

# Pulmonary Langerhans Cell Histiocytosis Masquerading as Adenocarcinoma of the Lung

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## Introduction

Langerhans cell histiocytosis (LCH), also designated as histiocytosis-X or eosinophilic granuloma, is an uncommon dendritic cell disorder characterized by the infiltration of abnormally proliferating Langerhans cells into 1 or more organs.<sup>1</sup> The clinical presentation of LCH varies depending on the site(s) of involvement and aggressiveness of disease. In children, it may present as Letterer-Siwe disease, an acute disseminated form of LCH that is invariably fatal if left untreated. Conversely, in patients with a unifocal lesion, it may remain undiagnosed for prolonged periods. Among adults, it usually occurs in association with smoking, either as a unifocal eosinophilic granuloma (approximately one-third of patients), or by affecting multiple organ systems; lungs and bones are the most commonly involved sites.<sup>1</sup>

## Case Presentation

A 47-year-old white woman with a 30-year smoking history presented with bilateral hip pain, increased fatigability, and weight loss (approximately 40 lb) during the prior 6 months. A positron emission tomography (PET)/computed tomography (CT) scan demonstrated bilateral pulmonary nodules with increased fluorodeoxyglucose (FDG) uptake, predominantly in the upper lobes. Needle core biopsy of a right pleural-based nodule revealed atypical pneumocytes, which were positive for CK-7 and TTF-1, and negative for cytokeratin-20 or CDX2 immunostains. Clusters of epithelioid macrophages with grooved nuclei and groups of eosinophils were also demonstrated. These findings were reported as moderately differenti-

ated adenocarcinoma at an outside facility. The slides were reviewed at 3 other pathology laboratories affiliated with National Cancer Institute (NCI)-designated cancer centers; 1 laboratory agreed with the diagnosis of adenocarcinoma of the lung whereas the other 2 believed that there was no conclusive evidence of malignancy and the findings were consistent with LCH. The patient received 2 cycles of carboplatin and paclitaxel and had partial radiologic response. She was then referred to the Indiana University Melvin and Bren Simon Cancer Center for a second opinion.

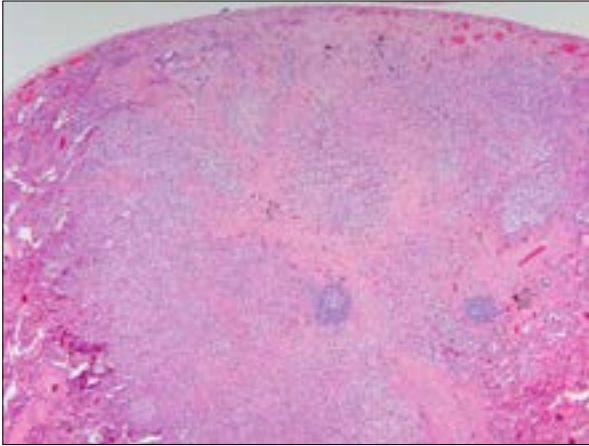
The patient refused a repeat biopsy at that time. In view of the clinical and radiologic response, she was recommended to complete 4 to 6 cycles of chemotherapy. Smoking cessation was encouraged and she was followed up for surveillance. Seven months later, she had radiographic evidence of progression but remained clinically asymptomatic. Owing to uncertainty regarding the initial diagnosis, thorascopic wedge resection of pulmonary nodules from the left lung was performed. The specimens demonstrated multifocal cellular infiltrates admixed with fibrous tissue, often in subpleural locations (Figure 1). Clusters of plump histiocytes with folded nuclei were noted within these areas, admixed with eosinophils (Figure 2). The Langerhans cell nature of histiocytes was demonstrated by strong membranous reactivity for CD1a (Figure 3), and nuclear and cytoplasmic reactivity for S-100. Hyperplastic type-2 pneumocytes lined thickened alveolar septa at the periphery of some lesions; however, there was no evidence of malignancy. Pharmacologic intervention for smoking cessation was initiated. The patient continues to be asymptomatic with stable radiologic findings.

