ECRONICON OPEN ACCESS

EC PULMONOLOGY AND RESPIRATORY MEDICINE

Review Article

Pulmonary Langerhans Cell Histiocytosis

Ali Nawaz Khan[1]*, Klaus Irion[2], Carolyn Allen Carolyn[3] and Koteyar Shyam Sunder Radha Krishna[4]

[1]*Consultant Radiologist/Professor Honorary, North Manchester General Hospital, United Kingdom*

[2]*Consultant Cardiothoracic Radiologist, Manchester Royal Infirmary the United Kingdom and Honorary Professor, Manchester University, United Kingdom*

[3]*Consultant Thoracic Radiologist and Clinical Director, North Manchester General Hospital, United Kingdom*

[4]*Consultant Radiologist, North Manchester General Hospital, Manchester, United Kingdom*

***Corresponding Author:** Ali Nawaz Khan, Consultant Radiologist/Professor Honorary, North Manchester General Hospital, United Kingdom.

Received: February 21, 2018; **Published:** March 14, 2018

Abstract

Pulmonary histiocytosis, eosinophilic granuloma, also known as pulmonary Langerhans cell histiocytosis X (PLCH). PLCH is a known but a rare cause of diffuse interstitial lung disease; linked to tobacco smoking; affecting young individuals usually in the third and fourth decades of life PLCH characterized by destructive granulomas containing a large number of Langerhans cells. The granulomas exclusive affect the terminal bronchioles, in young adult smokers. The disease may be diffuse or multifocal. High-Resolution Computed Tomography (HRCT) is a useful tool in the diagnosis of PLCH by allowing the identification of lung cysts and nodules. Bronchoalveolar Lavage (BAL) strongly supports the diagnosis in an occasional patient. The pathogenesis of PLCH remains unknown. A lung biopsy provides a specific diagnosis of PLCH; however, the procedure is invasive and not devoid of complications. BAL fluid Langerhans cells are not increased in PLCH; but, there is a low expression of CD80 and plasmacytoid and myeloid dendritic cells (DCs). The sensitivity and specificity of DCs is considerably higher in the currently recommended marker CD1a; however, CD80-positive bronchoalveolar lavage fluid has been shown to more optimal for the diagnosis of PLCH. The course of PLCH is unpredictable, varying from benign self-limiting disease with spontaneous regression, or a more severe path with progression to respiratory failure and death. The condition, when confined to the lungs, has a favorable outcome, with cessation of smoking. The authors consider PLCH of interest because of the low the frequency of the disease.

Keywords: *Pulmonary Histiocytosis; Eosinophilic Granuloma; Langerhans Cell Histiocytosis X; Diffuse Interstitial Lung Disease; HRCT; Tobacco Smoking; Bronchoalveolar Lavage; Lung Biopsy; Low Expression of CD80 and Plasmacytoid and Myeloid Dendritic Cells (DCs) Unpredictable Course, Favorable Outcome, with Cessation of Smoking*

Introduction

Microscopic examination of the lungs in PLCH reveals infiltration by activated Langerhans cells (LHC). The LHC is thought to represent differentiated cells of the dendritic cell system. The LHC is typically found in the skin, reticuloendothelial system, the lungs, the pleura and the heart. The LHC can be identified by immunohistochemical staining techniques/electron microscopy by demonstration of Birbeck granules. Birbeck granules are rod-shaped cytoplasmic bodies with a central linear density and a striated appearance, solely found in LHC; first described in 1961 by Birbeck MS, Breathnach AS, Everall JD [1].

The Birbeck granules form a part of normal Langerhans cell histology. The presence of Birbeck granules in lungs allows differentiation of Langerhans cell histiocytoses from other lung proliferative cell lines [1-3].

The pediatric histiocytic disorders, which refer to Letterer-Siwe disease and Hand-Schüller-Christian disease are typically a multiorgan disease; in contrast to PLCH, which usually affect the lung. However, 4-20% of patients with PLCH have been reported to have cystic lesions in the bones [4].

The cause of pulmonary histiocytosis X is unknown, but two recent series suggest a relationship with cigarette smoking [5].

