Pulmonary Langerhans Cell Histiocytosis
An Update From the Pathologists’ Perspective

Anja C. Roden, MD; Eunhee S. Yi, MD

Langerhans cell histiocytosis (LCH) is a rare disorder that is characterized by nodules composed of a heterogeneous cell population including cells that exhibit the phenotype of Langerhans cells and mixed acute and chronic inflammatory cells. Langerhans cell histiocytosis can involve almost any tissue and might lead to significant morbidity and mortality. Langerhans cells are a subtype of dendritic cells that function as antigen-presenting cells in the skin and mucosa. These cells express S100 protein, CD1a, and langerin (CD207) and contain intracytoplasmic Birbeck granules. They are named after Paul Langerhans (1847–1888), a German pathologist, physiologist, and biologist who discovered these cells in the skin and postulated that they were possibly nerve endings.

Pulmonary Langerhans cell histiocytosis (PLCH) is the involvement of the lung by LCH. Usually, PLCH is restricted to the lung but in some cases the lung is involved as part of systemic LCH. Pulmonary Langerhans cell histiocytosis is a form of interstitial lung disease (ILD) that is thought to be distinct from systemic LCH (Table 1). PLCH occurs almost exclusively in smokers or former smokers and is usually a disease of adults, while systemic LCH does not have any known environmental or occupational risk factors and most commonly is seen in young children.

We will review the clinical, radiologic, and histopathologic features of PLCH and the value of biopsies in the diagnosis of the disease. Furthermore, we will discuss pulmonary hypertension in the setting of PLCH. Recent developments in studies of the pathogenesis of PLCH will also be presented.

**Clinical Presentation**

The clinical presentation of patients with PLCH is variable (Table 2). Patients with PLCH are usually young adult smokers (Table 1). In fact, more than 90% of patients with PLCH are smokers or ex-smokers. Chest pain is usually of pleuritic quality owing to involvement of ribs by LCH or pneumothorax. Hemoptysis is very uncommon and another diagnosis might also be considered. Usually the duration of illness is less than 1 year before diagnosis. Although in general LCH nodules contain a variable number of eosinophils, the peripheral eosinophil blood count is normal.

For most patients with PLCH, pulmonary function tests show decreased carbon monoxide diffusing capacity (DLCO) with mean or median DLCO of 59% to 66% of predicted. In a study of 78 patients, the median DLCO was 66% of predicted (range, 26%–111%). In that study, of 81 patients, 11 (13.6%) had normal, 37 (45.7%) had restrictive, 22 (27.2%) had obstrusive, and 4 (4.9%) had...
mixed pulmonary function; 7 patients (8.6%) had an isolated reduction in DLCO. In general, in early disease restrictive findings are more common, while in advanced disease obstructive features predominate. The total lung capacity is usually preserved with a reported mean or median total lung capacity of 89% to 92% of predicted. Patients with PLCH and restrictive lung function might be older and have longer-standing disease.4

Patients with PLCH often have exercise limitations. In a study of 23 patients, the exercise capacity was severely reduced with only 54% ± 4% of the predicted workload achieved.4 Only 3 patients reached workloads of at least 80% of that predicted. This study also revealed that most of the variability in oxygen consumption and workload achieved at maximal exercise could be explained by the abnormal resting dead space over tidal volume (VDS/VT) and DLCO, suggesting that pulmonary vascular dysfunction likely plays a major role in limiting exercise performance in patients with PLCH. Hypoxemia may have contributed to limited exercise tolerance in some patients.

PLCH can be complicated by recurrent spontaneous pneumothorax (15%–25%)5 and pulmonary hypertension (see below). An increased number of secondary malignancies and nonmalignant tumors have also been observed in patients with PLCH, including lung carcinoma, Hodgkin and non-Hodgkin lymphoma, carcinoid tumor, and mediastinal ganglioneuroma.6–8 While the carcinogenic effect of cigarette smoke likely plays a role, other hypotheses include a defect in stem cells of hematologic lineage and/or chemotherapy-induced toxicity.

