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CASE REPORT

Pulmonary Langerhans Cells Histiocytosis with Concomitant Pleural Effusion: A Rare Presentation in an Adult

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Pulmonary Langerhans cells histiocytosis (PLCH) is a rare disorder of unknown etiology. It usually presents as an isolated lung disease in adults; however, involvement of other organ systems can occur occasionally. In the presence of characteristic findings, high-resolution computed tomography scan may be sufficient for a confident diagnosis of PLCH in an adult smoker. Pneumothorax is the most commonly reported pleural complication of PLCH, and pleural effusion is extremely rare. Herein, we present a case of advanced PLCH in an adult smoker presenting with concomitant exudative pleural effusion.

Key words: Langerhans cells, pulmonary Langerhans cells histiocytosis, bronchoalveolar lavage, pleural effusion

INTRODUCTION

Langerhans cells are differentiated cells of monocyte-macrophage lineage that function as antigen presenting cells. These cells are identified by the presence of two distinctive morphologic features, namely, the presence of Birbeck granules, which appear as pentalaminar, rod-shaped intracellular structures under electron microscopy and the strong presence of the CD1a antigen on the cell surface, a feature not observed in other cells of histiocytic origin. Langerhans cells histiocytosis (LCH) represents a group of disorders where there are clonal proliferation and tissue infiltration of these cells in various organ systems. LCH is classified into single system (one organ or system) or multisystem disease. Adults with LCH usually present as single system disease, whereas multisystem involvement is more common in children. Most commonly affected organs are bones, skin, and pituitary gland. Lymph nodes, liver, spleen, gut, the central nervous system, and the hematopoietic system are less frequently affected. Pulmonary LCH (PLCH) refers to the involvement of lung in isolation or in association with other organ systems. Typically, PLCH is a disease of adult smokers that usually occurs without other organ involvement.[1-3] Pleural effusion in adult LCH is extremely rare described in association with systemic disease.[4-7] We could find only one case report of isolated PLCH presenting with pleural effusion in the adult.[4] We herein report an elderly male presenting with PLCH and concomitant pleural effusion.

CASE REPORT

A 62-year-old man with a history of 20 pack years (10 cigarettes per day for 40 years) of smoking presented with 4 months of progressive breathlessness and productive cough for 2 months. He had no fever, chest pain, hemoptysis, or palpitation. He was a farmer and had no comorbid illness. He denied any history of bone or joint pain, neurological symptoms, or skin lesions. No other family member was suffering from similar symptoms or known to have any cystic lung disease. On admission, his vitals were as follows: respiratory rate = 26/m, heart rate = 102/m, blood pressure = 112/70 mmHg, and oxygen saturation of 95% in room air. General examination was unremarkable. Lung auscultation revealed normal breath sound with bilateral