The actual prevalence of PLCH is unknown. One study from the United States reported an incidence of < 5% of patients who underwent lung biopsy for the diagnosis of interstitial lung disease [6].

In another study, of 15 patients with PLCH were diagnosed after lung biopsy, compared with 274 cases of sarcoidosis. In PLCH most patients the lung changes resolve or stabilizes, leaving minor residual changes. Only a minority of patients with PLCH progress to parenchymal lung disease that is ultimately fatal [5,6].

The accumulation of Langerhans cells with exposure to cigarette smoking is based on the hypothesis that the early histologic and radiographic findings are peribronchiolar and most prominent in the upper and middle lung zones, as seen in other smoking-related lung diseases. The lung infiltrates in PLCH are composed of eosinophils, lymphocytes, plasma cells, macrophages, Langerhans cells, and fibroblasts, which form granulomatous nodules around the terminal and the respiratory bronchioles, destroying small airway. End-stage PLCH is associated with fibrotic stellate scarring often associated with lung cysts and honeycombing, which may be indistinguishable from other chronic interstitial diseases [5].

Discussion

Pathophysiology

Microscopic examination of the lungs in PLCH reveals infiltration by activated Langerhans cells (LHC). The LHC is thought to represent differentiated cells of the dendritic cell system. The LHC is typically found in the skin, reticuloendothelial system, the lungs, the pleura and the heart. The Langerhans cells can be identified by immunohistochemical staining techniques/electron microscopy by demonstration of Birbeck granules. Birbeck granules are rod-shaped cytoplasmic bodies with a central linear density and a striated appearance, solely found in Langerhans cells; first described in 1961 by Birbeck MS, Breathnach AS, Everall JD [1]. The Birbeck granules form a part of normal Langerhans cell histology. The presence of Birbeck granules in lungs allows differentiation of Langerhans cell histiocytoses from other lung proliferative cell lines [2,3]. The pediatric histiocytic disorders, which refer to Letterer-Siwe disease and Hand-Schüller-Christian disease are typically a multiorgan disease; in contrast to PLCH, which usually affect the lung. However, 4 - 20% of patients with PLCH have been reported to have cystic lesions in the bones [4]. The cause of pulmonary histiocytosis X is unknown, but two recent series suggest a relationship with cigarette smoking [5]. The actual prevalence of PLCH is unknown. One study from the United States reported an incidence of < 5% of patients who underwent lung biopsy for the diagnosis of interstitial lung disease [6].

In another study, of 15 patients with PLCH were diagnosed after lung biopsy, compared with 274 cases of sarcoidosis. In PLCH most patients the lung changes resolve or stabilizes, leaving minor residual changes. Only a minority of patients with PLCH progress to parenchymal lung disease that is ultimately fatal [5,6].

The accumulation of Langerhans cells with exposure to cigarette smoking is based on the hypothesis that the early histologic and radiographic findings are peribronchiolar and most prominent in the upper and middle lung zones, as seen in other smoking-related lung diseases. The lung infiltrates in PLCH are composed of eosinophils, lymphocytes, plasma cells, macrophages, Langerhans cells, and fibroblasts, which form granulomatous nodules around the terminal and the respiratory bronchioles, destroying small airway. End-stage PLCH is associated with fibrotic stellate scarring often associated with lung cysts and honeycombing, which may be indistinguishable from other chronic interstitial diseases [5].

Epidemiology

A study from Belgium reported that 3% of patients referred from 20 lung disease centers for further evaluation of diffuse lung disease were diagnosed with PLCH [7].

A large Japanese study estimated the prevalence of PLCH at 0.27 males and 0.07 females per 100,000 population based on hospital discharge summaries over a 1-year period. The authors added that epidemiological data available from the developing world was scant [8].