The true incidence and prevalence of PLCH is unknown. In a series of 502 open lung biopsies for diffuse ILD, PLCH was diagnosed in 17 biopsies (3.4%).9 Furthermore, PLCH comprises less than 2% of the cases in the database of the Denver Specialized Center of Research program in ILD.10 Although PLCH is almost always a sporadic disease, a few familial cases have been reported. For instance, an 11-year-old girl presented with LCH in the rib, while her mother, a 41-year-old heavy smoker, was diagnosed with PLCH 8 years after the onset of disease in her daughter.11

IMAGING STUDIES

Imaging studies in PLCH are characterized by bronchiolocentric lesions in a characteristic upper-middle lung distribution with relative sparing of the lung bases.12 In early disease, high-resolution computed tomography (HRCT) usually shows bronchiolocentric nodules that are in general 1 to 10 mm, possibly with surrounding ground-glass opacities (Figure 1, A). The nodules have stellate or irregular borders and on occasion can be larger than 10 mm and bizarrely shaped. They also may have a faint lucent costophrenic angle sparing. Fibrocystic changes can be seen in end-stage PLCH. The clinical and radiologic differential diagnosis of cystic lung disease, based on disease distribution with relative sparing of the lung bases,12 a combination of multiple cysts and nodules, with a mid to upper lung zone predominance, and interstitial thickening in a young smoker is so characteristic that it can be diagnostic of PLCH. Fluorodeoxyglucose–positron emission tomography (FDG-PET) scans may show increased uptake in patients with PLCH. In a study of 11 patients with PLCH, 5 had positive PET scan findings.13 Positron emission tomography scan

### Table 1. Clinical, Morphologic, and Pathogenic Features of Pulmonary and Systemic Langerhans Cell Histiocytosis (LCH)∗

<table>
<thead>
<tr>
<th>Pulmonary LCH</th>
<th>Systemic LCH</th>
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<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td>3–5 per 1 million children/</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Children (predominantly 1–3 years old)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Any age possible</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td>Male (in some studies but not all)</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>More common in northern European White</td>
</tr>
<tr>
<td><strong>Pathogenesis</strong></td>
<td>individuals and rare in African American</td>
</tr>
<tr>
<td><strong>Morphology</strong></td>
<td>individuals</td>
</tr>
<tr>
<td><strong>Immunophenotype</strong></td>
<td>Present/absent</td>
</tr>
<tr>
<td><strong>Ultrasound</strong></td>
<td>No known risk factors</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Clonal</td>
</tr>
<tr>
<td><strong>Frequency, %</strong></td>
<td>At least a subset might be neoplastic</td>
</tr>
<tr>
<td><strong>Dyspnea</strong></td>
<td>(myeloid neoplasm)</td>
</tr>
<tr>
<td><strong>Nonproductive cough</strong></td>
<td>39–87</td>
</tr>
<tr>
<td><strong>Chest pain (often pleuritic)</strong></td>
<td>32–70</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>9–21</td>
</tr>
<tr>
<td><strong>Pneumothorax</strong></td>
<td>16</td>
</tr>
<tr>
<td><strong>Weight loss</strong></td>
<td>12–18</td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td>9</td>
</tr>
<tr>
<td><strong>Symptoms related to extrapulmonary disease</strong></td>
<td>8–15</td>
</tr>
<tr>
<td>(polypuria, polydipsia, pain, and/or skin rash)</td>
<td>10–15</td>
</tr>
<tr>
<td><strong>Hemoptysis</strong></td>
<td>1–13</td>
</tr>
<tr>
<td><strong>Asymptomatic</strong></td>
<td>12–66</td>
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### Table 2. Symptoms of Patients With Pulmonary Langerhans Cell Histiocytosis at Time of Presentation

<table>
<thead>
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<th>Symptom</th>
<th>Frequency, %</th>
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<tr>
<td>Dyspnea</td>
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findings were more likely to be positive if patients had early disease with a predominantly nodular inflammatory lung disease (>100 nodules). In contrast, all patients with negative PET findings had predominantly cystic lung disease with fewer nodules (<25 nodules).