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diffuse coarse crackles and scattered wheeze. Examination of other systems was normal. His hemoglobin was 13 g/dl, white blood cell count was 8900/cmm (polymorph 60%, lymphocyte 37%, and eosinophil 3%), and platelet count was 246,000/cmm. Erythrocyte sedimentation rate at 1 h was 100. Serum electrolytes, fasting blood glucose, renal and liver function tests were normal. Chest radiograph showed bilateral nonhomogenous opacity predominantly in mid and lower zones that were clearly depicted as reticular and nodular shadows with some cystic shadows in upper zones in the scanogram and homogeneous opacification of the right costophrenic angle suggestive of pleural effusion [Figure 1]. Sputum for acid-fast bacilli and malignant cytology was repeatedly negative. Ultrasound-guided thoracentesis revealed straw-colored fluid that was biochemically an exudate (protein 4.8 g/dl) with high (75 U/L) adenosine deaminase value. Pleural fluid cytology demonstrated predominantly lymphocytes with few neutrophils and mesothelial cells and no malignant cell. High-resolution computed tomography (HRCT) scan performed for better characterization of the lung parenchymal lesion showed bilateral multiple cysts of variable sizes and shapes interspersed with nodules, a feature characteristic of PLCH [Figure 2a], and minimal right pleural effusion [Figure 2b]. Flexible bronchoscopy was performed to obtain bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) for cytohistological confirmation. Following the BAL (100 ml normal saline, 35 ml retrieval) under conscious sedation and supplemental oxygen, patient desaturated rapidly, became restless, and hence, TBLB was not attempted anticipating the risk outweighs the benefit. He required supplemental oxygen for next 36 h to maintain saturation above 90%. He denied a repeat bronchoscopy or further intervention of tissue diagnosis considering the risk-benefit ratio and possible need for invasive ventilation. BAL fluid analysis showed total cell count 320/cmm, histiocytes 72%, alveolar macrophages 22%, lymphocytes 2%, and neutrophils 4%. The histiocytes showed nuclear groove and kidney bean-shaped nuclei typical of Langerhans cells [Figure 3a] and clusters of foamy histiocytes [Figure 3b] were seen in BAL cytology. Specific immunostaining could not be performed on BAL fluid. Both pleural fluid and BAL smear for *Mycobacterium* and subsequently, culture results were reported negative. Thus, the diagnosis of PLCH was based on the characteristic findings in HRCT and BAL cytology. He could not perform a technically acceptable spirometry. Two weeks following bronchoscopy, he developed right pneumothorax necessitating tube thoracostomy. The air leak persisted, and the lung remained unexpanded. His subsequent hospital course was stormy. He continued to be dyspneic and required continuous oxygen supplementation to maintain normal saturation. On his request, he was discharged after thorough prognostication. He received supportive care and low dose prednisolone (20 mg/day) during the hospital stay.

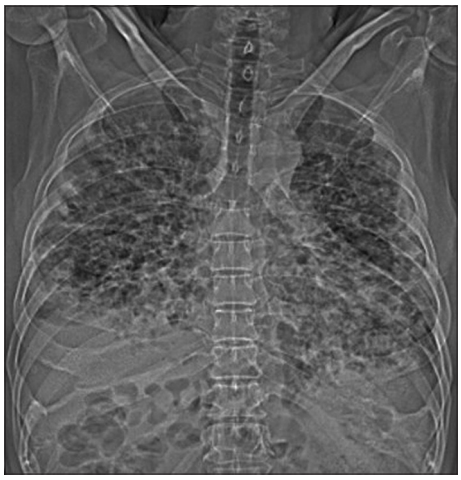

Figure 1: Chest scanogram on admission shows bilateral diffuse reticular and nodular opacities with few cystic lesions in upper zones and minimal right pleural effusion

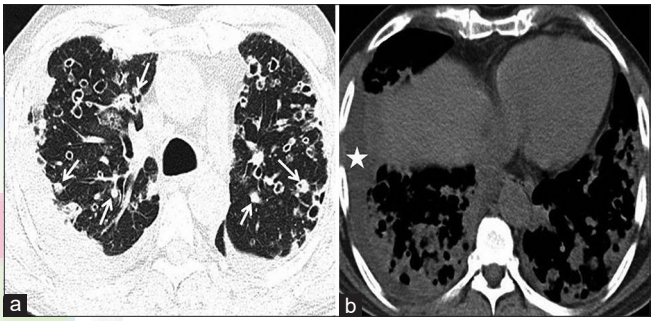

Figure 2: (a) High-resolution computed tomography scan chest demonstrates bilateral multiple cysts of variable sizes and shapes interspersed with surrounding nodules (arrows), (b) soft tissue window shows minimal right pleural effusion (star), and involvement of both lower lobes

