

CASE REPORT

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Adult Pulmonary Langerhans Cell Histiocytosis with Osseous Involvement: understanding this rare mimic of malignancy**Samantha A. Smith, MD¹, Adam M. Franks, MD², William Rollyson, MD², Doreen Griswold, MD³, Tammy Bannister, MD²****ABSTRACT**

Langerhans cells are dendritic cells that form the antigenic barrier of the human body. They occur in nearly any tissue but are most prevalent in the skin, submucosa of the bronchial tree, and other mucosae. Langerhans Cell Histiocytosis (LCH) develops when these cells damage the tissues in which they reside through a combination of inflammatory and monoclonal stimulation. The pulmonary variant of LCH involves the lung parenchyma and creates many disturbances, including pulmonary hypertension and obstructive and restrictive lung disease. Osseous involvement, in addition to the pulmonary variant, presents with pulmonary masses and lytic bone lesions, which sparks suspicion for malignancy. Early recognition of this rare pathology is important as early treatment is clinically beneficial. The following explores a case of adult Pulmonary Langerhans Cell Histiocytosis with osseous involvement.

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INTRODUCTION

Langerhans cells are dendritic cells that inhabit almost any tissue but are predominant in the skin and submucosal surfaces. They identify antigens via toll-like receptors and present them to T-lymphocytes within lymph nodes to induce a cascade of immunologic responses.^{1,2} Langerhans cells owe their name to German pathologist Paul Langerhans, who initially postulated them to be nerve endings.² Derangement of these cells creates damage in affected organs. This pathology was previously known as various syndromes: eosinophilic granuloma,³ Hand-Schuller-Christian disease, Letterer Siwe disease,⁴⁻⁹ congenital self-healing reticulohistiocytosis, Hashimoto-Pritzker disease⁴, and Erdheim-Chester disease.¹⁰ In 1964, Lichtenstein consolidated them into the syndrome Histiocytosis X before the final change in nomenclature to Langerhans Cell Histiocytosis (LCH).⁵

predominately a pediatric disease, seen in the first three to four years of life,^{2-4,7,14} but can extend into adolescence.^{5,9,13} Certain varieties of LCH can present in the third to fourth decades of adulthood.^{1,13,15} One of these "adult" variants is Pulmonary Langerhans Cell Histiocytosis (PLCH), which has an incidence of 0.27-0.7 per 100,000 people¹⁶ and accounts for 10-14% of all cases of LCH.⁴ More importantly, it accounts for approximately 3-5% of adult lung disease,² with over 90% of those affected being smokers.^{1-3,6,15} There is a slight male predominance. This difference, along with racial incidence, may be related to gender differences in the smoking rate.¹⁴ Though patients are not directly genetically predisposed to PLCH, familial cases are noted.^{1,5} It is important to keep in mind that this "adult" variant has occurred in children with extensive passive smoke exposure.¹¹

CASE PRESENTATION

LCH has an incidence of 1-2 cases per/million,^{1,6-8,11,12} with males more effected (2-4:1).^{1,4,6,13} It is

A 36-year-old white female former smoker with a ten pack per year history, who was previously lost



