

Case Report

Diffuse interstitial lung infiltrates in a smoker with human immunodeficiency virus infection

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ABSTRACT

Pulmonary Langerhans cell histiocytosis is a rare interstitial lung disease characteristically affecting middle-aged smokers. It has unpredictable clinical course and may be associated with malignant neoplasms. Opportunistic lung infections are frequently considered when patients with Human immunodeficiency virus (HIV) infection present with respiratory symptoms and an abnormal chest X-ray. Though fiberoptic bronchoscopy with bronchoalveolar lavage is diagnostic for infectious etiologies, surgical lung biopsies are preferred to diagnose noninfectious lung diseases and to help guide appropriate therapy. In the present study, we report a case of progressive bilateral lung infiltrates in a smoker with HIV infection which presented a diagnostic dilemma in view of coexistent HIV infection. Analysis of clinical symptomatology aided by surgical lung biopsy helped in diagnosis.

KEY WORDS: Human immunodeficiency virus, interstitial lung disease, open lung biopsy

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INTRODUCTION

Pulmonary langerhans cell histiocytosis (PLCH) is a rare disorder and the true prevalence is unknown. At one of a specialty referral center in the United States, PLCH was identified in less than 5% of patients who underwent lung biopsy for the diagnosis of interstitial lung disease. We are reporting a unique case of PLCH in association with HIV (Human Immunodeficiency Virus) infection.

CASE HISTORY

A 58-year-old African-American woman presented to our hospital with 2-week history of progressive dyspnea, nonproductive cough, and fever with night sweats. She admitted to weight loss of 35 pounds over a period of 8 to 10 months. She denied chest pain and hemoptysis. Significant medical history included hypertension,

diabetes mellitus, chronic obstructive pulmonary disease, an inadequately treated latent tuberculosis infection, and a sexually acquired HIV infection. She was an active smoker for 44 years. She denied intravenous drug use. Her home medications included metformin, metoprolol, nifedipine, enalapril, montelukast, tiotropium (via oral inhalation), and albuterol for rescue use. She was noncompliant with antiretroviral medications (efavirenz, emtricitabine, and tenofovir) and sulfamethoxazole/trimethoprim prophylaxis.

On physical examination, there was no palpable lymphadenopathy; lungs were clear to auscultation, cardiovascular examination was normal with no added sounds. Chest X-ray [Figure 1a] revealed diffuse interstitial nodular and cystic lung infiltrates predominantly in the upper lobes bilaterally. There was no pleural effusion or mediastinal lymphadenopathy. Arterial blood gas (ABG) study done on room air showed pH-7.49; PaCO₂ - 39 mmHg; PaO₂ - 70 mmHg; HCO₃ - 30 mmol/l; and O₂ saturation - 94%. Complete blood count was within normal limits. The CD4 count was 194/mm³ with a viral load of 2199 copies. Three sputum smears were negative for acid fast bacilli. Left heart catheterization during prior hospitalization six months before had revealed left ventricular ejection fraction of 65% with noncritical coronary artery occlusion on coronary angiogram. CT scan of chest [Figure 1b] showed emphysematous changes with diffuse bilateral pulmonary

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nodules predominantly in upper lobes and no significant mediastinal lymph nodes. PFT (pulmonary function test) showed Forced expiratory volume in one sec (FEV₁) - 1.94 l (82% of predicted), Forced vital capacity (FVC) - 2.69 l (91% of predicted), Ratio of FEV₁/FVC - 72%, Forced Expiratory Flow (FEF)_{25-75%} - 1.34 l/sec (43% of predicted), Total lung capacity (TLC) - 4.78 l (81% of predicted), Residual volume (RV) - 2.09 l (94% of predicted), and Diffusion capacity of carbon monoxide (DL_{CO}) - 9.9 ml/mmHg/min (38% of predicted) with no bronchodilator response. Patient agreed to undergo video-assisted thoracoscopy and surgical lung biopsy of right lung. Specimens were taken from upper, middle, and lower lobe.

On gross appearance, all three specimens from the right lung showed multiple white nodules (0.2 to 0.4 cm) having dense white parenchyma. These nodules were scattered in between normal dark tan spongy lung parenchyma with no necrotizing nodules and with no airway involvement. Microscopic examination with H and E stain [Figure 2a] showed pulmonary macrophages, mild interstitial inflammation, and mild to moderate interstitial fibrosis with patchy scarring and anthracotic pigment deposition. Multiple interstitial nodules comprising of central areas of Langerhans type histiocytes [Figure 2a], with eosinophils and other inflammatory cells were noted. The immunohistochemical stains for S100 [Figure 2b] and

CD1a [Figure 2c] which are confirmatory for Langerhans cells were done and were strongly positive. Special stains (Ziehl-Neelsen and Gomori methenamine silver) failed to reveal any *Mycobacteria*, fungi, or pneumocystis jiroveci.

