Clinical and radiological evolution in patients with pulmonary Langerhans’ cell histiocytosis

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ABSTRACT

Background: Pulmonary Langerhans’ cell histiocytosis (LCH) is a diffuse, smoking-related lung disease characterised pathologically by proliferation of abnormal Langerhans’ cells, cyst formation and vascular abnormalities, and physiologically by a decreased diffusing capacity. The aim of this study was to describe our experience with pulmonary LCH at our institution during the past 30 years, with particular reference to diagnosis and long-term outcome.

Patients and methods: Seven patients, two men and five women, mean age 33 years (range 26-49 years), who had been evaluated for pulmonary LCH, were retrospectively studied. All available clinical, diagnostic and pathological data were included.

Results: The patients presented with symptoms of dyspnoea, cough, pleuritic pain, anorexia and fatigue. Chest X-ray and high-resolution computed tomography (HRCT) showed bilateral nodular and cystic lesions, with a predilection for the middle and upper lung zones. In the majority of patients, lung function tests showed a decrease in diffusing capacity. In six patients the diagnosis of pulmonary LCH was made after immunohistochemical examination of an open lung biopsy specimen. In one patient a confident diagnosis was made radiologically.

During serial follow-up, median seven years (range 1-28 years), three patients stopped smoking and in four patients the tobacco consumption remained unchanged. For the whole group the evolution was benign, with all patients being asymptomatic or showing improvement in symptoms and regression of radiological signs.

Conclusion: Radiographic studies often provide clues to the diagnosis, but may not obviate the need for open lung biopsy in the majority of cases. Our study shows that irrespective of smoking cessation, spontaneous regression of symptoms and radiological signs and long-term survival are possible.

INTRODUCTION

Pulmonary Langerhans’ cell histiocytosis (LCH) appears to be primarily a reactive process in which non-lethal, non-malignant clonal evolution of LCH cells may arise in the setting of non-clonal LCH hyperplasia. Several organs may be involved in LCH. The term pulmonary LCH is used to refer to disease in adults that affects the lung, either in isolation or in addition to other organ systems. The natural history of pulmonary LCH is variable, difficult to predict and ranges from spontaneous resolution to progressive respiratory insufficiency and death, even after many years of apparent clinical stability. Since 1951, when two patients were reported with exclusively pulmonary LCH, more than one hundred cases have been reported. Recently, three review articles were published. However, the diagnosis is not readily recognised by all clinicians and pathologists. It has been suggested that smoking may play a role in causing LCH, because more than 90% of the patients with this disease are or have been smokers.

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The purpose of this study was to review a personal experience with pulmonary LCH, and describe the spectrum of the disease in terms of clinical presentation, pathological manifestations, diagnostic findings, and course.

**Patients and Methods**

During the last 30 years, the diagnosis of pulmonary LCH was made in seven patients at our institution. There were two men and five women, whose ages ranged from 26 to 49 years, with a mean of 33 years, at the time of diagnosis (tables 1 and 2). We retrospectively reviewed the records of these patients, including all available clinical, diagnostic and pathological data. Clinical follow-up ranged from 1 to 28 years, with a median of seven years.

**Results**

The results of the clinical, radiographic and pathological data and the results of the lung function tests at the time of first presentation and last follow-up are outlined in tables 1, 2 and 3.

**Clinical presentation**

All patients had symptoms for between two to three months before they were admitted to hospital. Almost all patients complained of dyspnoea and cough. A few of them had symptoms including pleuritic pain, anorexia and fatigue (cases A, B, C and E). Patient F had a bone lesion in the right femur. All patients had a history of smoking. There was no relation with occupation, hobbies or contact with pets, including birds. There was no history or evidence of exposure to medications, tuberculosis contact or recent travel. Previous medical histories were unremarkable.

**Radiology**

A chest radiograph was performed in all patients. On the chest X-ray six patients had bilateral nodular abnormalities in the upper lobes, one of them also had increased interstitial markings, and patient D had increased interstitial markings with reticulation. A high-resolution computed tomography (HRCT) of the thorax was carried out in five patients. The HRCT showed cysts and/or nodules in the lungs, with a predilection for the middle and upper lung zones in these patients.