**ROLE OF BIOPSY IN THE DIAGNOSIS**

In the appropriate clinical setting, the presence of typical findings on HRCT scan is often sufficient to establish the diagnosis of PLCH. For instance, HRCT showing nodular and cystic changes in an upper and mid lung distribution in a 30-year-old smoker makes the diagnosis almost certain and a lung biopsy might not be necessary. However, if imaging studies and/or clinical presentation are atypical, tissue might be required to render a definite diagnosis of PLCH.

Although surgical lung biopsy is regarded as a diagnostic tool for PLCH (Figure 2, A), histopathologic findings of PLCH can be identified in transbronchial biopsies in 17% to 50% of patients (Figure 2, B). Baqir et al. studied the utility of bronchoscopy in the diagnosis of PLCH in a series of 38 patients with PLCH. At least 6 transbronchial biopsy specimens were obtained during bronchoscopy for each patient, and the diagnosis required the presence of typical histopathologic features of PLCH accompanied by clinical and typical chest computed tomography findings. In this series of 38 patients, the diagnosis of PLCH was established by transbronchial biopsy in 19 (50%), by surgical lung biopsy in 17 (45%), by biopsy of extrapulmonary sites in 4 (11%), and/or by bronchoalveolar lavage with 5% or more CD1a+ cells in 3 (8%). All patients who had to undergo surgical lung biopsy for diagnosis had a prior transbronchial biopsy that was nondiagnostic. Overall, transbronchial biopsy appears to be diagnostic in a considerable subset of patients with PLCH, suggesting that surgical lung biopsy might be reserved for cases in which bronchoscopic specimens are not diagnostic. Furthermore, transbronchial biopsies might also be important to exclude clinical and radiologic mimickers of PLCH such as sarcoidosis, hypersensitivity pneumonitis, infections, or lymphangioleiomyomatosis. Limitations of transbronchial biopsies for the diagnosis of PLCH include (1) sampling bias due to focal and patchy disease and the paucity or absence of cellular/active nodules in advanced disease, (2) location of disease with findings usually more distally, (3) crushing of Langerhans cells and difficulty in appreciating the "stellate scar," (4) the requirement for a high level of suspicion to order the appropriate immunostains, and (5) increased risk of pneumothorax.

Surgical lung biopsies should be guided by computed tomography findings. Multiple biopsies from multiple lobes are recommended.

Although studies support that bronchoalveolar lavage with at least 5% CD1a+ cells in the correct clinical setting might be diagnostic of PLCH, this technique can be difficult to perform in daily practice owing to its infrequent use. The infrequent use leads to problems with associated costs and quality assurance.

Transbronchial cryobiopsies have recently become more popular, particularly for the diagnosis of ILDs. Preliminary data suggest that this technique is safe and provides larger specimens with enhanced quality, while cellular structures and microscopic architecture appear to be preserved and immunohistochemical staining can be reliably performed. Although no larger studies using cryobiopsies have been reported yet, Fruchter et al. included 3 cases of PLCH diagnosed on cryobiopsy in a recent study.

| Table 3. Clinical and Radiologic Differential Diagnosis of Cystic Lung Disease Based on Disease Distribution |
|---|---|---|
| **Upper Lung** | **Lower Lung** | **Entire Lung** |
| Pulmonary Langerhans cell histiocytosis | Panacinar emphysema | Lymphangioleiomyomatosis |
| Centrilobular emphysema | Usual interstitial pneumonia | Congenital bronchiectasis |
| Sarcoid | Birt-Hogg-Dubé syndrome | Infectious |
| | | Lymphoid interstitial pneumonia |
| | | Cancer |
GROSS FINDINGS

On gross examination of a wedge biopsy, a fine nodular infiltrate might be identified. The nodules are in general small and range in size usually up to 15 mm, although larger nodules can also be seen on occasion.

Lung explants usually appear hyperinflated and will show advanced disease characterized by cystic changes predominantly in an upper lobe distribution. Middle lobe and upper part of the lower lobes might also be involved (Figure 3). Sometimes the cystic changes of PLCH are difficult to distinguish from advanced emphysema. Honeycomb changes can be found in the mid and upper lung but can also involve lower lung lobes. A nodular infiltrate might be seen but nodules may be absent in advanced disease.

