CASE REPORT

Pulmonary Langerhans cell histiocytosis concurrent with bronchial hyperresponsiveness on a nonsmoker adult presenting with spontaneous pneumothorax

Wudthichai Suttithawil*, Pattanasak Lertpradit, Panuch Yenarkarn, Satien Techapaitoon, Manop Huntrakoon, Yongyudh Ploysongsang

Department of Pulmonary and Critical Care Medicine, Bumrungrad International Hospital, 33 Sukhumvit 3 (Soi Nana Nue), Wattana, Bangkok 10110, Thailand

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Summary
We report a nonsmoker adult with histologically proven pulmonary Langerhans cell histiocytosis (PLCH) with bronchial hyperresponsiveness (BHR) presenting with spontaneous pneumothorax. An 18-year-old, nonsmoker student had shortness of breath for a decade. PFTs and lung volume study (obtained one month post-operation) showed a mild obstructive airway with bronchodilator response and a decreased DLco with a positive methacholine challenge test (PC20<8 mg/ml). Chest radiograph revealed right-sided pneumothorax and diffuse reticular infiltrates. HRCT revealed scattered, thin-walled lung cysts in all lobes without sparing of the costophrenic angles. The patient underwent a thoracotomy for wedge resection and the diagnosis of PLCH was confirmed by a demonstration of the accumulated Langerhans cells histiocytes (positive CD1a) in lung tissue. Pneumothorax was managed by bleblectomy and pleurodesis. This case report demonstrates BHR concurrent with PLCH on a nonsmoker patient. The combination of BHR and PLCH may confer a detrimental synergistic effect on the respiratory symptoms, deterioration of lung function, lung cysts and hence spontaneous pneumothorax on these patients.

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Introduction
Pulmonary Langerhans cell histiocytosis (PLCH), an uncommon disorder of young adults, characterized by a monoclonal proliferation and infiltration of multiple organs by activated Langerhans cells, one of the family of dendritic cells without known genetic factor. Even though the association between PLCH and cigarette smoking seems strong, the occurrence of this disease among young children and nonsmoker adults needs explanations. Common organ involvement includes lungs, bone, skin, pituitary gland,
liver, lymph nodes and thyroid glands. The diagnosis was generally made by the demonstration of Birbeck granules in the lesional cells on electron microscopy or the presence of CD1a antigenic determinants on the surface of cells by immunohistochemistry technique. The etiology of LCH remains unestablished to date. Pathologically, there is an accumulation of activated histiocytes, organizing into granulomas, particularly involving the distal bronchioles. Even though the disease characteristically affects the small airways and can produce clinical manifestations mimicking asthma, there has never been a report, demonstrating BHR and its impact on these patients. We describe an interesting case of PLCH on nonsmoker with positive MCT, presenting with spontaneous pneumothorax.

Case report

An 18-year-old man had a decade long-history of progressive dyspnea, chest pain, cough and paroxysms of wheezes. He had been diagnosed to have asthma and received asthmatic medications for 4 years. Over the past few years, he had more frequent episodes of chest tightness, pleuritic chest pain, abdominal pain, anorexia, and weight loss. Chest examination revealed decreased breath sound on the right-sided and wheezes at both lower lungs. He had no finger clubbing and skin lesions. Laboratory studies showed a hemoglobin of 14.6 g/dL, a WBC count of 11.1 x 10^9/L (65.5% neutrophils, 5.8% eosinophil), alpha-1 antitrypsin level of 183 mg/dL (normal values: 90–200) and normal urine analysis. Skin prick tests showed a positive reaction to house-dust-mite. Radiographs of the chest revealed right-sided pneumothorax with reticular infiltrates in bilateral lungs. The HRCT of the chest revealed scattered, variable-sized thin-walled lung cysts, all lobes were involved without sparing of the costophrenic angle regions (Figure 1) Fiberoptic bronchoscopy showed no abnormalities. PFTs, obtained one month post-operation, revealed a mild obstruction with reversible to bronchodilator of 12% and 420 mL improvement in FEV1% (Figure 2); FEV1, 2.27L (60% of predicted); FEV1/FVC ratio, 70.9%; residual volume (RV), 2.54L (222% of predicted); total lung capacity (TLC), 5.83L (104% of predicted); RV/TLC, 43% of predicted normal; and diffusing capacity of the lung for carbon monoxide (DLco), 22.3 mL/mmHg/min (72% of predicted). MCTs demonstrated bronchial hyperresponsiveness (BHR) (PD_{20} FEV1 <8 mg/ml). Thoracotomy was performed to obtain a biopsy specimen (Figure 3), bleblectomy and pleurodesis. The lung biopsy showed a densely cellular infiltrate of histiocytes and other inflammatory cells within the interstitial and airspaces (Figure 4). Corticosteroid in addition to a combination of inhaled corticosteroid and long-acting β2 agonist was administered as a maintenance therapy for controlling PLCH and BHR. The patient was doing well after 1-month of follow-up.