PLCH is a rare entity, and no definitive epidemiologic data are available on racial and gender bias. The peak incidence of PLCH occurs in the 20- to 40-year age group [12]. However, a study by Vassallo., *et al*. a survey of 102 patients showed a female predominance of 61%. Patients with PLCH commonly present with shortness of breath, cough, fatigue and occasionally by chest pain secondary to a pneumothorax. Clinical examination of PLCH reveals non-specific signs; including rales, a wheeze, or decreased breath sounds on auscultation. The pulmonary function tests in PLCH also show a mixed pattern may reveal an obstructive, restrictive, or mixed. There is a reduction in the carbon monoxide diffusion capacity in the majority of patients. A decrease in carbon monoxide diffusing capacity is present in up to 90% of patients [9-11].

Case Reviews

Spontaneous Pneumothorax: Minghini A and Trogdon SD described a Recurrent spontaneous pneumothorax in pulmonary histiocytosis X. in a young adult male that was successfully treated with thoracoscopic stapling of bullae and pleural abrasion [14].

Callebaut W, Demedts M, and Verleden G published a detailed retrospective analysis of 8 cases of PLCH to bring the clinical features, the imaging features and the therapeutics aspects up-to-date. The patients represented 2.8% of cases of PLCH registered with pulmonary physicians in Flanders. In this study, 75% of patients were active smokers. Clinically patients with PLCH presented with a cough, shortness of breath and non-specific constitutional symptoms. Recurrent spontaneous pneumothorax was frequent was relatively common at 37.5%, during the disease, requiring chemical or surgical pleurodesis. The spirometric pattern was variable in PLCH, but there was a significant reduction in the CO-transfer factor in all the patients. Lung nodules and cystic lesions on imaging, but transbronchial biopsies were found insensitive. Open lung biopsies were much more efficient, leading to diagnosis in 6 of 8 patients. Systemic staging revealed a second focus in half the patients. Corticosteroids and immune suppressive drugs showed no apparent response. The ultimate treatment of patients with PLCH associated with diffuse interstitial lung disease in 25% is lung transplantation, however bilateral pleurodesis is regarded as a contraindication for lung transplantation in some centers [15].

Prognosis

The course and prognosis in PLCH are variable and is related to smoking cessation; there is a progression of disease in patients who continue to smoke, but the condition stabilizes or regresses in patients that quit smoking. There are several factors associated with an adverse prognosis; including extremes of age, chronic lung changes such as cysts and honeycombing are seen on imaging, prolonged use of corticosteroids, abnormal lung function, multiorgan involvement a recurrent pneumothorax, severe pulmonary artery hypertension, and patients with diabetes insipidus. The prognosis is favorable in patients with radiographic sparing of the costophrenic, and cellular infiltrates and lack of fibrosis on a lung biopsy specimen. Some patients may progress to end-stage lung fibrosis. A retrospective study by Vassallo R. and associates showed median survival with PLCH of 12.5 years after diagnosis. Another European study showed a median survival of 13 years in PLCH [10,13].

The imaging findings in PLCH depends at the stage of the lung disease at the time of diagnosis. In the early stage of disease may show ill-defined nodules. As the disease is linked to smoke inhalation; the middle and upper lung zones predominately involved. The nodules may cavitate due to cystic degeneration, and with the progression of the disease, there is a superimposition of the reticular pattern seen as cysts on a CXR. [12]. The combination of cysts and lung parenchymal undergo fibrosis and eventually to a honeycomb pattern [9]. HRCT plays a pivotal role in diagnosis/differential diagnosis of PLCH.

The diagnosis PLCH is apparent on HRCT when both ill-defined nodules and cysts are seen in a heavy smoker. However, the accuracy of HRCT falls considerably when nodules or cysts alone are present. Most of these cases are confirmed by lung biopsy [9,12].

Favourable outcome; Miadonna A., *et al*. described a patient with PLCH that presented with pyrexia, shortness of breath, non-specific constitutional symptoms, including nocturnal hyperhidrosis and chest pain, that had a favourable outcome. The HRCT and lung biopsy were suggestive of PLCH. The disease was confined to the lungs to the lungs; the patient responded well to cessation of smoking and corticosteroids. A follow-up HRCT showed partial resolution of lung lesions [16].