HISTOPATHOLOGIC FEATURES

Histopathologic findings of PLCH are summarized in Table 4 and Figure 4. Langerhans cells characteristically are relatively large with moderate amount of eosinophilic cytoplasm and pale nuclei (Figure 4, A). The nuclei have prominent nuclear grooves that are sometimes compared with wrinkled tissue paper. One or 2 small nucleoli are present in general. In early PLCH, cellular inflammation is prominent and is characterized by loose cellular nodules forming adjacent to small airways, scattered throughout the lung (Figure 4, B). Organizing pneumonia might occur at the edge of the cellular nodules. Interstitial inflammation can also be seen but is usually not a prominent feature.

The cellular nodules can lead to destruction of the bronchiolar wall and adjacent alveolar structures (Figure 4, C). The destructive bronchiolitis will result in progressive dilatation of the lumina of small airways. Eventually, the small airways will be surrounded by fibrous tissue and irregular parenchymal cystic lesions and stellate scars form while cellularity diminishes. These stellate scars have also been described as “star fish–like” or “Medusa head–like” fibrosis. Traction emphysema of alveoli adjacent to the stellate scars might be seen. Eventually, Langerhans cells cannot be identified anymore and the disease might only be suspected by the form and distribution of the scars in the context of the clinical presentation and HRCT findings (Figure 4, D). These lesions are sometimes also referred to as “burnt-out” PLCH. In end-stage disease, honeycomb changes might occur but this finding is uncommon in PLCH.

Given that most patients with PLCH are smokers, it is not surprising that the background lung parenchyma might show smoking-related changes including respiratory bronchiolitis, desquamative interstitial pneumonia, and/or emphysema (Figures 2, B, and 4, E).

IMMUNOHISTOCHEMICAL STUDIES

Although the morphology of cellular nodules in PLCH might be classic, immunohistochemical confirmation is useful in rendering the diagnosis, especially on small transbronchial biopsy specimens. S100 protein was the immunohistochemical stain of choice (Figure 5, A) until...
more specific immunostains such as CD1a and langerin (CD207) became available (Figure 5, B and C). Langerin appears to be exclusively expressed by Langerhans cells, as it has been shown to be involved in the formation of Birbeck granules.25

While S100 protein is a nuclear and cytoplasmic stain, CD1a stains the cell membrane and langerin has a membranous and cytoplasmic granular or Golgi staining pattern.26 Sholl et al26 showed that all cases that were histologically and immunohistochemically confirmed as PLCH, with S100 protein and CD1a, expressed langerin. These cases contained greater than 30 langerin-positive and CD1a+ cells per high-power field (HPF) with a mean of greater than 100 cells per HPF in lesional tissue. Langerin expression was strong in the lesional tissue of all cases. Among other ILDs, only cases of usual interstitial pneumonia contained increased numbers of langerin-positive Langerhans cells within epithelium and interstitium (mean, 14 cells per HPF) as compared with normal lung (mean, 6 cells per HPF). Furthermore, the expression pattern of langerin and CD1a was similar. The study confirmed that langerin and CD1a can serve as specific diagnostic markers in distinguishing PLCH from other interstitial and inflammatory processes. S100 protein−positive cells even though they might show a variable number of scattered Langerhans cells in the interstitium and the bronchiolar mucosa. Furthermore, histiocytes in lung diseases other than PLCH do not stain for langerin and CD1a; however, they might express S100 protein. While ECD is also characterized by infiltrating clusters and nodules of histiocytes, these histiocytes are characterized by a rather foamy cytoplasm and lack the typical nuclear grooves of Langerhans cells. Similar to PLCH, lesional histiocytes in ECD can be located peribronchial; however, overall, in ECD the histiocytes follow a lymphangitic distribution and are also found subpleurally, in interlobular septa, and perivascularly.

