CASE REPORT

Rapid resolution of pulmonary Langerhans cell histiocytosis

Sy Giin Chong,¹ Mario Samaha,² Georges Samaha,² Brian Casserly¹

¹Midwestern Regional Hospital, Limerick, Ireland

²Post Graduate Medical School, University of Limerick, Limerick, Ireland

Correspondence to

Mario Samaha,
mario.j.samaha@gmail.com

SUMMARY

A 38-year-old woman with a long-term history of smoking presented to the lung cancer clinic with weight loss and recurrent lower respiratory tract infections. A diagnosis of Langerhans cell histiocytosis was made by specimen samples taken from video-assisted thoracoscopic surgery. She was advised to stop smoking, which she adhered to. She was followed up in the respiratory clinic with pulmonary function tests every 6 months, which were all normal. Follow-up chest x-ray showed complete resolution of the multifocal interstitial infiltrates, and with smoking cessation, the patient has sustained an excellent quality of life.

BACKGROUND

Langerhans cell histiocytosis (LCH) is a rare disease, which affects men twice as often as women. Lung involvement manifests as isolated lung lesions (pulmonary LCH) or part of a multi-system disease including skin rashes, hepatosplenomegaly or the development of diabetes insipidus. Clear guidance from the literature on the most appropriate treatment therapy is lacking. This case demonstrates that smoking cessation alone is an extremely effective treatment for pulmonary LCH. It also highlights that pulmonary LCH needs to be considered in rapidly progressive lung disease in a woman smoker.

CASE PRESENTATION

A 38-year-old woman was referred to rapid access lung cancer clinic owing to recurrent lower respiratory tract infections and weight loss of greater than a stone over the past 6 months. Of note, she was a smoker of 20-pack year. There was no history of recent travel. Her background history was non-contributory. She was not on any medication. On examination, she looked cachectic and her weight was around 48.3 kg. Her vitals were normal. There was no evidence of clubbing, lymphadenopathy or hepatosplenomegaly. Chest was clear on auscultation with reduced air-entry bilaterally. Blood tests were normal, including inflammatory markers.

INVESTIGATIONS

Chest x-ray (CXR) (figure 1) on admission showed multifocal infiltrates throughout both lungs. This suggested either a peribronchial or endobronchial pattern of disease, or tuberculosis (TB), both of which needed to be excluded. No osseous involvement was seen on skeletal radiograph. The patient tested negative for both antineutrophil cytoplasmic antibody and HIV. The patient then underwent CT

Figure 1 Chest x-ray on admission showing multifocal infiltrate (29-9-2011).

of chest, which showed that both lungs were diffusely abnormal. CT brain was normal. There were ill-defined pulmonary nodules measuring 8 mm with small cavitating lung lesions (figure 2). She had bronchoscopy with biopsy performed. Bronchoscopy showed no endobronchial lesions and a normal biopsy. There was no evidence of malignancy or TB on bronchoalveolar lavage. She then had repeat CT chest that showed significant interval deterioration. She was referred to the cardiothoracic team for video-assisted thoracoscopic

Figure 2 CT thorax on admission showed ill-defined pulmonary nodules with cavitating lung lesions.

To cite: Chong SG, Samaha M, Samaha G, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-009948

surgery (VATS) procedure. Specimens taken from VATS showed numerous airway-centred and airway-destructive nodules composed of eosinophils and large histiocytes with vesicular chromatin that were CD1a. This is consistent with LCH (figure 3).

TREATMENT

The patient was advised to quit smoking, which she adhered to. Follow-up CXR taken on 10 August 2012 (figure 4) and 11 January 2013 showed complete resolution of the multi-focal interstitial infiltrates.

OUTCOME AND FOLLOW-UP

The patient was last reviewed in outpatients on 12 April 2013, 2 years since the diagnosis, and is well and asymptomatic. She is still tobacco free with no signs of relapse. Diffusing capacity of the lung for carbon monoxide (DLCO) studies performed on her last outpatient visit on follow-up showed a predicted DLCO and DLCO/alveolar volume (Va) of 73% and 87%, respectively.

DISCUSSION

LCH is a rare disease of unknown aetiology.¹ It is characterised by an uncontrolled proliferation and accumulation of clonal dendritic cells in organs.¹ These cells are identical to the Langerhans cells found on the epidermis of the skin and mucous membranes, hence its name.¹ It is hypothesised that LCH resulted from an interplay between clonal evolution of the dendritic cells and inflammatory cells, including antigen-presenting cells and regulatory lymphocytes.¹ LCH cells can affect single or multiorgan system, and form characteristic granulomas with lymphocytes, eosinophils, neutrophils and multinucleated giant cells.¹

LCH has been classified as single organ involvement, such as pulmonary LCH, or LCH with multiorgan involvement (also termed as systemic histiocytosis X, Letterer-Siwe disease and Hand-Schuller-Christian disease).² Pulmonary Langerhans cell histiocytosis (PLCH) was first described by Farinacci in 1951.² Pulmonary involvement may also be part of a multisystem disease.³ It is estimated that cystic bone is found in 4% and 20% of patients with PLCH.³ In addition, there are various case reports demonstrating PLCH with the involvement of other organs such as pituitary gland, skin, gut, heart and brain.³

The exact prevalence of PLCH is unknown.⁴ Reports by Colby⁴ and Lombard in 1983 stated that only 15 patients were

Figure 3 Sections of lung show numerous airway-centred and airway-destructive nodules composed of eosinophils and large histiocytes with vesicular chromatin that are CD1a.