## Discussion

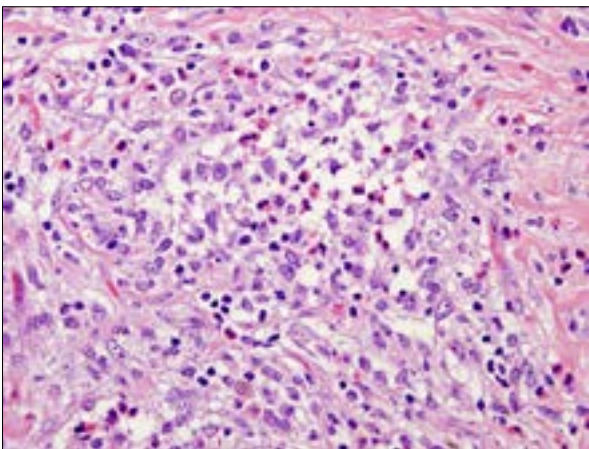
The current case illustrates that distinguishing LCH from lung cancer can present a diagnostic challenge. We now believe that the pulmonary nodules at initial presentation

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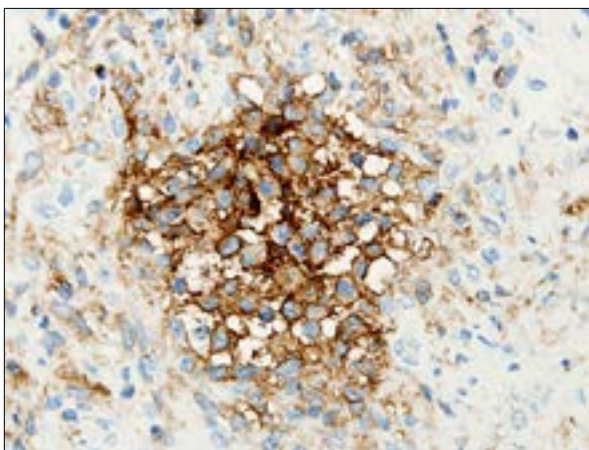
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**Figure 1.** The alveolar air spaces are effaced by a subpleural cellular infiltrate admixed with bands of fibrous tissue.



**Figure 2.** Clusters of Langerhans cells with folded nuclei admixed with eosinophils in the central portion of this lesion.



**Figure 3.** The Langerhans cells show strong membranous reactivity for CD1a.

consisted of LCH; hyperplastic type-2 pneumocytes were the likely source of diagnostic uncertainty. However, the possibility of coexisting adenocarcinoma remained a serious clinical concern.

LCH is associated with an increased incidence of cancers, with lung cancer representing the most common solid organ malignancy.<sup>2</sup> Approximately 5% of patients with pulmonary LCH develop lung cancer, thought to be secondary to chronic inflammation; smoking is a common etiologic factor for both diseases.<sup>3,4</sup> FDG uptake and response to chemotherapy support the diagnosis of lung cancer; however, both of these can occur in LCH as well.<sup>5,6</sup> Moreover, reduction of smoking could have contributed to the response in our patient. If she truly had stage IV lung cancer, progression would have most likely occurred by now.

In conclusion, distinguishing between LCH and lung cancer can be challenging. Definitive evaluation by an experienced pathologist is needed, as treatment options and prognosis vary widely.

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# Commentary

## Pulmonary Langerhans Cell Histiocytosis

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### Introduction

Langerhans cell histiocytosis (LCH) is a disorder characterized by infiltration of organs by a type of dendritic cell known as the Langerhans cell (LC).<sup>1</sup> LCs are distinguished from others by the presence of intracellular Birbeck granules, the expression of the surface of these cells of the CD1a receptor, and cytoplasmic reactivity to S-100.<sup>2,3</sup> LCH may affect a single organ or be part of a multisystem disorder that affects multiple sites around the body, such as the lungs, bone, brain, skin, and thyroid. This is also true of pulmonary LCH (PLCH), which can present as an isolated syndrome or as a systemic disease.<sup>4</sup>

### Epidemiology

Typically, PLCH affects smokers between the ages of 20 and 40 years, with an equal preponderance for men and women.<sup>4</sup> Studies at tertiary referral centers have highlighted the rarity of this disease, with less than 5% of lung biopsies testing positive for PLCH.<sup>5,6,7</sup> Most of the published cases on this disorder have involved white patients, although there have been recent reports of Asian patients being affected by PLCH.<sup>8</sup> Although isolated PLCH occurs sporadically, cases of familial variants of the disease have been described.<sup>9,10</sup> It is an extremely rare disease and its incidence and prevalence are difficult to estimate, owing to a lack of population-based studies; however, the incidence has been estimated to be between 3 and 5 per million by a Danish registry.<sup>11</sup>

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### Diagnosis and Evaluation

As illustrated by the case presented by Khawaja and associates,<sup>12</sup> the diagnosis of PLCH is a challenging one. Although this was primarily a histologic diagnosis, there was a discrepancy between the centers reporting on the core biopsy of the right lung nodule. Although the hyperplastic pneumocytes were noted to be a cause for diagnostic uncertainty, an experienced pathologist should be able to identify surrounding features—such as the presence of LCs—with appropriate staining in order to make a diagnosis. It would have been interesting to view the initial biopsy slides of the patient, as this would inevitably have strong implications with regard to tailoring management and ultimately disease prognosis.