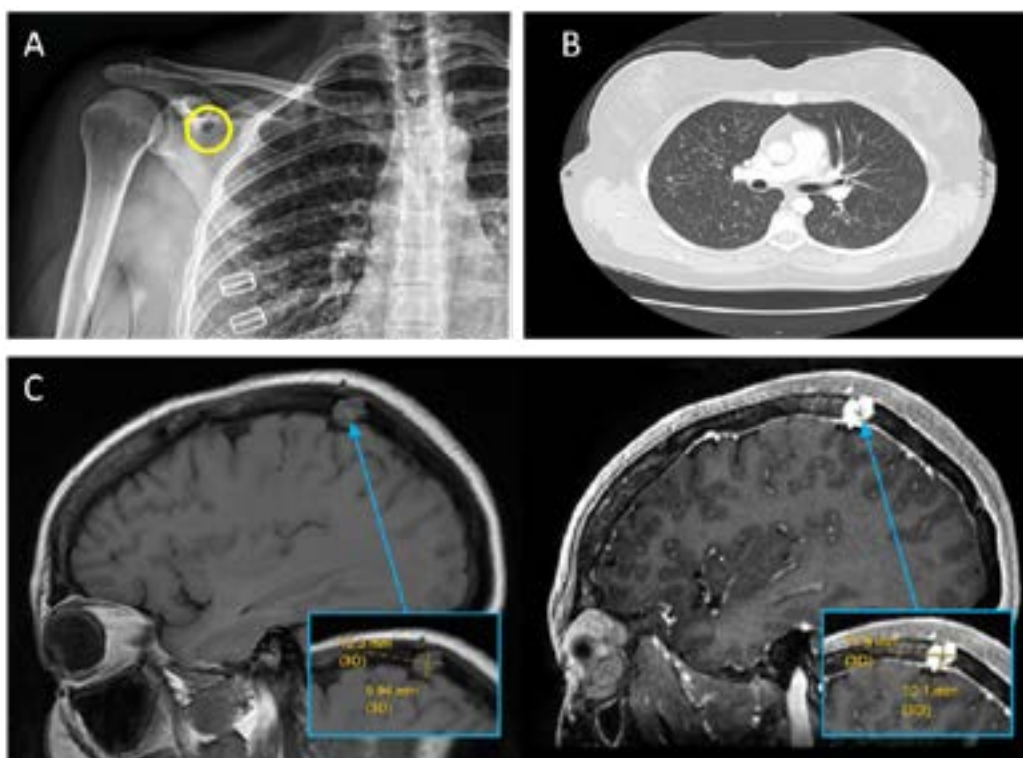


FIGURE 1: 1A: X-ray of R shoulder and lytic lesion of scapula (yellow circle). 1B: CT of mediastinum. Diffuse small nodularity throughout both lungs (R>L), predominantly upper lobe. 1C: MRI of 12 x 10 mm intensely enhancing extra-axial lesion of the parietal bone.

to follow-up after a breast mass biopsy, presented with a several-month complaint of atraumatic right shoulder pain and arm weakness. Her exam revealed limited passive and active ROM of the shoulder due to pain, with tenderness noted anteriorly. Shoulder radiography revealed a lytic lesion in the right scapula, as well as multiple lung nodules (Figure 1a). A follow-up computed tomography (CT) scan of the chest demonstrated “innumerable bilateral pulmonary nodules concerning for metastatic disease” (Figure 1b). Additionally, there were lytic lesions in the ninth right rib and both the twelfth thoracic and first lumbar vertebral bodies, suggestive of an osseous focus of this “metastatic disease.”

The patient was referred to oncology for further evaluation. Two weeks later, a Positron Emission Tomography (PET) scan revealed hypermetabolic lytic bone lesions in the proximal left humerus and right scapula. There was no hypermetabolic activity of the ninth rib, either vertebral lesion, or any other areas, including the multiple lung nodules. A bone biopsy of the left humeral lesion demonstrated sheets of eosinophils and histiocytes, most with

mono-lobulated, but some with multi-lobulated nuclei (Figure 2). Neutrophils, lymphocytes, and plasma cells were present, along with patchy areas of necrosis. Staining demonstrated CD68, S100, and CD1a (Figure 3). A follow-up MRI of the brain revealed a 12 x 10 mm enhancing parietal bone lesion without parenchymal lesions or other abnormalities (Figure 1c). The patient underwent a regimen of cytarabine (AraC), and PET scanning revealed a positive response to treatment with only minute areas of residual hypermetabolic activity. The patient continues to report significant bone pain, including headaches in the area of the parietal lesion, as well as incapacitating fatigue. She is receiving symptom and pain management and will continue to follow up with oncology.