**Lung function tests**

Lung function, including volumes (vital capacity: VC), forced expiratory volume in 1 second (FEV₁), total lung capacity (TLC) and diffusing capacity (DLCO and KCO), was measured according to the guidelines of the European Respiratory Society (ERS) and expressed as obstructive (low FEV₁ and low FEV₁/VC ratio) or restrictive syndrome (low TLC).

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**Table 1**

Clinical and diagnostic features of the seven patients at time of presentation

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>AGE AT TIME OF DIAGNOSIS</th>
<th>SEX</th>
<th>TOBACCO USE</th>
<th>SYMPTOMS</th>
<th>CHEST RADIOGRAPH</th>
<th>HRCT</th>
<th>OPEN LUNG BIOPSY</th>
<th>BAL</th>
<th>TRANSBRONCHIAL BIOPSY</th>
<th>DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>29</td>
<td>F</td>
<td>10 py</td>
<td>Cough, anorexia</td>
<td>Diffuse nodular opacities upper lobes</td>
<td>Multiple micronodules with central cavities</td>
<td>LCH</td>
<td>N</td>
<td>ND</td>
<td>Definitive LCH</td>
</tr>
<tr>
<td>B</td>
<td>49</td>
<td>M</td>
<td>40 py</td>
<td>Dyspnoea, cough, pleuritic pain</td>
<td>Diffuse bilateral nodular shadows</td>
<td>Multiple thin-walled cysts upper lobes and middle lobes</td>
<td>LCH</td>
<td>N</td>
<td>ND</td>
<td>Definitive LCH</td>
</tr>
<tr>
<td>C</td>
<td>49</td>
<td>F</td>
<td>5 py</td>
<td>Dyspnoea, cough, fatigue</td>
<td>Diffuse nodular opacities upper lobes</td>
<td>Diffuse increased interstitial markings with macro- and micronodules</td>
<td>LCH</td>
<td>N</td>
<td>ND</td>
<td>Definitive LCH</td>
</tr>
<tr>
<td>D</td>
<td>34</td>
<td>F</td>
<td>15 py</td>
<td>Dyspnoea, cough</td>
<td>Diffuse bilateral increased interstitial markings with reticulation</td>
<td>Bilateral thin-walled cysts with some micronodules upper lobes</td>
<td>LCH</td>
<td>N</td>
<td>ND</td>
<td>Definitive LCH</td>
</tr>
<tr>
<td>E</td>
<td>33</td>
<td>F</td>
<td>8 py</td>
<td>Dyspnoea, cough, pleuritic pain</td>
<td>Bilateral increased interstitial markings with nodules</td>
<td>Bilateral increased interstitial markings with small cysts</td>
<td>NP</td>
<td>N</td>
<td>ND</td>
<td>Presumptive LCH</td>
</tr>
<tr>
<td>F</td>
<td>26</td>
<td>M</td>
<td>10 py</td>
<td>Dyspnoea, cough</td>
<td>Bilateral nodular opacities upper lobes</td>
<td>Bilateral nodular opacities upper lobes</td>
<td>NP</td>
<td>LCH</td>
<td>NP</td>
<td>Definitive LCH</td>
</tr>
<tr>
<td>G</td>
<td>31</td>
<td>F</td>
<td>5 py</td>
<td>Dyspnoea, cough</td>
<td>Bilateral nodular opacities upper lobes</td>
<td>Bilateral nodular opacities upper lobes</td>
<td>NP</td>
<td>LCH</td>
<td>NP</td>
<td>Definitive LCH</td>
</tr>
</tbody>
</table>

HRCT = high-resolution computed tomography, py = pack years, LCH = Langerhans’ cell histiocytosis, BAL = bronchoalveolar lavage, N = normal, NP = not performed, ND = not diagnostic.
The diffusing capacity was expressed as percentage of predicted.

At the time of diagnosis four patients had a normal lung function, two (cases E and F) had an airway obstruction and one (case A) an obstructive and restrictive pulmonary function (table 2). The majority had a decreased diffusing capacity.

**Bronchoalveolar lavage (BAL)**

Lavage with 4 x 50 ml saline was performed in five patients. The differential cell counts of the BAL fluid showed normal results. Neither microbiological agents nor other foreign substances were found. We could not demonstrate any sign of malignancy.