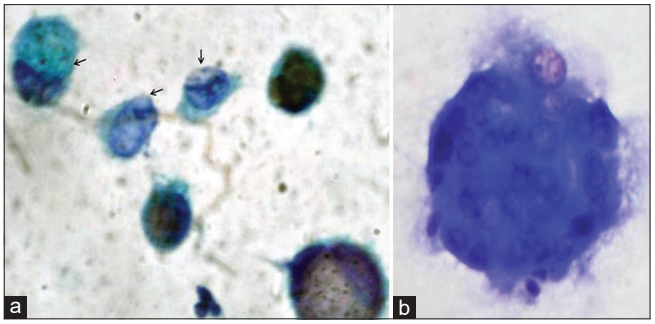

Figure 3: (a) Bronchoalveolar lavage fluid cytology (PAP, ×1000) demonstrates Langerhans cells (arrows) with typical nuclear grooving and (b) cluster of histiocytes

DISCUSSION

The precise incidence or prevalence of PLCH is not known, but available literatures suggest it to be a rare disease accounting for <5% of all biopsy-proven interstitial lung diseases.[1,2] This is most commonly diagnosed in young (20–40 years) adults. Although earlier reports suggested a female preponderance, no such sexual predilection is noted in recent observation. The majority (90%) of the patients are either current or former smoker. PLCH is almost always sporadic in nature and has no genetic or familial predisposition. It affects mostly light-skinned people and is uncommon in the Asian population. The etiopathogenesis of PLCH is imprecisely understood. Normally, Langerhans cells are found in BAL fluid of otherwise healthy smokers. Because the majority of the patients with PLCH are adult smokers, it is proposed that Langerhans cell accumulation occurs as a response to cigarette smoke. This proposition is supported by the demonstration of increased numbers of such cells in the BAL fluid of smokers, along with abnormal T-cell proliferative responses to tobacco glycoprotein in patients with PLCH. Furthermore, PLCH predominates in the upper and mid lung zones, a feature common in many smoking-related lung diseases. However, the lack of association between extrapulmonary LCH lesions and smoking, and the inconsistent result of smoking cessation in resolving PLCH lesions challenges the hypothesis of causal relationship between PLCH and smoking. In addition, it is unclear why only a small percentage of smokers develop this disease, suggesting that other unknown factors have a role. Other postulated etiologies include viral infections, aberrant immune responses by dendritic cells, and cytokine triggers. Granulocyte macrophagecolony-stimulating factor is found in early PLCH granulomas and in bronchiolar epithelial remnants in stellate lesions, suggesting its role in airway Langerhans cells expansion. The presence of interleukin (IL)-1, IL-4, tumor necrosis factor-α, and especially, transforming growth factor-β in extrapulmonary LCH lesions suggests that multiple cytokines participate in the development of PLCH lesions. Langerhans cells from PLCH lesions differ from those present in normal lung or accumulating in other pathologic lung disorders in that these cells express lymphostimulatory molecules that facilitate T-lymphocyte activation, suggesting a role of aberrant immune response in the pathogenesis of PLCH. Although accumulation of Langerhans cells in LCH lesions are clonally-derived, such a feature is uncommon in adult PLCH. At present, available evidence is insufficient to conclude whether PLCH represents a neoplastic or reactive disorder.[1,8]

The clinical presentation of PLCH is variable. Up to 25% of patients are asymptomatic on presentation. Nonproductive cough and dyspnea are the most common presenting symptoms. One-third of patients may present with constitutional symptoms such as weight loss, fever, and anorexia mimicking occult cancer or tuberculosis. Hemoptysis occurs in <5% of patients. The occurrence of hemoptysis in an adult with PLCH should not be attributed to the underlying disease until other causes, such as bronchogenic carcinoma, have been excluded from the study. About 5–15% of patients may present with extrapulmonary manifestations such as bone pain, skin rash, lymphadenopathy, abdominal discomfort due to infiltration of liver and spleen and polyuria, and polydipsia with diabetes insipidus related to hypothalamic involvement. Chest pain is infrequent if occurs it is pleuritic in nature and suggests the onset of pneumothorax. Histologically, Langerhans cells typically proliferate in a peribronchial fashion forming nodules mostly ranging from 1 to 5 mm in diameter, but some may be as large as 1.5 cm in size. These nodules consist of a mixed population of cells with a variable number of Langerhans cells, eosinophils, lymphocytes, plasma cells, fibroblasts, and pigmented alveolar macrophages. Langerhans cells stain positive for CD1a, Langerin (CD207), S-100 protein, and HLA-DR on immunohistochemistry. These nodules undergo cavitations forming the typical cysts that are characteristic of PLCH.[1-3]