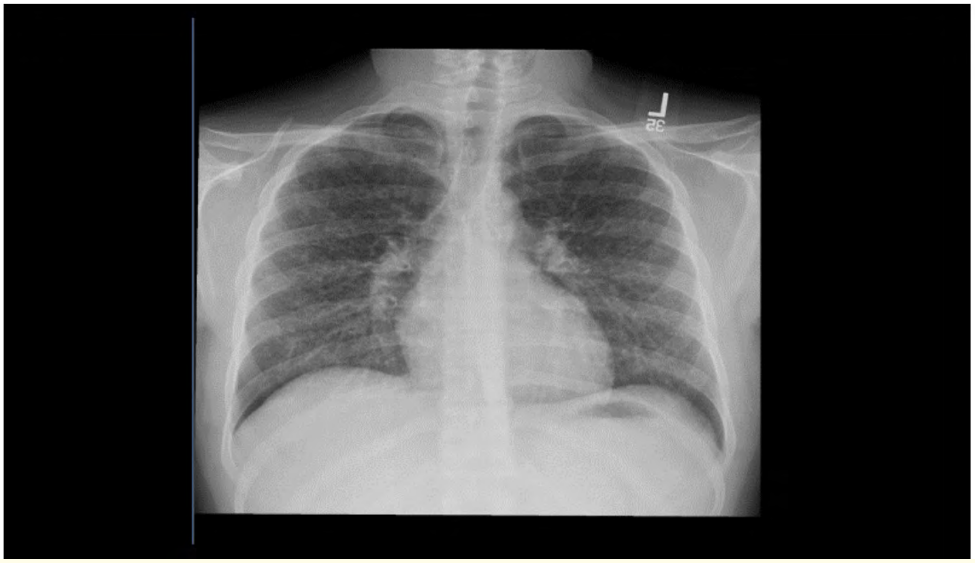

Figure 1: *A CXR of 27-year-old-male with a Histiocytosis X with a long history of smoking.*

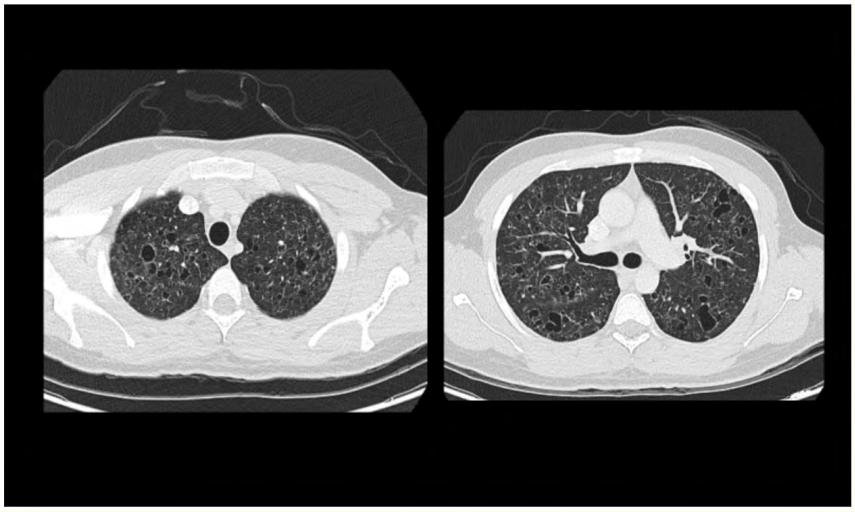

Figure 2: *HRCT axial scans on the same patient as in figure 1: Show a combination of cysts, lung parenchymal undergo fibrosis and a honeycomb pattern. HRCT plays a pivotal role in diagnosis/differential diagnosis of PLCH.*

