Pulmonary Langerhans cell histiocytosis (PLCH) is an uncommon disorder of young adults that results in significant pulmonary impairment and morbidity. Advances in the knowledge of PLCH have included better understanding of Langerhans cells (LCs)—the primary offenders in PLCH—and better definition of PLCH lesions by high-resolution CT (HRCT). This review focuses on evolving concepts in the pathobiology of PLCH, the clinical implications, and the role of HRCT in the diagnosis of progression of PLCH, using illustrative examples from affected patients.

Nomenclature and Historical Perspective

Attributing LC as causal to the lesions of PLCH took over a century since the original description of dendritic cells by Paul Langerhans in 1868. In 1973, Nezelof and colleagues reported in a classic article that histiocytes in PLCH share a common cytoplasmic organelle by electron microscopy (the Birbeck granule) with the LCs of the skin. Litchenstein had previously suggested that a common histiocytic cell pool populated the pathologic lesions of three disparate clinical conditions: eosinophilic granuloma, Letterer-Siwe disease, and Hand-Schüller-Christian disease. Unfortunately, this lumping of diseases with very differing presentations did not further the etiopathologic underpinnings of each disorder; therefore, in 1985 the Histiocyte Society was founded to address the study of disorders of histiocytes. Currently, pulmonary eosinophilic granuloma (also called pulmonary histiocytosis X) is referred to as PLCH to reflect the cellular basis of the disease and the relatively isolated pulmonary involvement when compared to the multiorgan LC disorders, Letterer-Siwe disease and Hand-Schüller-Christian disease.
Etiologic Considerations

The LC is a specialized immune cell belonging to the family of dendritic cells that form a network of antigen-presenting and migratory cells in lymphoid and nonlymphoid organs such as the skin, heart, and lung.6 Closely related to the monocyte-macrophage system, the dendritic cell system originates from a common bone marrow progenitor and undergoes differentiation under the influence of specific growth factors.5,7 The origins of tissue dendritic cells are controversial. Three developmental pathways have thus far been identified (Fig 1).8,9 Both CD34+ bone marrow precursors and CD11c+ blood precursors give rise to two types of immature dendritic cells found in nonlymphoid tissues: interstitial cells and LCs (Fig 1). Immature resident dendritic cells monitor interfaces of the host with the environment, as in skin and mucosa where they play vital roles in antigen uptake and processing.9 Due to their potent antigen presenting capabilities, dendritic cells are key to the development of either immune activation or tolerance.10 Dendritic cells also respond to other signals that portend tissue damage, such as tumor antigens and inflammatory cytokines.9 Following activation, they migrate to draining lymph nodes where their maturation is completed with acquisition of superior antigen-presenting capacity and ability to initiate immune responses following interaction with

DENDRITIC CELL DIFFERENTIATION

<table>
<thead>
<tr>
<th>BLOOD PRECURSOR</th>
<th>CD34+ myeloid</th>
<th>CD34+ lymphoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monocyte</td>
<td>DC precursor</td>
<td>Plasmacytoid DC precursor</td>
</tr>
<tr>
<td>CD11c+</td>
<td>CD11c+</td>
<td>CD11c-</td>
</tr>
<tr>
<td>CD13+</td>
<td>CD13+</td>
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<td>CD33+</td>
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<tr>
<td>CD14+</td>
<td>CD14-</td>
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</tr>
</tbody>
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**MATURE CELL**

**Cell Markers**
- CD11c, CD13, CD33: +
- CD123: -
- CD40, CD54, CD80, CD86: +
- CD11b: +
- MHC Class II: +
- CD1a: -
- Birbeck granules: -
- Langerin: -
- E-cadherin: -