Typically, chest radiograph in early stage shows bilateral and symmetric micronodular or reticulonodular shadow predominantly in mid and upper lung zones with sparing of costophrenic angles. Initially, nodules and cysts may appear in conjunction and as the disease advances nodules become infrequent and cystic lesions predominate. In our case, there was diffuse lung involvement with larger cysts in lower lobes, an atypical presentation of PLCH described occasionally. The lung volume appears to be preserved in chest radiograph, and this feature helps to differentiate PLCH from other (excluding lymphangioleiomyomatosis) interstitial lung diseases that are almost always associated with reduced lung volume. HRCT is helpful in differentiating PLCH from other cystic lung diseases. The most commonly noted finding on HRCT is the presence of multiple cysts of variable sizes (usually <2 cm) and shape, thin wall (1 mm or less) in the upper, and middle lobes. The presence of ill-defined, stellate-shaped nodules in the pericystic parenchyma characteristically distinguishes PLCH from other cystic lesions. In the presence of typical HRCT findings, a confident diagnosis of PLCH can be made obviating the need for a lung biopsy. If HRCT is nondiagnostic BAL should be performed to establish the diagnosis. The presence of >5% CD1a-positive cells in BAL fluid is usually considered as confirmatory of PLCH.[1-3] Langerhans cells are characteristically seen as large cells with clear and velvety cytoplasm, oval or kidney-shaped vesicular nuclei with

irregular shapes nucleoli, frequent grooves, and indentation on Giemsa stain. The previous study has shown that analysis of Giemsa-stained BAL fluid is as good as immunostaining in identifying these cells. The percentage of cells positive for CD1a or S-100 protein was comparable to percentages of Langerhans-like histiocytes stained with Giemsa stain. The cellular morphology was similar between the cells that were thought to be Langerhans cells on Giemsa stain to that stained positive for S-100.[9] This suggests that BAL fluid analysis is sufficient to diagnose PLCH in an adult smoker who had consistent clinical and radiological findings. If BAL is inconclusive, TBLB or surgical lung biopsy may be done to confirm the diagnosis. TBLB has a very poor yield (10–40%) due to small tissue sample and patchy nature of the disease and involves a significant risk of pneumothorax, especially in advanced stage.[1-3] Wherever facility available thoracoscopic biopsy is preferable over open lung biopsy. There is no specific therapy for PLCH. Smoking cessation remains the first-line treatment. Symptomatic patients may be given a trial of corticosteroid and response should be assessed. Lung transplantation should be offered to those with disabling symptoms.[1-3]

Most common pleural complication in PLCH is pneumothorax[1,2,10] and pleural effusion is an extremely rare feature described in association with systemic LCH[4,5,7] or intrapleural rupture of eosinophilic granuloma of rib.[6] The mechanism of effusion is probably due to pleural infiltration by histiocytes as demonstrated in pleural biopsy. The effusion is an exudate with high lymphocytes mimicking tuberculosis.[4,5] Sometimes, the effusion may demonstrate high number of eosinophils and histiocytes that may stain positive for S-100 protein.[6,7] In conclusion, PLCH is a rare disorder seen almost always in adult smokers. Very rarely, the patients may present with concomitant pleural effusion with cytological and biochemical characteristics similar to tuberculosis.

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Conflicts of interest

There are no conflicts of interest.

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