Figure 4 Repeat chest x-ray showed complete resolution of the bilateral interstitial infiltrate (10-8-2012).

identified with PLCH in lung biopsy specimens over a 6-year period. Over the same period, 274 patients were diagnosed with sarcoidosis, demonstrating the rarity of the disease. While it is said that PLCH frequently affects young adults⁵ multisystem LCH frequently affects young children¹; however, the disease can be found in any age group.

Over 90% of patients with PLCH have a smoking history. Few hypotheses exist to explain the association of smoking with PLCH.⁴ First, the cigarette smoke causes the accumulation of Langerhans cells through the activation of local cytokines such as tumour necrosis factor- α and granulocyte-macrophage colony stimulating factors.⁴ Bombesin-like peptides from neuroendocrine cells in the lung are also secreted upon activation by cigarette smoke, promoting the growth of lung fibroblasts.⁴ Moreover, tobacco glycoprotein contained within cigarette smoke induces lymphocyte differentiation and lymphokine production within the lung causing them to respond abnormally.⁴

Development in gene expression study has also contributed to the research on PLCH by showing an association between smoking and PLCH.⁶ Through gene expression study it is shown that osteopontin, a glycoprotein, is present abundantly in patients with PLCH. This glycoprotein has cytokine properties and prochemotactic activity for macrophages, monocytes, Langerhans cells and dendritic cells.⁶ Prasse *et al*⁷ had demonstrated that nicotine stimulates further release of osteopontin on cells obtained by bronchoalveolar lavage of patients with PLCH as compared with other patients with interstitial lung disease.

The diagnosis of PLCH requires a high index of clinical suspicion.⁶ About 25% of patients are asymptomatic at presentation.⁵ Patients most commonly presented with shortness of breath and an unproductive cough.⁶ Constitutional symptoms such as fever, sweats and weight loss are the main features in about 15–20% of patients with PLCH.⁶ Reports of patients presenting with spontaneous or recurrent pneumothorax are recognised and are most likely owing to destruction of lung parenchyma with associated cystic changes.⁸

The association of PLCH with malignant disease such as bronchogenic carcinoma and lymphoma has been described.⁵ The development of PLCH may occur before, during or after the development of the malignant disease.⁵ The presence of smoking history and pulmonary fibrosis predispose a patient to bronchogenic carcinoma.⁵ There are also reports of patients

who develop PLCH following irradiation or chemotherapy for Hodgkin's lymphoma.⁴ The reason for these remains unknown.⁶ Therefore, careful and close clinical follow-up of the patients with PLCH should be taken.⁵ Pathologists examining the pathological specimens should conduct a thorough and careful examination needed to identify any potential indicator of development of malignancy.

Most case studies reported symptomatic and radiological improvement in patients with PLCH after undertaking smoking cessation. Patients with rapidly progressive PLCH and patients with multisystem LCH are treated with a combination of glucocorticoids and systemic chemotherapy.¹ These will inhibit the proliferation of LCH, lymphocytes and macrophages by switching off the cytokine expression.¹

Six factors are associated with a poor prognosis in PLCH. These include extremes of age, multiple pneumothoraces, extensive multisystem disease, prolonged constitutional disturbances, extensive cysts or honeycombing on chest radiography and markedly decreased diffusing capacity.⁵ For patients with multisystem LCH, the prognosis is related to the age of onset, the involvement of high-risk organs at diagnosis, and response to therapy.¹

While substantial progress has been made to familiarise ourselves with PLCH, there is still much that remains unknown. Some of the unresolved issues are related to its pathogenesis, characterisation of the disease, evaluation, evolution and treatment of PLCH. The link between cigarette smoke exposure and disease development remains to be defined, as well as the external factors predisposing to the development of PLCH. Needless to say, advice regarding smoking avoidance and cessation remains the most fundamental step, not just to prevent the development of PLCH and malignancy, but also to maintain general pulmonary health.

Contributors SGC, MS and GS wrote the initial draft of the case report, followed up on the patient's clinical progression and researched discussion. BC is consultant in charge of patients care, provided the case and acted as editor of the final manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- Smoking cessation appears to be the cornerstone of treatment for pulmonary Langerhans cell histiocytosis (LCH)
- Rapid radiological and clinical resolution of LCH is possible with smoking cessation.
- Corticosteroids and chemotherapy are second line treatment even for rapidly progressing LCH.
- Local and multisystem LCH are different diseases with different prognoses.
- Always consider local LCH as differential diagnosis in women smokers.

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