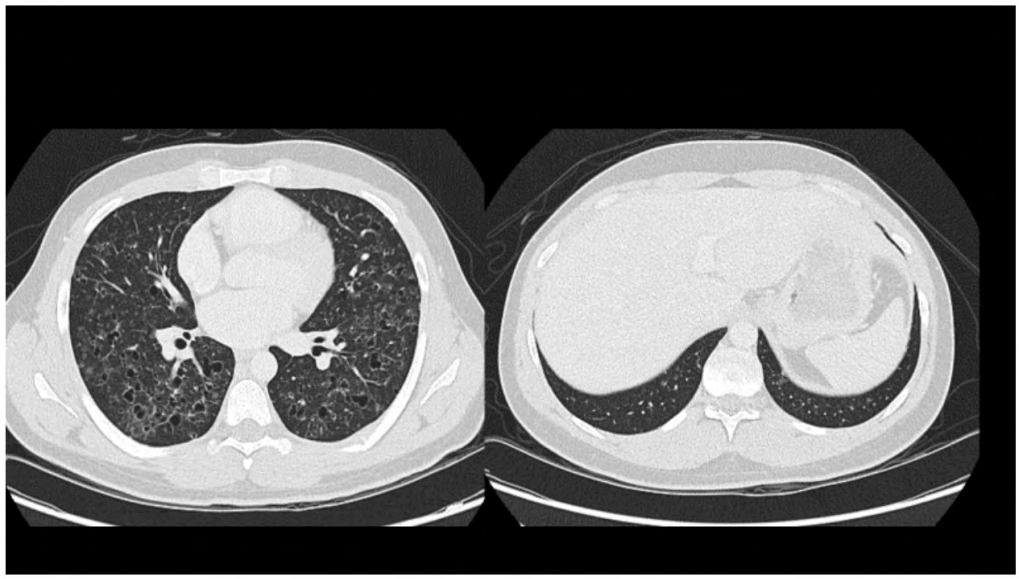

Figure 3: *HRCT axial scans on the same patient as in figure 1: Show a combination of cysts, lung parenchymal undergo fibrosis and a honeycomb pattern. HRCT plays a pivotal role in diagnosis/differential diagnosis of PLCH.*

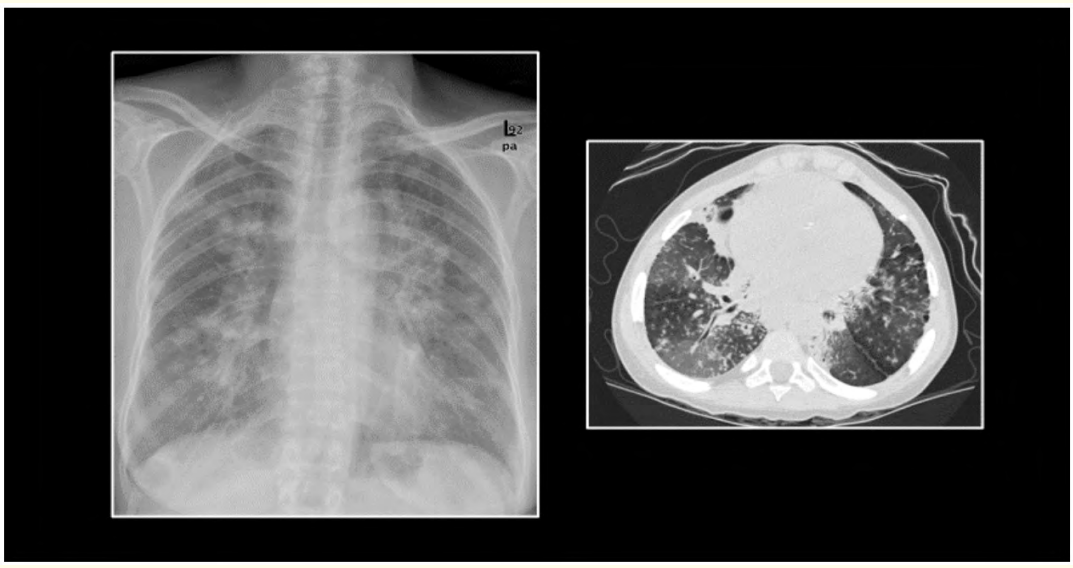

Figure 4: *Histiocytosis X; a 33-year-old man with a long history of smoking, showing interstitial shadowing on a CXR and HRCT.*