**Histology**

Transbronchial biopsies were performed in five patients and showed no specific abnormalities on immunohistochemical examination.

Six patients underwent an open lung biopsy. In these patients the diagnosis of pulmonary LCH was made after immunohistochemical examination of the biopsy specimen, which confirmed the presence of Langerhans’ cells based on their morphology and immunophenotype (S100, CD1a, CD68 positive). None of the specimens were examined for the presence of Birbeck granules by electron microscopy. Patient F also had a histopathologically proven bone lesion of LCH.

### Table 2

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>FOLLOW-UP (YEARS)</th>
<th>SMOKING CESSATION?</th>
<th>TOBACCO USE</th>
<th>RESOLUTION OF SYMPTOMS?</th>
<th>REMISSION ON HRCT AND CHEST X-RAY?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>7</td>
<td>Yes</td>
<td>10 py</td>
<td>Complete</td>
<td>Complete</td>
</tr>
<tr>
<td>B</td>
<td>5</td>
<td>No</td>
<td>49 py</td>
<td>Complete</td>
<td>Complete</td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>Yes</td>
<td>5 py</td>
<td>Complete</td>
<td>Partial</td>
</tr>
<tr>
<td>D</td>
<td>4</td>
<td>Yes</td>
<td>15 py</td>
<td>Complete</td>
<td>Partial</td>
</tr>
<tr>
<td>E</td>
<td>7</td>
<td>No</td>
<td>12 py</td>
<td>Complete</td>
<td>Complete</td>
</tr>
<tr>
<td>F</td>
<td>22</td>
<td>No</td>
<td>32 py</td>
<td>Partial</td>
<td>Complete</td>
</tr>
<tr>
<td>G</td>
<td>28</td>
<td>No</td>
<td>15 py</td>
<td>Partial</td>
<td>Partial</td>
</tr>
</tbody>
</table>

HRCT = high-resolution computed tomography, py = pack years.

### Table 3

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>FOLLOW-UP (YEARS)</th>
<th>SMOKING CESSATION?</th>
<th>TOBACCO USE</th>
<th>RESOLUTION OF SYMPTOMS?</th>
<th>REMISSION ON HRCT AND CHEST X-RAY?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>7</td>
<td>Yes</td>
<td>10 py</td>
<td>Complete</td>
<td>Complete</td>
</tr>
<tr>
<td>B</td>
<td>5</td>
<td>No</td>
<td>49 py</td>
<td>Complete</td>
<td>Complete</td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>Yes</td>
<td>5 py</td>
<td>Complete</td>
<td>Partial</td>
</tr>
<tr>
<td>D</td>
<td>4</td>
<td>Yes</td>
<td>15 py</td>
<td>Complete</td>
<td>Partial</td>
</tr>
<tr>
<td>E</td>
<td>7</td>
<td>No</td>
<td>12 py</td>
<td>Complete</td>
<td>Complete</td>
</tr>
<tr>
<td>F</td>
<td>22</td>
<td>No</td>
<td>32 py</td>
<td>Partial</td>
<td>Complete</td>
</tr>
<tr>
<td>G</td>
<td>28</td>
<td>No</td>
<td>15 py</td>
<td>Partial</td>
<td>Partial</td>
</tr>
</tbody>
</table>

**DLCO and KCO** = lung diffusing capacity of carbon monoxide, **FEV1** = forced expiratory volume in 1 second, **VC** = vital capacity, **TLC** = total lung capacity.
Treatment
All patients were advised to stop smoking. Patient F, who also had an extrapulmonary manifestation of LCH, received corticosteroid therapy for one year and furthermore the bone lesion was removed surgically.