**PULMONARY HYPERTENSION IN PULMONARY LANGERHANS CELL HISTIOCYTOSIS**

Pulmonary hypertension (PHT) is commonly identified in patients with PLCH and can be severe. In fact, PHT has been reported in 17% to 92% of patients with PLCH.3,28,29 In a study of 17 patients with PHT who presented with dyspnea, 15 had a pulmonary artery systolic pressure (PASP) at rest of greater than 35 mm Hg by echocardiography.28 Thirteen (of 15) patients without another known cause of PHT had a median PASP of 67 mm Hg (range, 41.2–90.6 mm Hg) with 9 patients having a PASP of greater than 50 mm Hg. Seven patients with PASP greater than 65 mm Hg had an enlarged right ventricle with impaired systolic function. In a study of 36 patients who underwent lung or heart–lung transplant for PLCH and also right heart catheterization, 92% of patients had a mean pulmonary artery pressure (mPAP) greater than 25 mm Hg and 72.5% had an mPAP of at least 35 mm Hg.29

Vasculopathy in PLCH can involve pulmonary arteries (Figures 6, A through D) and veins. In a study of 12 patients with PLCH and severe PHT (mPAP, 59 mm Hg), vascular changes included mild to severe intimal fibrosis and medial hypertrophy of pulmonary arteries and mild to severe intimal fibrosis and moderate to severe muscularization of pulmonary veins.30 In 7 biopsies, venous obliteration was identified. Venooclusive-like disease with venular obliteration, hemosiderosis, and capillary dilatation was seen in one-third of the patients. In about half of the patients, vascular changes occurred in areas uninvolved by parenchymal lesions. In patients with 2 consecutive available lung samples (taken before and after the clinical occurrence of PHT), pulmonary vasculopathy worsened, whereas parenchymal and bronchial lesions remained unchanged. These findings suggest that PHT in PLCH is likely a primary pulmonary vascular disease, in which the pulmonary vasculature is involved independently of small airway and lung parenchymal injury.

Pulmonary hypertension in patients with PLCH appears to be associated with increased mortality. Of 13 patients with PLCH and PHT, 8 patients were alive after a median of

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<tr>
<th>Table 4. Histopathologic Features of Pulmonary Langerhans Cell Histiocytosis (PLCH)</th>
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<tr>
<td><strong>Early PLCH</strong></td>
</tr>
<tr>
<td>- Bronchiolocentric cellular nodules</td>
</tr>
<tr>
<td>- Cellular nodules composed of Langerhans cells and various proportions of lymphocytes, macrophages, eosinophils, plasma cells, and neutrophils</td>
</tr>
<tr>
<td>- Destruction of bronchiolar wall and adjacent lung parenchyma</td>
</tr>
<tr>
<td>- Interstitial inflammation may be seen</td>
</tr>
<tr>
<td><strong>Advanced PLCH</strong></td>
</tr>
<tr>
<td>- Cysts</td>
</tr>
<tr>
<td>- Bronchiolocentric stellate scars</td>
</tr>
<tr>
<td>- Scarring of airways</td>
</tr>
<tr>
<td>- Traction emphysema of alveoli adjacent to stellate scars</td>
</tr>
<tr>
<td>- Langerhans cells might not be detectable</td>
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**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of PLCH includes histiocytic/macrocystic lesions and eosinophil-rich diseases. Among the histiocytic/macrocystic lesions are respiratory bronchiolitis and desquamative interstitial pneumonia, Erdheim-Chester disease (ECD), and hypersensitivity pneumonitis. Eosinophilic pneumonia represents an eosinophil-rich lesion that might also be considered in the differential diagnosis. All these diseases lack large clusters and nodules of Langerhans cells even though they might show a variable number of scattered Langerhans cells in the interstitium and the...
81.4 months; 5 patients died owing to the underlying lung disease after a median of 7.6 months. World Health Organization functional class was the only variable that was significantly associated with death.31

There are no markers that might predict the occurrence and severity of PHT in PLCH. Except for an inverse correlation between forced vital capacity and PASP, no other pulmonary functional parameters have been associat-
ed with PASP in PLCH. These findings suggest that severe PHT is not limited to patients with end-stage pulmonary disease due to PLCH and that advanced pulmonary parenchymal destruction is not essential for the development of PHT.