Conclusion

PLCH is a rare cause interstitial lung disease; linked to tobacco smoking; affecting young individuals usually in the third and fourth decades of life. PLCH is associated with destructive granulomas containing a large number of Langerhans cells. The granulomas exclusive affect the terminal bronchioles, in young adult smokers. The disease may be diffuse or multifocal. HRCT is an essential tool in the diagnosis of PLCH by allowing the identification of lung cysts and nodules. BAL strongly supports the diagnosis in an occasional patient. The pathogenesis of PLCH remains unknown. A lung biopsy provides a specific diagnosis of PLCH; however, the procedure is invasive and not devoid of complications. PLCH has an unpredictable course, varying from benign self-limiting disease with spontaneous regression, to a more aggressive course leading to respiratory failure and death. PLCH has a favorable outcome when the disease is confined to the lungs has a favorable outcome, with cessation of smoking. The authors consider PLCH of interest because of the low the frequency of the disease.

Bibliography

1. Birbeck MS., *et al*. "An electron microscope study of basal melanocytes and high-level clear cells (Langerhans cells) in vitiligo". *Journal of Investigative Dermatology* 37.1 (1961): 51-64.

2. Podbielski FJ., *et al*. "Eosinophilic granuloma of the lung and rib". *Asian Cardiovascular and Thoracic Annals* 17.2 (2009): 194-195.

3. Mc Dermott R., *et al*. "Birbeck granules are subdomains of the endosomal recycling compartment in human epidermal Langerhans cells, which form where langerin accumulates". *Molecular Biology of the Cell* 13.1 (2002): 317-335.

4. Szturz P., *et al*. "FDG-PET positive pilomatrixoma--reconsidering multicentricity in Langerhans cell histiocytosis". *Nuclear Medicine Review. Central and Eastern Europe* 17.2 (2014): 94-96.

5. Colby TV and Lombard C. "Histiocytosis X in the lung". *Human Pathology* 14.10 (1983): 847-856.

6. Gaensler EA and Carrington CB. "Open biopsy for chronic diffuse infiltrative lung disease: clinical, roentgenographic, and physiological correlations in 502 patients". *Annals of Thoracic Surgery* 30.5 (1980): 411-426.

7. Thomeer M., *et al*. "Registration of interstitial lung diseases by 20 centres of respiratory medicine in Flanders". *Acta Clinica Belgica* 56.3 (2001): 163-172.

8. Watanabe R., *et al*. "Clinico-epidemiological features of pulmonary histiocytosis X". *Internal Medicine* 40.10 (2001): 998-1003.

9. Abbott GF., *et al*. "Pulmonary Langerhans cell histiocytosis". *RadioGraphics* 24.3 (2004): 821-841.

10. Vassallo R., *et al*. "Pulmonary Langerhans'-cell histiocytosis". *New England Journal of Medicine* 342.26 (2000): 1969-1978.

11. Vassallo R., *et al*. "Clinical outcomes of pulmonary Langerhans'-cell histiocytosis in adults". *New England Journal of Medicine* 346.7 (2002): 484-490.

12. Sundar KM., *et al*. "Pulmonary Langerhans cell histiocytosis: emerging concepts in pathobiology, radiology, and clinical evolution of disease". *Chest* 123.5 (2003): 1673-1683.

13. Delobbe A., *et al*. "Determinants of survival in pulmonary Langerhans' cell granulomatosis (histiocytosis X). Groupe d'Etude en Pathologie Interstitielle de la Société de Pathologie Thoracique du Nord". *European Respiratory Journal* 9.10 (1996): 2002-2006.

14. Minghini A and Trogdon SD. "Recurrent spontaneous pneumothorax in pulmonary histiocytosis X". *American Surgeon* 64.11 (1998): 1040-1042.

15. Callebaut W., *et al*. "Pulmonary Langerhans' cell granulomatosis (histiocytosis X): clinical analysis of 8 cases". *Acta Clinica Belgica* 53.5 (1998): 337-343.

16. Miadonna A., *et al*. "Favourable outcome of a case of pulmonary Langerhans' cell histiocytosis". *Monaldi Archives for Chest Disease* 55.1 (2000): 3-5.

Volume 7 Issue 4 April 2018