DISCUSSION

PATHOPHYSIOLOGY

The pathophysiology of LCH is not well understood. It is a dual process of inflammation and clonal



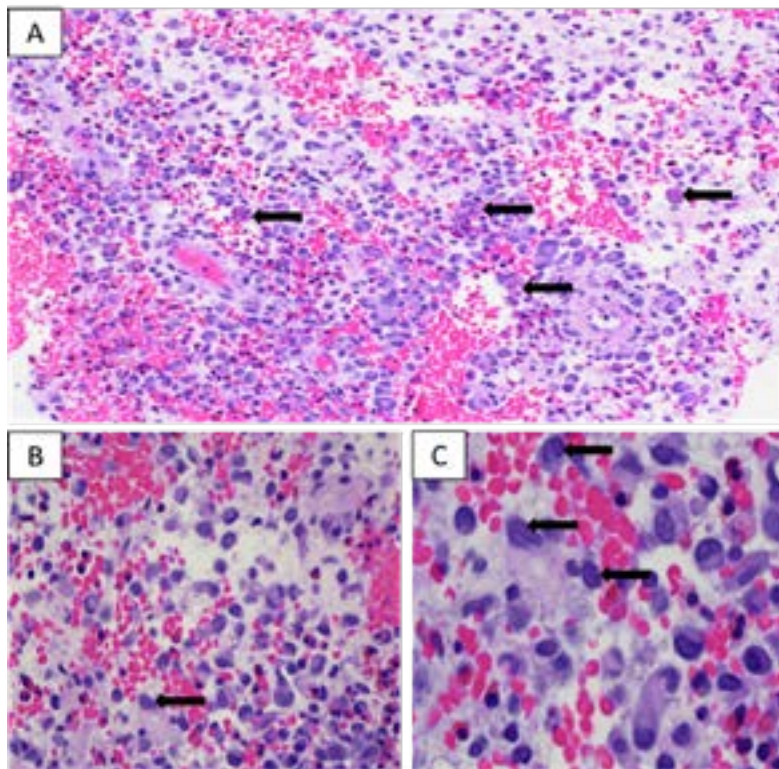


FIGURE 2. Figure 2A top image depicts eosinophils (pink) admixed with the neoplastic LCH cells (purple). Evidence of macrophage activation with hemophagocytosis is noted (arrows). (H&E stain at 200x magnification). Figure 2B left lower image shows the “coffee-bean” nuclear appearance of the LCH cells (arrow). (H&E stain at 500x magnification with oil). Figure 2C right lower image shows the delicate nuclear grooves in LCH cells (arrows). (H&E stain at 1000x magnification with oil).

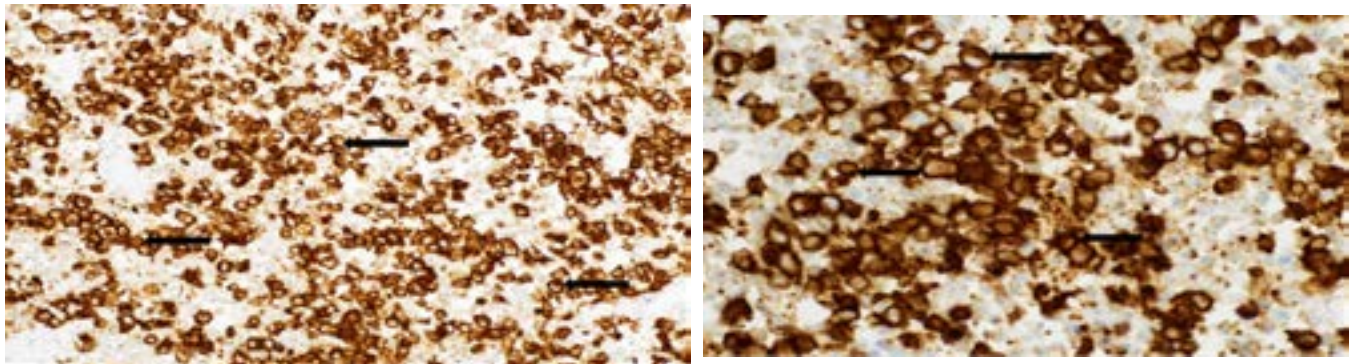


FIGURE 3: Top image shows the strong expression of CD1a in the neoplastic cells (arrows), characteristic of LCH cells. The cells are also positive for S100 with paranuclear dot-like expression of CD68 (not pictured); CD1a immunohistochemical stain; Top image 200x magnification. Bottom image is CD1a at 400x magnification.

proliferation,¹⁵ as evidenced by cytokine and inflammatory cell presence for the former^{7,8,16} and immature myeloid dendritic cell production (many with oncogenic mutations in BRAF V600E)^{1-4,8,10,15} from abnormal bone marrow for the latter.^{1,3,7} The location of these cells upon alteration determines the clinical picture.