The initial clues to a diagnosis of PLCH are usually observed from a high resolution computed tomography (HRCT) scan, especially in advanced stages of the disease and in patients with abnormal infiltrates (in whom this condition should be suspected). HRCT can distinguish PLCH from other cystic lung diseases, such as lymphangioleiomyomatosis (LAM) and Birt-Hogg-Dube syndrome.<sup>13,14</sup> Nodules and cysts that have a characteristic distribution in the upper- to mid-lung zones can be visualized. Furthermore, fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning can determine PLCH lesions and the extent of disease with a higher sensitivity than HRCT in other areas of the body, such as bone, lymph nodes, and brain.<sup>15-17</sup> Studies have also shown that FDG-PET can be used to monitor response to therapy. However, one of the main diagnostic dilemmas regarding this modality is when lung cancer is suspected, which is not easily distinguishable from PLCH, as was evident in this case.

Fifteen percent to 40% of patients are diagnosed using bronchoscopy with transbronchoscopic lung biopsy (TBLB) and bronchoalveolar lavage (BAL). The detection of greater than 3% CD1a positive lungs in the right clinical context is highly suggestive of PLCH.<sup>18</sup> TBLB and BAL are particularly useful in narrowing the differential diagnoses for cystic and noncystic lung diseases, such as mycobacterial infections, sarcoidosis, granulomatosis with polyangiitis, cavitated pulmonary metastases, bronchiolar-alveolar carcinoma, septic emboli, cavitated *Pneumocystis jirovecii* pneumonia, LAM, and Birt-Hogg-Dube syndrome.<sup>19</sup>

### Management

The management of PLCH can be divided into lifestyle measures, medical management, and surgical treatment. Smoking cessation has been associated with stabilization of disease and even complete resolution of disease in some

cases.<sup>20,21</sup> Studies have shown that smoking triggers LC recruitment and activation in patients with PLCH.<sup>22</sup> Medical management uses immunosuppressants to control moderate to severe disease in the lung and when there is systemic involvement, which is commonly the case with children.<sup>23</sup> Prednisolone has been used to manage progressive disease with mixed responses; cladribine, cyclophosphamide, and methotrexate have been used with success.<sup>24,25</sup> The patient in the case described received 6 courses of carboplatin and paclitaxel with stable radioactive findings but no progression, which has not been documented before. It is recommended that patients with PLCH have echocardiography to evaluate pulmonary hypertension, which is associated with poor survival in these patients.<sup>26,27</sup> It would have been interesting to see what the patient's lung function tests and echocardiography would have shown.

Lung transplantation should be considered for severe respiratory disease that is resistant to medical management and when there is evidence of pulmonary hypertension. In a multicenter study of 39 transplantation patients, 15 patients received a 1 lung transplantation, 15 patients received 2 lungs, and 9 patients had a heart-lung transplantation.<sup>28</sup> Seventy-six percent of patients survived at least 1 year and 54% of patients were alive at 10 years.

Patients with PLCH do have an increased incidence of malignancies, especially lymphomas.<sup>29</sup> Could the patient described in the above case have a lung malignancy as well as PLCH? Although this is a possibility, it seems unlikely with regard to the stable nature of the disease over time. It does not mean, however, that she cannot develop this in the future.

## Conclusion

PLCH is a rare disorder of the lung that can be easily missed by clinicians. The case described by Khawaja and colleagues illustrates the diagnostic difficulties that can be encountered; the lung biopsy proved to be the object of controversy, even though it is intended to be a definitive tool. All specimens in such cases should be examined carefully by expert histopathologists. Fortunately, the patient was eventually diagnosed with PLCH and managed accordingly after an additional biopsy. In a relatively young patient with features suggestive of an alternative diagnosis, clinicians must be vigilant for rare syndromes, such as PLCH.

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