A 55-year-old African-American woman presents with progressive shortness of breath, non-productive cough, and muscle aches for two weeks. Her medical history is non-contributory. She is a current smoker with a 20-year history of smoking one pack per day. Vital signs and oxygen saturation are normal. Physical exam reveals crackles over the right middle lobe of her lung. The remainder of her physical exam is unremarkable. Blood tests demonstrate a mild leukocytosis.

Figure 1: Posteroanterior chest radiograph demonstrates diffuse reticulonodular changes and subtle cysts with relative sparing of the lung bases.

Figure 2a and 2b: Axial computed tomography (above) and coronal reconstruction (bottom) demonstrate innumerous cysts of varying sizes with few interspersed scattered nodules. There is relative sparing of the lung bases and subpleural spaces.
DISCUSSION

Pulmonary Langerhans Cell Histiocytosis (PLCH) is a rare lung disease caused by the accumulation of inflammatory cells in small airways of the lung, leading to nodular granulomatous changes of the lung parenchyma, which over time, progress to reticular and cystic changes. There are no data regarding the overall prevalence of PLCH in the adult population. However, two series of patients undergoing lung biopsy for diffuse interstitial disease reported PLCH in 3%-5% of all diffuse lung disease biopsies, in comparison with sarcoidosis, which was found in 12.5% of the same patients. It has been hypothesized that PLCH is likely underdiagnosed because it can be asymptomatic and sometimes undergoes spontaneous remission.

The incidence of PLCH peaks in young adults between ages 20-40. Gender distribution of PLCH has recently been shown to be equal. As the rates of smoking between men and women have evened out over the past few decades, so has the incidence of the disease.

PLCH is strongly associated with smoking tobacco cigarettes. More than 90% of adult patients are smokers. It has been suggested that cigarette smoke may irritate the small airways, leading to injury and inflammation.

Langerhans cells are a subgroup of antigen-presenting dendritic cells found in the skin and in the epithelium of the tracheobronchial tree. Their normal function is to survey antigens that are deposited in the airway during inhalation. Activation of Langerhans cells leads to a cascade of signaling, leading to an adaptive immune response. PLCH is characterized by peribronchiolar proliferation of Langerhans cells, forming stellate nodules that cavitate and form cysts. The advanced disease is characterized by scarring of Airways and pulmonary vascular remodeling.

The etiology of PLCH is poorly understood. It has been proposed that PLCH is an immune response to an unknown antigen, leading to T-cell activation. The unknown antigen likely is related to cigarette smoking. However, there are also host factors involved, as only a small percentage of cigarette smokers develop PLCH. Theories that have been proposed include a viral origin, neoplastic proliferation, and immune system dysregulation.

PLCH has also been shown to be associated with lymphoma and is more likely to be diagnosed in a patient previously treated with chemotherapy and radiation therapy, usually for Hodgkin’s disease.

Many patients with PLCH are asymptomatic, leading to diagnosis based on chest radiograph for other indications. Symptomatic patients typically present with a nonproductive cough, dyspnea, an abnormal chest radiograph, or recurrent spontaneous pneumothorax. Diagnosis of PLCH is difficult based on these nonspecific symptoms. A minority of patients may also experience fever, weight loss, and malaise.

Laboratory findings tend to be within normal limits in PLCH patients, with the exception of a possibly moderately elevated erythrocyte sedimentation rate. Pulmonary function tests can show an obstructive, restrictive, or mixed pattern. Vital capacity is often low, and residual volume is often normal or increased, leading to a total lung capacity that is relatively normal.

In most adult patients, LCH affects only the lungs. However, the most likely extrapulmonary findings in PLCH are cystic bone lesions, diabetes insipidus (DI), and skin lesions. Patients should be carefully examined for these other signs with a skeletal survey and physical exam if diagnosed with PLCH.

PLCH is not typically a strictly nodular or cystic disease but a spectrum of varying degrees of granulomatous nodular changes, which predominate earlier in the disease process and cystic changes which predominate later in the disease process. Brauner proposed that the initial nodules eventually cavitate, leading to thick-walled cysts, which then mature to thin-walled and ultimately confluent cysts.

Imaging is fundamental for diagnosis of PLCH, as symptoms are non-specific. Early nodular PLCH is characterized by radiography, computed tomography (CT), and high-resolution CT as bilateral mid- to upper-lung zone distribution of pulmonary nodules with relative sparing of the lung bases, especially the costophrenic sulci, and normal to increased lung volumes. The nodules are typically irregularly marginated, 1 to 10 mm in size, and can range from a few scattered nodules to innumerable and/or confluent nodules. A chest radiograph is the initial imaging modality of choice; however, high-resolution CT (HRCT) is markedly more sensitive and specific for PLCH.

The differential diagnosis for nodular PLCH includes sarcoidosis, silicosis, metastasis, and hematogenous infectious processes such as military tuberculosis. HRCT is utilized to narrow the diagnosis by distinguishing the centrilobular distribution of PLCH nodules from the peripheric distribution of sarcoidosis, silicosis, and lymphangitic carcinomatosis.

Cystic lesions of PLCH can also be difficult to distinguish from bullous emphysema, lymphangioleiomyomatosis (LAM), bronchiectasis, and honeycombing associated with end stage fibrotic lung diseases. However, an emphysematous bulla is typically a focus of parenchymal destruction lacking a cyst wall. LAM occurs almost exclusively in females and has a diffuse bilateral distribution and more uniform appearing cysts. Cystic bronchiectasis has a communicating branching pattern. Honeycombing tends to be peripheral and basilar in distribution with associated ground glass opacity and parenchymal architectural distortion. HRCT can often be utilized to reach an accurate diagnosis in 84% of cases and can preclude the need for an invasive lung biopsy.

Pneumothorax can occur as a complication of PLCH and may be the initial presenting clinical and imaging finding. Lymphadenopathy, air-space consolidation, and a solitary pulmonary nodule are rare imaging findings of PLCH. Advanced disease can be associated with pulmonary hypertension.

First-line treatment for PLCH is immediate cessation
of smoking. Symptoms will stabilize in the majority of patients with no need for further treatment. Cessation of smoking can also reduce incidence of associated malignancies. Corticosteroid therapy is another option that has demonstrated beneficial effects in stabilization. However, no randomized trials have been conducted to compare the efficacy of corticosteroid treatment with that of smoking cessation alone. Severe PLCH has been treated with chemotherapeutic agents (cladribine, cyclophosphamide, and methotrexate) without significant effect. Pleurodesis may be required in patients with recurrent pneumothoraces. Lung transplantation should also be considered for patients with rapidly deteriorating lung function or disease refractory to medical treatment.

Patients with PLCH generally have a good prognosis. However, it has been shown that patients have a decreased average survival rate compared to the general population and have a poorer health-related quality of life than would be expected. Spontaneous regression has been reported in up to 25% of patients and stabilization in up to 50% of patients. The remaining 25% of patients follow a variably deteriorating course culminating in diffuse cystic change and lung destruction, sometimes complicated by pulmonary hypertension or respiratory insufficiency leading to death. Relapse may occur, even with lung transplantation, especially if the patient continues to smoke. Long-term follow-up of PLCH patients is necessary because of the risk of relapse, even years after disease resolution. Adult patients with PLCH are at an increased risk for developing malignant neoplasm of the lung, as well as lymphoma as mentioned earlier. However, this may be due to the high prevalence of cigarette smoking. Patients should be monitored for these complications.

REFERENCES


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