**Functions**
- CD4 & CD8 priming: +
- IL-12 secretion: +

**Other**
- Induces B-cell differentiation
- Secretes IFN-α

**Granulocytes**

**Plasmacytoid DC precursor**

**Granulocytes**

**GM-CSF**

**IL-4/TNF-α**

**IGF-1/TNF-β**

**IL-3**

**FIGURE 1.** Dendritic cell (DC) differentiation pathways from myeloid and lymphoid bone marrow precursors (adapted with permission from Lipscomb and Masten9). DCs of myeloid origin serve as an interface between the adaptive and innate immune system functioning as antigen-presenting cells at bodily interfaces with the environment, skin, or mucosa.9,10 Dendritic cells of lymphoid origin are dedicated to the adaptive immune system and located primarily in T-cell zones of lymphoid organs and thymus.10 NK = natural killer; MHC = major histocompatibility complex; IFN = interferon; TGF = transforming growth factor.
antigen specific CD4+ T lymphocytes. Immature dendritic cells originating from the marrow also appear to separate into epithelial-associated and nonepithelial-associated surveillance populations. It is also believed that part of the dendritic cell population in peripheral tissues may be monocyte derived, although unlike macrophages, dendritic cells (prototype being LCs) are poorly phagocytic. Subsets of dendritic cell populations in the circulation and peripheral organs are now being defined based on surface marker analyses. Further information on dendritic cell responses to humoral mediators, cellular adhesion molecules, and changes in gene expression will delineate triggers accounting for local and systemic dendritic cell activation and explain their physiologic roles in the circulation, lymphatic network, and respiratory tract.

PULMONARY LC HISTIOCYTOSIS VS DISSEMINATED LC HISTIOCYTOSIS

LC accumulation in tissues can occur as a result of a local reaction to inflammatory/neoplastic stimuli as is seen in lungs of smokers, or with certain lymphomas and solid tumors. LC histiocytes (LCHs), however, are comprised of disorders characterized by disease manifestations that are explained by excess activated LCs in various tissues. Depending on the extent of organ involvement, LCHs are classified as LCH with single-organ involvement (eg, PLCH), LCH with multiorgan involvement (as in Hand-Schüller-Christian disease), or multisystem disease (formerly Letterer-Siwe disease, seen rarely in adults). LCs isolated from these “histiocytoses” differ from quiescent LCs and dendritic cells. LCs in LCHs are rounded instead of the usual dendritic shape. They display increased numbers of Birbeck granules, and exhibit some mitotic activity (especially in multisystem LCH, formerly Letterer-Siwe disease). Unlike typical malignant cells, the LCs from LCHs do not display DNA or chromosomal abnormalities, and transfer of LCs isolated from patients with histiocytoses to immunosuppressed mice does not evoke lesions similar to that seen in humans. These data, however, do not exclude a neoplastic potential for the LCs isolated from the different LCHs. By flow-cytometric techniques, LCs from pulmonary, bone, and skin lesions appear to be clonally expanded. Clonal expansion also has been shown using DNA probes that identify patterns of X-chromosome inactivation based on polymorphisms at different loci, namely the phosphoglycerate kinase and hypoxanthine phosphoribosyl transferase loci, the hypervariable locus DXS255, and the X-linked human androgen receptor (HUMARA) gene locus. The HUMARA locus is reportedly more reliable for the determination of clonality due to its high rate of heterozygosity and consistent methylation pattern indicative of activation. The percentages of clonal cell populations identified by HUMARA assays correlate strongly with the percentages of CD1a+ LCs from lesions of patients with disseminated or multifocal LCH, indicating that LCs in these lesions most likely represent a monoclonal population.

In PLCH, pulmonary involvement by typical histiocytic lesions is more difficult to categorize in terms of a localized LC accumulation vs an isolated organ involvement as a part of systemic histiocytosis. Between 4% and 20% of patients with PLCH display cystic bone lesions, and a number of case reports demonstrate involvement of other sites, including mediastinal lymph nodes, pituitary gland, skin, gut, heart, and brain. Such involvement suggests that PLCH may be an isolated organ manifestation of a generalized systemic histiocytosis. Studies have demonstrated that although the proliferative activity of lung LCs in PLCH is low, activated LCs in pulmonary lesions appear to be clonally derived. Activated LCs from PLCH lesions express molecules that facilitate T-lymphocyte activation, suggesting that aberrant immune responses are operative in the pathogenesis of PLCH. Such expression of lymphostimulatory molecules is not seen in normal pulmonary LCs or LCs accumulating in other pathologic lung disorders.