DISCUSSION

PLCH, also previously called as eosinophilic granuloma of the lung, or pulmonary histiocytosis X, is a rare disease and constitutes only 3 to 5% of biopsy-confirmed chronic diffuse interstitial lung disease.^[1] It is primarily seen in young adults between 20 and 40 years of age; 90 to 95% of patients are smokers, and many are heavy smokers.^[2] Caucasians are affected more commonly than individuals of African or Asian descent.

It involves clonal proliferation of Langerhans cell which are important antigen-presenting cells of the immune system and are differentiated from the monocyte-macrophage line.^[3] There is proliferation of Langerhans cells in response to cytokines and growth factors secreted by alveolar macrophages in response to cigarette smoke. Early inflammatory lesions surround the smaller bronchioles and usually contain an admixture of eosinophils, lymphocytes, and neutrophils. Pulmonary involvement in LCH is characterized by a granulomatous infiltration of the alveolar septa and bronchial walls by Langerhans

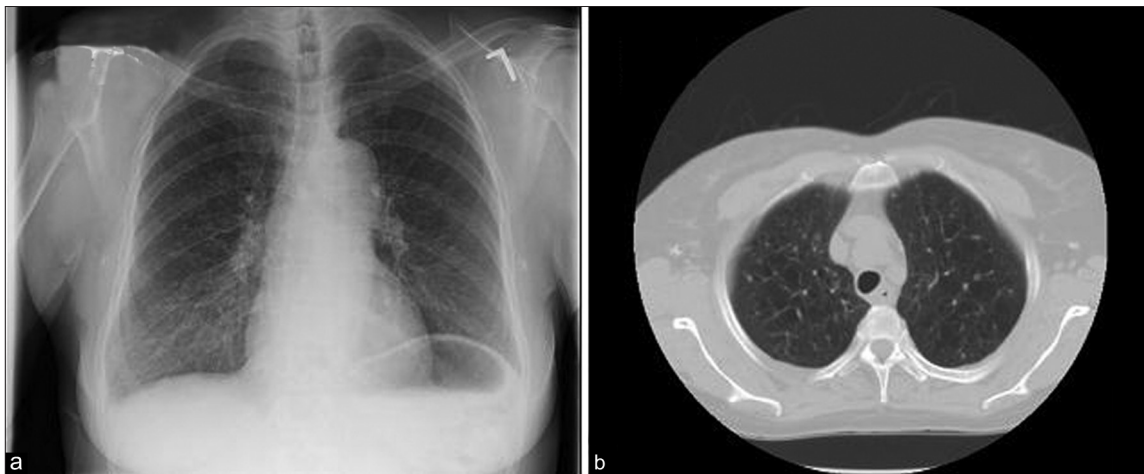


Figure 1: (a) X-ray of chest PA view; (b) CT scan of chest

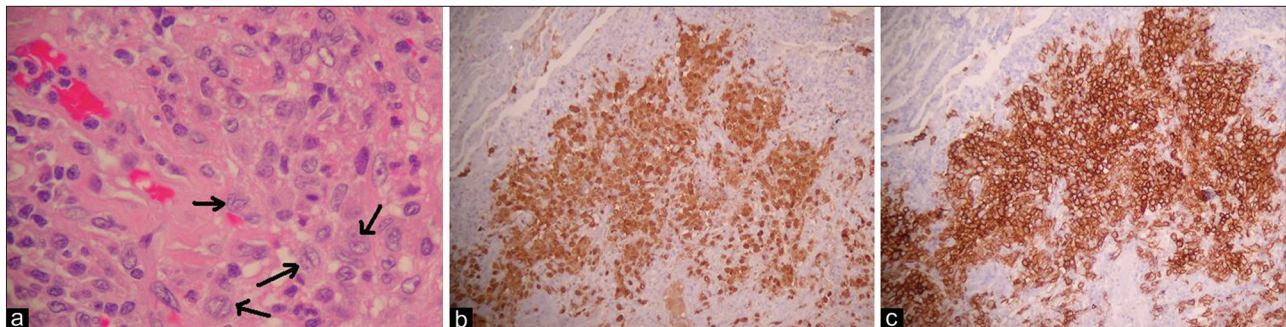


Figure 2: (a) Lung tissue with H and E stain; (b) Lung tissue with immunostain for S-100; (c) Lung tissue with immunostain for CD1a antigen

cells that produces small, 1 to 5 mm nodules. The infiltrate can result in progressive lung destruction and widespread cystic change. There is often a predominance of disease in the mid to upper zones of the lung, in contrast to the typical lower zone predominance of idiopathic pulmonary fibrosis. Lesions frequently extend widely into the parenchyma of the lung surrounding the bronchovascular structures, producing the so-called stellate lesions that are characteristic of this disorder. Interstitial fibrosis and small cyst formation occur with advancing disease.