Discussion

PLCH has an unpredictable course and can cause significant pulmonary impairment owing to its complications. The most common presenting symptoms are cough, exertional dyspnea and constitutional symptoms. Other uncommon symptoms include chest pain, pneumothorax and hemothysis. Chest examinations may reveal normal, rhonchi, wheezing, or decrease breath sounds. The interval between the onset and the diagnosis is highly variable with an
average of 6 months (range: a few days and 5 years). In our patient, the age at onset of his symptoms and the diagnosis was 10 years and 18 years, respectively.

Pulmonary function tests in PLCH are variable. It may be normal in 10–15% whereas some show only a little impairment despite extensive radiological changes. Typically, obstructive dysfunction in PLCH is associated with worsening of the cystic lesions, which coalesce into bullae in advanced stage. Owing to cellular aggregation and encroachment of distal bronchioles, it can cause small airways luminal narrowing with associated air trapping and secondary lung cyst formation. It appears to correlate with the extent of the HRCT abnormalities and exercise limitation. In advanced stage of the disease, PFTs may show restrictive or combination. The most consistent abnormality of lung volume study is the reduction of DLco. The degree of airway obstruction seems to be out of proportion of the total cigarette consumption and should reflect the predominantly bronchiolar involvement of PLCH. Our patient is non-smoker. Reversible obstructive changes on his PFTs and positive MCT accompanying a response to the asthmatic medications should suggest asthma as a comorbid disease.

BHR defined as an exaggerated bronchoconstrictor response to a wide variety of stimuli that generally elicits little or no response in a normal individual. This entity could be found in healthy adult up to 27%. Recently, it was found to be associated with the development of respiratory symptoms, an increased annual loss of FEV1, asthma and COPD. Only one study described the patients, demonstrating significant bronchial hyperreactivity to carbachol than the controls. However, there has never been a study, describing PFTs including MCT on the patients with PLCH.

Most common chest radiograph are peribronchiolar micronodular and interstitial infiltration, with a predominance of middle- and upper-lobe involvement. Characteristically, HRCT also reveals nodular abnormality accompanied by cystic changes, predominantly at the same areas. It is usually bilateral and symmetric involvement. In later stages, cystic changes may become more prominent and can coalesce into bullae with honeycombing appearance. However, the distribution of lung cysts in our patient did not spare the lower lung base and costophrenic angles as the typical patterns. This process may be accelerated by an air trapping of BHR.

Considering PLCH is a smoking-related interstitial lung disease and progressive cystic changes that predispose to
occurrence of pneumothorax. Thin-walled confluent cysts, nodules with or without cavitation, hyperinflation in addition to probable asthma in our patient could contribute to the scattered large bullae and spontaneous pneumothorax (Figure 1).\(^2,6\) Pneumothorax can occur as the initial manifestations of PLCH in 11% with the reported incidence between 4% and 17%. Some authors recommend the interventions since the first episode of pneumothorax, particularly in the case of low surgical risk owing to the higher recurrent rate of secondary spontaneous pneumothorax (11–79%).\(^6\)

To date, there is no standard treatment for PLCH. Several patients resolve spontaneously with smoking cessation alone. Corticosteroid has been the mainstay treatment for symptomatic PLCH whereas combined chemotherapy is administered in severe multisystemic LCH. In case of rapid deterioration and development of respiratory failure, lung transplantation should be considered.\(^3,4\) Administration of corticosteroid in addition to a combination of inhaled corticosteroid and long-acting \(\beta_2\) agonist improved his symptoms with a much improved quality of life. Physicians should consider this disease even in nonsmokers.

Conflicts of Interest Statement

Wudthichai Suttithawil, Pattanasak Lertpradit, Panuch Yenar-karn, Satien Techapaitoon, Manop Huntrakoon, and Yongyudh Ploysongsang have declared no conflict of interest.

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