Outcome
During serial follow-up three patients stopped smoking and four continued.
In the patients who continued smoking, the tobacco consumption remained unchanged throughout the years.
Two patients were symptom-free after a period of three months and two patients showed stabilisation of symptoms during follow-up. In this group, patients B, E and F had complete radiological remission, confirmed both on chest radiography and HRCT, after a median follow-up of ten months and patient G showed a stabilisation of the radiographic abnormalities. The lung function showed slow progressive airway obstruction in patients E, F and G and was still normal in patient B. The diffusing capacity decreased in patient B, was stable in patients E and G and was still normal in patient F.
In the non-smokers group all patients were symptom-free after a mean follow-up of three months. In this group patient A had a complete radiographic remission and patients C and D showed an improvement in the radiological abnormalities. The pulmonary lung function was still normal in patients C and D after serial follow-up and showed a progressive airway obstruction with the occurrence of hyperinflation in patient A. The diffusing capacity improved in patient C, improved to a normal value in patient A and was still normal in patient D.
For the whole group the evolution was benign, with all patients being asymptomatic or showing improvement of symptoms. Spontaneous regression of symptoms and radiological signs occurred in most cases.

DISCUSSION
Incidence, age at diagnosis, aetiology
The precise incidence and prevalence of LCH are unknown. The incidence is probably underestimated. The relative frequency in men and women is controversial. Most patients are 20 to 40 years of age. The overwhelming majority of patients have a history of smoking. Little is known about the aetiology and pathophysiology of pulmonary LCH. It is assumed that smoking is a major risk factor for LCH. \(^{1,9-11}\)
Cigarette smoking is associated with the induction of several immune mechanisms, which may be responsible for the local accumulation of Langerhans’ cells on the epithelial surface of the lower respiratory tract and the subsequent development of lung injury. \(^{12-18}\) Besides, there is evidence implicating the role of genetic and additional environmental factors. \(^{19,44}\)

Pathology, BAL findings
Histologically, pulmonary LCH begins as a proliferation of Langerhans’ cells along the small airways and the pulmonary blood vessels. \(^{19}\) The cellular lesions expand to form nodules. The nodules include Langerhans’ cells (LHC), eosinophils, lymphocytes, plasma cells, fibroblasts and pigmented alveolar macrophages. \(^{44,45}\) With progression fibrotic nodules are identified, which may connect with other nodules to form a honeycomb-like structure. At the end stage the histological findings consist of fibrosis and honeycombing, without features of LCH. The LHC can be characterised by their morphotype (nuclei with fine chromatin and grooves of folds), immunophenotype (S100, CD1a, CD68 positive) and structure (cytoplasmic Birbeck granules) (figure 1). \(^{23,24}\)
Differential cell counts of the BAL may reveal a moderate increase in the percentage of neutrophils and eosinophils above that seen in smoking control subjects. The proportion of lymphocytes is normal or reduced and the CD4/CD8 ratio is decreased, as in cigarette smokers. \(^{11}\) In our study the differential cell counts of the BAL were normal in five cases. \(^{8}\)
Immunohistochemical confirmation of the diagnosis may be obtained by BAL, transbronchial lung biopsy or surgical lung biopsy. The presence of more than 5% CD1a-stained cells in the BAL makes the diagnosis of pulmonary LCH very likely. \(^{25-28}\) The test, however, has quite a low sensitivity (<25%). \(^{4}\) As transbronchoscopic biopsy has a poor sensitivity, the usual procedure to obtain sufficient specimens of lung tissue for pathological interpretation is open lung biopsy. \(^{29}\)
In our study the diagnosis was made by open lung biopsy in six patients.

Figure 1
Details of the cellular infiltrate in lesions of pulmonary LCH (115x), including Langerhans’ cells with the typical delicate and folded nuclei (panel A, haematoxylin and eosin chain) and the presence of the CD1a antigen on the cell surface (panel B)
Clinical signs, pulmonary function tests
Our study confirms that patients with LCH usually present with a non-productive cough, dyspnoea on exertion or chest pain.9,10 Fever, weight loss, haemoptysis and wheezing are occasionally noted, and spontaneous pneumothorax occurs in about 10% of patients.9,10 Bone involvement, presenting in one patient in our series, is found in a minority of cases in which there is lung disease.9,10 Less commonly associated findings are posterior pituitary involvement with diabetes insipidus and skin involvement.9,10 Less commonly, up to 25% of patients are asymptomatic at presentation.10 Development of dissemination after the initial diagnosis of pulmonary LCH is very rare.