The case-patient exhibits PLCH with osseous involvement based on the above presentation. In the lungs, Langerhans cells are essential in the antigenic barrier of the submucosa and have potent lymphostimulatory capacity.¹⁴ Cigarette smoke, which is involved in 90-95% of cases,^{1,3,5,6,14,15} can incite lymphocytic accumulation^{1,3} and inflammation through cytokine induced^{1,3,7,14} macrophage activation (Figure 4).³ This leads to parenchymal fibrosis through remodeling, as 1-10 millimeter ground-glass nodules with lucent centers appear near bronchioles early in the disease. Later in the disease, nodules regress and leave cysts in the negative space. These cysts enlarge further with the traction of the developing parenchymal fibrosis, creating an irregularly shaped honeycomb pattern.^{1,2,6} Furthermore, these changes occur within the tissue around the arterial-venous vascular bed, blurring the architecture and thickening the vascular walls. Advanced pulmonary vascular thickening leads to pulmonary hypertension and can eventually affect cardiac function.^{1,2,15}

PULMONARY LANGERHANS HISTIOCYTOSIS

At the time of diagnosis, 25% of patients with PLCH are asymptomatic.^{1,6,16} Presentation is insidious and variable,^{2,14} with initial pulmonary or constitutional symptoms preceding diagnosis by 6-12 months.¹ Pulmonary symptoms are prevalent in two-thirds of cases and include cough, dyspnea, exercise intolerance, and pneumothorax, the latter of which is the presenting symptom 10-30% of the time.^{1,14,15} Usually, there are no abnormal lung sounds,^{1,14,15} and hemoptysis is uncommon.^{1,2,15} Constitutional symptoms can consist of weight loss, fatigue, and night sweats in 10-20% of cases.^{1,15} Late symptoms include both obstructive and restrictive lung disease,¹⁵ right-sided heart failure, and pulmonary hypertension.^{1,2}

Initial assessment of PLCH is directed by the variable

nature of the disease process. Work-up should involve evaluation of disease extent⁷ and functional restrictions, in addition to the diagnosis (Table 1). Imaging of the pulmonary fields shows the above-mentioned lesions that spare the bases of the lungs early in the process and transform into a “tree-in-bud” appearance when the cysts’ walls thicken.^{2,15} Since malignancy is primary in the differential, tissue collection through biopsy via bronchoscopy and bronchoalveolar lavage is common. Unfortunately, this modality is poorly sensitive, providing a 10-50% chance of diagnosis. Poor sensitivity is attributed to this focal pathology’s uneven distribution and accessibility.^{1,2,14,15} Also, later in the disease, the tissue can appear “burnt out” by yielding only fibrotic tissue to sample.² Open lung biopsy guided by CT is more definitive in its sampling but can further compromise lung function, so it should be used with caution.^{1,4,15}

If appropriate tissue is obtained, electron microscopic evaluation of histological studies showing Langerhans cells containing Birbeck’s granules and immunochemical studies for S-100, CD1a, and Langerin can better secure the diagnosis.^{2,5,6,14} PET scans may show uptake early in the process, potentially confusing the differentiation from malignancy.^{2,15} Skeletal survey, panorex radiographs, and laboratory evaluation revolve around determining extra-pulmonary involvement.¹⁵ Pulmonary function tests (PFTs) are within normal limits 10-20% of the time.^{1,15} Spirometry may reveal an overall mixed pattern: restrictive with total lung capacity less than 80% of predicted early in the disease^{2,15} and obstructive from hyperinflation^{1,2,14} later on.¹⁵ A decrease in diffusion capacity of carbon monoxide (DLCO) is demonstrative of a defect in oxygen diffusion and seen in 80-90% of cases.^{1,2,14,15} Echocardiography is important to diagnose pulmonary hypertension as a pulmonary artery pressure greater than 35 mmHg carries increased mortality.^{2,15}