The relatively selective lung involvement in patients with PLCH, the majority of whom are adult heavy smokers, has given rise to the hypothesis that LC accumulation in PLCH occurs as a response to cigarette smoke. The finding of increased numbers of LCs in the BAL fluid of smokers, along with abnormal T-cell proliferative responses to tobacco glycoprotein in patients with PLCH, lends support to this hypothesis. PLCH initially involves the lungs in a peribronchiolar fashion consistent with an inhaled antigen. Radiographically, PLCH predominates in upper and mid-lung zones, a feature common to many smoking-related lung illnesses. The demonstration of pulmonary LC-rich granulomatous inflammation in mice exposed to tobacco smoke also points to PLCH being a reactive process. In a murine model, female BALB/c mice exposed to tobacco smoke displayed increased numbers of pulmonary LCs that remained elevated for the duration of smoke exposure. In addition, interstitial granulomas observed in the lungs of tobacco smoke-exposed mice showed star-shaped extensions into adjacent alveoli akin to thestellate lesions of human PLCH. However, the lack of association between extrapulmonary LCH lesions and smoking, and the
poorly reported efficacy of smoking cessation in resolving PLCH lesions challenges the hypothesis of PLCH being causally related to smoking.\textsuperscript{18,20} Although PLCH occurs predominantly in smokers, it is unclear why only a small percentage of smokers have this problem, suggesting that other unknown factors are in play. Other postulated etiologies include viral infections, but molecular studies of tissue specimens fail to consistently show an association.\textsuperscript{17} The development of PLCH following Hodgkin disease or its treatment raises the question of common etiologic factors or aberrant immune responses by dendritic cells following iatrogenic immunosuppression.\textsuperscript{28,29}

Cytokine triggers have been postulated to account for LC accumulation in the lung.\textsuperscript{7,12} Transgenic murine models of granulocyte-monocyte colony-stimulating factor (GM-CSF) overexpression have demonstrated an accumulation of macrophages and a unique dendritic cell population around the airway epithelium.\textsuperscript{30} Bronchiolar GM-CSF–driven LC accumulation has been seen in bronchogenic carcinomas\textsuperscript{31} and postransplantation bronchiolitis obliterans syndrome.\textsuperscript{32} GM-CSF is found in early PLCH granulomas and in bronchiolar epithelial remnants in stellate lesions, suggesting a role for GM-CSF in airway LC expansion.\textsuperscript{33} However with disease progression, GM-CSF expression declines.\textsuperscript{33} The progression of PLCH lesions despite extensive bronchiolar destruction and the presence of interleukin (IL)-1, IL-4, tumor necrosis factor (TNF)-α, and especially transforming growth factor-β in extrapulmonary LCH lesions suggests that multiple cytokines participate in the development of PLCH lesions.\textsuperscript{34,35}

**Pathology of PLCH and Disease Course**

Histologically, early PLCH lesions are characterized by cellular interstitial infiltrates composed of LCs, lymphocytes, macrophages, eosinophils, plasma cells, and fibroblasts.\textsuperscript{36} These infiltrates enlarge to form nodules centered on small airways.\textsuperscript{25,40} Cavitary lesions within nodules represent either an airway remnant or de novo caviation due to an enlarging inflammatory infiltrate.\textsuperscript{25,40} Centriple replacement of granulomatous nodular infiltrates by fibroblasts results in symmetric stellate lesions that form the classic histology of PLCH.\textsuperscript{40} Disease progression is characterized by increasing numbers of nodules, cavitary granulomas, and the appearance of fibrotic scars.\textsuperscript{25} In any given specimen, lesions of different ages are seen.\textsuperscript{25} End-stage PLCH is characterized by prominent fibrotic scars, some of which surround cystic spaces of variable diameter forming large areas of honeycombing and paracartilaginous emphysema prominent in the upper lobes.\textsuperscript{25,39,40}

Based on this pathologic framework, PLCH may be construed to follow one of the three courses: progression, stabilization, or resolution. The majority of patients with PLCH stabilize or resolve their disease when observed over a short period of time. However, longer periods of observation may be necessary to fully appreciate the disease course in an individual patient.\textsuperscript{36,41} In a European study,\textsuperscript{42} that observed 45 patients with PLCH for a median of 6 years, 27% died or required lung transplantation. The median survival from the time of diagnosis was 13 years.\textsuperscript{42} Similar survival rates were observed in a North American analysis of 102 histopathologically proven patients with PLCH, of whom a third succumbed to respiratory failure.\textsuperscript{43} Two recent case reports indicate that PLCH can recur following lung transplantation despite aggressive immunosuppressive therapy, indicating that the disease may follow a protracted course.\textsuperscript{44,45}