The physical examination can be normal, but decreased breath sounds and rates are common. Individuals with LCH often present to medical attention with abnormal lung physiology. The most sensitive parameters in early disease are the pulmonary diffusing capacity and arterial blood gases at rest and/or during exercise.31 At time of presentation, the results of pulmonary function tests are either normal or demonstrate mild obstructive, restrictive or mixed abnormalities.10

Radiological findings
In most patients, the chest radiograph shows typically diffuse, symmetrical micronodular, reticulonodular and interstitial abnormalities, predominating in the upper and middle lobes (figure 2).10,31,32 HRCT has proved to be of considerable value in the diagnosis of pulmonary LCH and allows a precise identification of both nodular and cystic lesions.31 The combination of diffuse, irregularly shaped cystic spaces with small peribronchial nodular opacities, predominantly in the middle and upper lobes, allows the clinician to make a diagnosis of LCH without open lung biopsy (figure 3).31,34 We agree that the diagnosis can be strongly suggested radiologically, but diseases that may resemble pulmonary LCH, such as sarcoidosis, tuberculosis, lymphangioleiomyomatosis, chronic hypersensitivity pneumonitis and idiopathic pulmonary fibrosis, need to be excluded by histopathological analysis of an open lung biopsy specimen.

Treatment, outcome, follow-up
Because of the rare occurrence and the high rate of spontaneous remissions of the disease, there are no reliable data on the efficiency of the various treatment regimens. It appears reasonable to stop smoking, but there are no conclusive data on the effect of this measure. In most patients this advice leads to stabilisation of symptoms.35,36 A few reports also document objective radiographic and physiological improvement in lung function after smoking cessation.35,36 In one study, continuation of tobacco consumption was not associated with diminished survival.37 In the study by Friedman et al. there was no evidence that a longer...
or heavier smoking history predisposed to more severe disease.\(^{18}\) Irrespective of smoking cessation, we found a complete or partial improvement in symptoms and radiographic data in almost all patients with pulmonary LCH. Results of prospective treatment with systemic corticosteroids are fairly encouraging.\(^{31}\) This treatment should generally be attempted only after smoking cessation has been achieved and progression of symptoms or disease occurs. Corticosteroids in combination with cytostatics were tried, but the usefulness of this therapy could not be demonstrated as in generalised disease.\(^{39}\)

Lung transplantation may be proposed as an efficient treatment for end stage LCH, although there is a risk of recurrence of the disease when systemic disease is present or when patients continue smoking.\(^{38}\) The natural history of pulmonary LCH is variable, difficult to predict and ranges from spontaneous resolution to progressive respiratory insufficiency and death, even after many years of apparent clinical stability.\(^{1}\) Therefore patients with pulmonary LCH require long-term follow-up to detect potential disease progression and relapse. In the majority the course is generally benign.\(^{10}\) Our study confirms that long-term survival is possible for pulmonary LCH patients. Controversy remains about which tests are most effective for judging natural progression of interstitial lung disease in general or assessing therapeutic improvement. Simple lung function tests may be the best to follow, but improvement is rarely dramatic.\(^{39}\) Yet follow-up revealed that even in cases of radiological remission there is usually a persisting disturbance of gas exchange and lung perfusion, suggesting that healing as a rule leaves scars and is not complete.\(^{33,40}\) This finding is also in accordance with our study results: an improvement in radiographic data was not always associated with a normalisation of the diffusing capacity. HRCT scans are helpful in evaluating the histopathological activity of pulmonary LCH and are being used widely.\(^{41}\)

**CONCLUSION**

Pulmonary LCH is a diffuse, smoking-related lung disease characterised pathologically by proliferation of abnormal Langerhans’ cells, cyst formation and vascular abnormalities, and physiologically by a decreased diffusing capacity. The diagnosis should be considered when a middle-aged smoker presents with aspecific pulmonary symptoms, symmetrical interstitial abnormalities in the upper and middle lobes on the chest X-ray and a decreased diffusing capacity. We have described our experience with seven patients with pulmonary LCH and support the view that although the HRCT scan often provides clues to the diagnosis, there is still a need for bioptical clarification of the diagnosis of pulmonary LCH, especially in those patients in whom other differential diagnoses cannot be excluded with certainty based on clinical-radiological findings.

We conclude that irrespective of smoking cessation, long-term survival with an improvement in symptoms and radiological signs is possible for pulmonary LCH patients.

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**REFERENCES**