EXTRA-PULMONARY INVOLVEMENT OF PULMONARY LANGERHANS HISTIOCYTOSIS

PLCH is classified as single-system LCH (SS-LCH) when confined to the lung and occurs in 20-55% of cases.^{2,17} Extra-pulmonary involvement with PLCH is possible, favoring bone^{3,13} and the posterior pituitary.^{1,3,16} The skin,^{3,4,13} thymus,¹ lymph nodes,^{1,4,13}



spleen,^{4,13} liver,^{1,4,13} thyroid,^{11,16} intestine,^{1,11} oral mucosa,⁴ and central nervous system (CNS)⁴ have also been reported. Not only do the symptoms change depending on the system involved, but extra-pulmonary involvement also alters the classification to multi-system LCH (MS-LCH).^{1,4,6,15,16} With this change, prognosis is negatively affected by high-risk organ involvement, for which bone marrow, the spleen, liver, and CNS qualify.^{1,4,6,15,16} This patient qualifies for MS-LCH due to osseous involvement of the parietal region of the skull, scapula, vertebrae, and ribs. When bone is involved, it appears as sharply demarcated lytic lesions,^{3,13} favoring the skull (26-29%), long tubular bones (11-12.4%), ribs (11.1-12%), mandible (9%), and spine (7%).^{4-6,8,9,11,13} Thoracic (54%) and lumbar (35%) vertebrae outpace cervical (11%) in frequency.⁹⁹ Onset of osseous involvement is slow and may be either painless or painful.¹³ A biopsy revealing CD207/CD1a+ histocytes, eosinophils, and multinucleated cells¹³ is needed to distinguish LCH from primary or metastatic malignancy,^{4,8} fibrous dysplasia, and hyperostosis.¹³

TREATMENT OF BOTH LUNG AND BONE

Early treatment initiation is key for potential success as late cystic lesions tend to resist improvement.⁶ Smoking cessation is paramount in treating PLCH as this removes an inflammatory instigator and allows for potential regression.^{1-3,6,14,15} Any lower lung disease should be aggressively treated with steroids, beta-agonists, and oxygen. Influenza and pneumonia vaccines (PCV-13 and PCV-23) should be strongly encouraged. Symptomatic drainage and pleurodesis of symptomatic, recurrent pneumothorax are important¹⁵, and lung transplants may be contemplated.^{3,15} Immune modulators, such as glucocorticoids^{1-3,15} and cytotoxic agents, may include methotrexate,¹⁻³ Vinblastine,^{1,15} Cladribine,^{6,15} Cyclophosphamide,³³ and Etoposide,³³ can modify the progression of the disease. Generally, cytotoxic agents are reserved for MS-LCH with high risk or critical organ involvement; however, they can be used for SS-LCH with multiple or high-risk lesions, allowing utilization of steroids for more focal disease.^{1-3,11} These guidelines may be employed differently depending upon the patient's age.^{1,15,17} The risk of disease progression should determine treatment of osseous lesions. Observation^{8,13} and local treatment consisting of curettage, intra-lesional

steroids, bracing, and radiation^{4,7,8,13} are reserved for osseous SS-LCH.^{4,13} More aggressive categories can require systemic treatments with immune modulators or cytotoxic agents as above.^{4,7}

PROGNOSIS OF PLCH

Patients with PLCH can experience a spontaneous regression,^{8,9} especially if smoking cessation is successful early,^{1,3,6,14,15} but there is a 40% recurrence rate.¹¹ Forty percent, however, will experience a significant decrease in FEV1 and DLCO in the first two years after diagnosis, and 10-20% eventually develop progressive respiratory failure and cor pulmonale.¹⁵ Survival rates approach 75% at five years and between 50-64% at ten years.^{1,2} Median survival is 12.5 years.² Poor prognosis is associated with complications, extremes of age, prolonged symptoms and treatment, decreased lung function, and multiorgan involvement.^{1,3,7,11-15,18}

CONCLUSION

Adult patients with lytic bone lesions and multiple lung masses usually signal advanced lung cancer to most physicians and carry a poor prognosis. Rarely is a form of LCH considered in adults due to its pediatric etiology. Physicians should be familiar with this variant to rapidly initiate treatment and smoking cessation. Additional cases of LCH should be reported to further our understanding of this diverse pathology.

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