Compared to patients with COPD or other interstitial lung diseases, patients with PLCH have pulmonary hypertension far out of proportion to their indices of ventilatory or gas-exchange limitation.\textsuperscript{46,47} Exercise intolerance in patients with PLCH has been ascribed to limitations from vascular involvement rather than from gas-exchange or ventilatory abnormalities.\textsuperscript{47} Pathologic findings of a pulmonary vasculopathy (occurring in areas of the lung far removed from parenchymal nodules) suggest that pulmonary vascular involvement is a prominent feature of late-stage PLCH.\textsuperscript{47} This vasculopathy takes the form of intimal fibrosis, medial hypertrophy, or luminal obliteration with occasional infiltration into vessel walls by lymphocytes and/o eosinophils.\textsuperscript{47,48} Both venules and arteries are affected.\textsuperscript{47} One instance of

**Clinical Picture**

The majority of patients with LCH are smokers who commonly acquire disease in the third or fourth decade of life.\textsuperscript{25,36–40} Although there does not appear to be a gender preponderance, female patients with PLCH tend to present later in life.\textsuperscript{39} Estimates of the incidence of PLCH may be biased, as most studies are based on histopathology results from open-lung biopsies.\textsuperscript{39} The clinical presentation of PLCH varies; dyspnea, cough, and chest pain are the predominant symptoms.\textsuperscript{19,37} Constitutional symptoms and hemoptysis can occur.\textsuperscript{19} The physical examination is quite notably unremarkable.\textsuperscript{19,39} Measures of gas exchange are more sensitive in detecting lung involvement than are measures of lung mechanics that may show normal, obstructive, restrictive, or mixed patterns.\textsuperscript{37} With disease progression, clubbing and cor pulmonale may be observed.\textsuperscript{36–39}
Vascular infiltration by LCs has been described. Progression of vascular pathology may account for development of pulmonary hypertension that is a feature of late PLCH. This development of pulmonary vascular disease may in part explain the limited value of pulmonary function testing and physical examination in predicting an individual’s disease course. Better long-term prognostic indexes are needed especially when nodular/cystic changes are few and no significant derangement of lung functions is present.

**Radiologic Spectrum of PLCH**

An abnormal chest radiographic finding may be the only clue to the disease in the 25% of asymptomatic patients with PLCH. Pneumothorax with chest pain is the initial clinical manifestation in 15% of patients with PLCH. Pneumothoraces may be recurrent, requiring thoracotomy and chest tube placement for relief of symptoms. A spectrum of chest radiographic abnormalities is seen in patients with PLCH with ill-defined nodules and curvilinear/reticular opacities predominating in most patients. The reticular areas seen on plain radiographs correspond to areas of superimposed cysts observed on thin-section CT. The reticulonodular changes predominate in the mid-lung zones with some radiographic series reporting more upper-lobe involvement. Significant lower-lobe involvement has been reported as well, but is less common. The opacities tend to be symmetric without predilection for the central or peripheral zones of the lungs. The costophrenic angles are generally spared. (Fig 3) A sign reportedly associated with a better prognosis. Lung volumes on chest radiographs are generally preserved or increased. With time, the number of radiographic nodules decreases and cystic changes increase. However, chest radiographic findings can remain stable or improve. Unusual radiographic findings include mediastinal adenopathy, presentation as a solitary pulmonary nodule, consolidative opacities, and pleural effusions. One instance of an effusion secondary to pleural seeding from a solitary rib eosinophilic granuloma has been reported.

Lung perfusion scintigrams show that areas of abnormal perfusion predominate in the upper and mid-lungs, but the distribution of reticular and nodular changes does not correlate with areas of disturbed lung perfusion. This is consistent with findings of pulmonary vasculopathy observed in areas of lung not involved by parenchymal nodules.

