Diffusion capacity was also decreased.

The pathological cell type of pulmonary PHX is the Langerhans cell. Electron microscopy can demonstrate the classic pentalaminar cytoplasmic inclusion or Birbeck granule (X body). Langerhans cells can be diagnosed by their characteristic staining for S-100 cytoplasmic protein and CD-1A surface antigen (12). Langerhans cells can be detected in increased amounts in BAL of current smokers and in other lung diseases like interstitial pulmonary fibrosis (3,13). In pulmonary PHX, Langerhans cells are characteristically found in clusters and significantly outnumber those seen in other lung disorders. Early inflammatory lesions are centered around the small bronchioles and usually contain a mixture of eosinophils, lymphocytes and neutrophils (3). In our case pathological findings were consistent with PHX.

Clinical history and chest x-ray findings help in the assessment of initial diagnosis. CT or HRCT scans can be diagnostic. A sufficiently characteristic chest CT in association with the appropriate history is believed by many to obviate tissue confirmation. BAL can be of diagnostic value in cases of suspected pulmonary PHX. A BAL cell differential with more than 5 percent Langerhans cells strongly suggests the diagnosis (14). When tissue confirmation is sought, transbronchial biopsy can be sufficient to make the diagnosis. Open or video assisted thoracoscopic lung biopsy is generally definitive (4). In our case, transbronchial biopsy was nondiagnostic, so open lung biopsy was performed to obtain the diagnosis.

Most subjects demonstrate radiological progression with continued smoking and regression with smoking cessation (15). It is therefore important to stress smoking cessation in these patients. The role of corticosteroids in the treatment of PHX is uncertain. Cytotoxic drugs have not been shown

to produce benefit. Lung transplantation has been successfully accomplished in a number of centers (16). In symptomatic bone lesions, radiotherapy may be used. Prednisolone treatment was not helpful in our case since the lesions were mostly cystic late-stage lesions.

The natural history of pulmonary PHX is extraordinarily variable, with some patients experiencing spontaneous remission of symptoms and others progressing to end-stage fibrotic lung disorder. It has also been reported that PHX may be a neoplastic rather than a reactive process (12). Presentation at extremes of age, multi-organ involvement, low diffusion capacity and recurrent pneumothoraces are independent indicators of poor prognosis (10). We didn't detect any progression or remission in lung lesions during follow up.

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