Clinical presentation is variable.^[4,5] Some patients are asymptomatic, diagnosed incidentally because of lung nodules and cysts on radiographs. The symptomatology of our patient was matching most of the common symptoms seen in a patient with PLCH which include nonproductive cough (56-70%), dyspnea (40-87%), chest pain, which is frequently pleuritic (10-21%), fatigue (approximately 30%), weight loss (20-30%), fever (15%), and recurrent spontaneous pneumothorax (15-25%).^[6] A number of malignant and nonmalignant tumors have been found in association with PLCH.^[7] These include bronchogenic carcinoma, Hodgkin's and non-Hodgkin lymphoma, pulmonary carcinoid tumor, and mediastinal ganglioneuroma. The malignancy may precede, follow, or occur concomitantly with the diagnosis of PLCH. The carcinogenic effect of cigarette smoke is probably the cause of some of these tumors.

The combination of multiple cysts and nodules, with a mid to upper zone predominance, interstitial thickening, preservation of lung volume, and costophrenic angle sparing in a young smoker, as seen in our case, is so characteristic that it can be diagnostic of PLCH.^[8-10] The differential diagnosis depends on the stage of the disorder. The TLC was well-preserved in this case, as seen in the majority. Airflow limitation and hyperinflation occur in a minority of patients, typically in patients with more advanced, cystic disease.^[11] A disproportionate reduction in carbon monoxide diffusion capacity was noted as seen in 60 to 90% of patients with PLCH.^[4] Other notable features of PFT were a reduction in FEV₁. Measurement of arterial blood gases in the patient at rest usually shows a normal alveolar-arterial oxygen difference and a normal PCO₂ and pH. Thus, resting arterial blood gases are an insensitive indicator of disease.

Definitive diagnosis in these kinds of chronic diseases, if necessary, can be made by identification of Langerhans cell granulomas in lung biopsy samples acquired by video-assisted thoracoscopy. Biopsy sites are selected on the basis of high-resolution CT findings.^[12] Transbronchial biopsy has a low diagnostic yield (10-40%) because of the patchy nature of the disease and the small amounts of tissue obtained.^[13] The course of pulmonary disease varies. Remission occurs in approximately 25 to 30% of patients, stabilization in 30 to 50%, and progression of the disease in 25 to 30% with complications such as pulmonary fibrosis and pulmonary hypertension.^[2,6] Death from respiratory failure or cor pulmonale occurs in 5%. Asymptomatic

or minimally symptomatic patients tend to have the best outcomes. Recurrent pneumothoraces, lower FEV₁/FVC ratio, and higher total lung volume at diagnosis are associated with decreased survival. Treatment consists of smoking cessation which usually stabilizes the symptoms in most patients.^[14] Immunosuppressive therapies, such as glucocorticoids and cytotoxic agents, are of limited value. Corticosteroids are used in progressive or systemic disease. Cytotoxic agents (e.g., cyclophosphamide) can be employed for patients who do not respond to smoking cessation and steroids. No treatment has been confirmed to be useful, and no double-blind therapeutic trials have been reported. Our patient has remained clinically stable over a follow-up period of 2 years without any specific therapy. Follow-up PFT done 2 years since the first one revealed FEV₁ - 1.92 l (82% predicted), FVC - 2.95 l (101% of predicted), FEF 25-75% - 0.93 l/sec (30% of predicted), FEV₁/FVC% - 65%, TLC - 5.24 l (89% predicted), RV - 2.29 l (102% of predicted), and DL_{CO} - 9.2 ml/mmHg/min (38% predicted). ABG done on room air along with the PFT was as follows: PH - 7.45; PaCO₂ - 36 mm Hg; PaO₂ - 62 mmHg; HCO₃ - 25 mmol/l; and O₂ saturation - 92%.

Four cases of extrapulmonary LCH in association with HIV have been reported.^[15-18] To our knowledge, this is the first case of PLCH in association with HIV to be reported. The stable course of the disease despite coexistent HIV is difficult to explain.

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