Chest CT findings vary depending on the stage of the disease. Cysts (80%) and nodules (60 to 80%) are present in the majority of patients. Early stage PLCH is characterized by a centrilobular pattern with ill-defined nodules distributed around small airways. Micronodules (1 to 5 mm) are typical, although macronodules (> 1 cm) can also be seen. Although the combination of nodules along with cysts is typical, patients early in the disease course may exhibit only nodules on radiographs leading to difficulties differentiating PLCH from other granulomatous diseases and cancer. PLCH nodules may be profuse and are generally solid, although with time they may cavitate. Cystic changes appear later and vary in shape, size, and wall thickness. Cysts are usually round with uniform wall thickness and < 10 mm in diameter. Confluence of adjacent cysts can lead to bizarre-shaped spaces with bilobed, cloverleaf, or branching appearances. Some of these cystic spaces may attain bulla sizes of up to 80 mm. The cyst walls can vary up to several millimeters in thickness, with thick-walled cysts more suggestive of ectatic bronchioles. In addition to cysts and nodules, reticulation and rarely ground-glass opacities may be observed. As seen on chest radiographs, these abnormalities are typically...
distributed over the upper and mid-lungs. There is usually no involvement of the lung-pleural interface as shown by the radiographic sparing of the lingular/middle lobe tips and lung bases.

The CT appearance of cysts and nodules in an adult heavy smoker is virtually diagnostic of PLCH. Reports confirm the high diagnostic reliability of HRCT in PLCH. Less interobserver variability has been reported with the radiographic diagnosis of PLCH as compared to other lung diseases. Diagnostic dilemmas arise when the CT scan shows isolated nodules or cysts. When cysts alone are seen, a distinction has to be made between PLCH, emphysema (cysts do not have walls) and lymphangioleiomyomatosis (LAM). Although there are no significant differences between cyst sizes, configuration, thickness of cyst wall, or proximity to vascular structures in PLCH and LAM, the distribution of cystic abnormalities may help differentiate the two disorders. LAM tends to uniformly involve all regions of the lungs and does not spare the costophrenic angles, features unusual for PLCH. When difficulty distinguishing PLCH and LAM arises, additional scans of the costophrenic angle regions should be obtained, placing the patient prone if necessary. The high diagnostic accuracy of HRCT

**Figure 3.** A 30-year-old man who smoked 2 packs a day presented with a right-sided pneumothorax. Top: Posteroanterior radiograph obtained after thoracotomy tube placement demonstrated bilateral upper-lung zone curvilinear opacities and lucent cystic regions. Bottom: Thin-section CT of upper lobes reveals the coalescent cysts with bilobed and branching patterns. The reticular opacities on the radiograph correspond to the cyst walls. PLCH was diagnosed on open-lung biopsy.
in PLCH has resulted in fewer invasive pathologic studies, especially since there is no current specific treatment modality for disease.61

Two studies evaluated the evolution of HRCT findings of PLCH lesions63 and correlated them with the histopathologic activity of lesions.64 CT scans done in early PLCH demonstrate more nodules than cysts as compared to scans performed later in the disease course (median interval between scans in the study was 14 months with a range of 4 months to 7 years).64 The majority of lesions in early disease were pulmonary micronodules distributed in a centrilobular fashion.64 Patients who had predominantly nodular disease on HRCT demonstrated florid granulomas on histopathology; the number and density of radiographic nodular lesions correlated well with the density of granulomatous lesions.64 A few cavitated nodules were seen in CT scans done early in disease course; the histopathology likewise showed cavitated nodules and fibrous cysts on a background of nodular lesions.64 On initial CT scans, lesions were distributed in the upper or mid-lung zones or diffusely.64 No air-trapping was observed on expiratory studies.63 Follow-up scans showed a decreasing preponderance of nodules and increasing number of thin-walled cysts.63,64 Histopathology showed that these thin-walled cysts represented either cavitary granulomas, fibrous cysts, or cavitary granulomas associated with cysts.64 In both studies, a cystic pattern on HRCT was associated with a later disease stage and probably resulted from the transformation of nodular lesions.63,64 Full or partial resolution of lesions occurred in a small number of patients with nodular lesions, indicating that nodules may represent the only reversible lesion in this disease.63 However,
cystic lesions remained unchanged or worsened with time, suggesting a pattern of evolution from nodules in the following manner: nodule, cavitated nodule, thick-walled cyst, and thin-walled cyst.63 The mechanism of cyst formation is thought to be from cavitation within a centrilobular nodular lesion followed by progressive bronchiolar dilatation resulting from the granulomatous destruction and supervening fibrosis in the periphery of the lesion.63 Increase in cyst size is hypothesized to occur from traction bronchiolectasis or a ball-valve effect in partially obstructed bronchioles.63 Late-stage disease is characterized by large areas of honeycombing predominant in the upper lungs corresponding to joined or confluent cysts.63 These changes may be visible on routine chest radiography and tend to appear as coarse reticulations rather than the classic honeycombed pattern.51 Advanced disease is characterized by substantial architectural distortion due to cysts with few nodules (Fig 11). Small granulomas are still observed in majority of pathologic lung specimens from patients with the cystic pattern of advanced disease, indicating ongoing disease activity.64

**Therapeutic Considerations**

Smoking cessation is recommended because of a potential pathogenetic association,23,24 the rarely documented resolution of disease following cessation of smoking52 and the increased risk of bronchogenic cancer in PLCH.65 The nature of cancer in patients with PLCH does not appear to be that of a scar cancer.66 Bronchogenic cancers have been reported most commonly in those who continue to smoke heavily.66 Corticosteroids and other immunosuppressive therapies26 have not been evaluated in well-designed clinical trials, in large part because of the relative rarity of the disorder and the confusion...
in segregating the adult pulmonary histiocytosis from diffuse LCHs of the pediatric age group. Reports of improved outcome with IL-2 and anti–TNF-α therapy in cases of pediatric disseminated histiocytoses unresponsive to conventional therapy may lead to similar trials in adult PLCH. Poor outcome in PLCH has been associated with an older age at diagnosis, increasingly severe airway obstruction (lower FEV<sub>1</sub>/FVC ratio and higher residual volume/total lung capacity ratio), reduced carbon monoxide diffusion capacity, and use of steroid therapy during follow-up.

**CONCLUSION**

Current understanding of PLCH has evolved in terms of the basic processes contributing to the natural history of the disease. The LC, a cell belonging to the dendritic cell system, accumulates in the lungs along with macrophages, lymphocytes, and eosinophils, and gives rise to typical granulomas centered on small airways. These cells differ from the quiescent LCs of the skin. They have larger and more pleomorphic Birbeck granules and express markers of activation. LCs in PLCH lesions are monoclonal in origin but demonstrate low proliferative activity. These findings need further clarification in order to better understand the processes that trigger the accumulation of and subsequent lung destruction by LCs.

HRCT has proven to be a superior modality in diagnosing PLCH as compared to plain chest radiography. Thin-walled cysts are visualized more often as reticular opacities than clear-cut cystic changes on chest radiography. Diagnosing cystic changes due to PLCH is important, as these changes represent later stages of disease; honeycombing, a late PLCH manifestation may be the only cystic abnormality diagnosed with reliability on chest radiographs.

HRCT defines the numerous nodular and cystic lesions characteristic of PLCH and provides a high diagnostic specificity often preventing the need for an invasive diagnostic procedure. HRCT may also be useful in prognosticating disease by quantifying the profusion of cystic lesions as compared to nodular lesions. Follow-up scans may show resolution of nodular lesions, evolution to cystic lesions from nodular opacities, or increasing numbers of cystic and nodular lesions with architectural distortion. Nodular lesions representing cavitary or noncavitary granulomas are correlated with pathologic activity; however, the finding of granulomas on the pathology of patients with predominant cystic patterns indicates that HRCT, despite its degree of resolution,
may still miss active disease. It remains to be seen whether using serial HRCT to follow up chest lesions will be a useful and cost-effective way to predict evolution of disease. Given the varying disease activity in individual patients, follow-up over long durations of time is required to assess the overall course of disease. Better understanding of adult PLCH with increasing interest in defining disease course have led to a call for a multicenter cooperative study that should yield more information on the disease.20

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