Decreased exercise capacity in advanced PLCH does not appear to be related to decreased pulmonary function but may be related to pulmonary vascular dysfunction. When patients with advanced PLCH and severe PHT (mPAP, 59 mm Hg) were compared to patients with chronic obstructive pulmonary disease (COPD) (mPAP, 36 mm Hg) or idiopathic pulmonary fibrosis (mPAP, 33 mm Hg), the degree of PHT was not related to pulmonary function in patients with PLCH in contrast to patients with COPD or idiopathic pulmonary fibrosis. Pulmonary hypertension in PLCH is thought to represent a specific pulmonary vasculopathy rather than a secondary finding because in 8% to 70% of patients, walls of small and medium-sized pulmonary arteries within prominent PLCH nodules are infiltrated by inflammatory cells (Figure 6, E). Furthermore, cytokines and growth factors that are known to be released by PLCH nodules and that have been implicated in the pathogenesis of PHT, such as interleukin (IL)–1, IL-6, transforming growth factor β (TGFβ), and platelet-derived growth factor, might lead to diffuse pulmonary vascular remodeling and could explain vascular changes not only found in the vicinity to the PLCH nodules but also away from the nodular lesions. The absence of any correlation between pulmonary function and hemodynamic changes in PLCH argues against pulmonary mechanics or hypoxemia causing PHT in PLCH. Lastly, cigarette smoke is a known inducer of pulmonary vascular remodeling and might also play a role in the vascular changes of PLCH.

Given the relative high incidence of PHT in PLCH it is recommended to screen affected patients with at least echographic studies for the possibility of PHT even if patients do not have symptoms. If the estimated right ventricular systolic pressure exceeds 40 mm Hg or there is evidence of reduced right-sided cardiac function, right heart catheterization might be considered.

**TREATMENT**

The most important “treatment” of PLCH is smoking cessation. However, in some patients the disease progresses despite smoking cessation; in other cases, disease is stable even though the patient continues to smoke. There are no biologic prognostic markers or markers to predict behavior of PLCH.

Corticosteroids, cyclophosphamide, and methotrexate are sometimes used for patients with PLCH who have severe or progressive decline in lung function; however, these medications seem to be of limited value. Cladribine (2-chlorodeoxyadenosine), an agent cytotoxic to lymphocytes and monocytes, has been used in LCH and recently has also been tried for a few patients with PLCH. In a recent series, 5 patients with PLCH were treated with cladribine because of progressive pulmonary disease with obstructive lung function despite smoking cessation and/or corticosteroid therapy. Four patients had an improvement in the functional class dyspnea; forced expiratory volume in 1 second increased in all cases. Features on chest HRCT improved in 4 patients. Hemodynamic improvement was observed in 1 patient with precapillary PHT. The results suggested a greater treatment effect in subjects with nodular lung lesions and/or thick-walled cysts on HRCT, with diffuse hypermetabolism of lung lesions on PET scan, and with progressive disease despite smoking cessation.

Treatment of patients with PLCH and PHT, including endothelin receptor antagonist and/or phosphodiesterase 5 inhibitor, or inhaled iloprost with or without a second treatment agent, resulted in a decrease of mPAP and pulmonary vascular resistance. There was no significant worsening of oxygenation observed with treatment.

Lung transplant might be considered for patients with advanced, progressive disease. Recurrence of PLCH in the
transplanted lung may occur. In a recent retrospective multicenter study of 39 patients who underwent lung or heart-lung transplant for PLCH, the disease recurred in 8 patients (20.5%); however, recurrence did not appear to affect the overall outcome.29

POSTULATED PATHOGENESIS OF PLCH

The pathogenesis of PLCH is still largely unknown and controversial. Langerhans cells are a subpopulation of dendritic cells. In the lung, Langerhans cells can be found in the mucosa of the tracheobronchial tree where they act in the defense and surveillance of inhaled antigens.38 Here they likely play important roles in mediating tolerance toward inhaled antigens and probably are important in preventing unnecessary airway inflammation to innocuous antigens deposited in the airways. Danger signals, including Toll-like receptors expressed on infectious pathogens or factors released by injured or necrotic cells, might lead to the activation of Langerhans cells.

It has also been postulated that PLCH might be immune modulated. As alluded to earlier, PLCH nodules contain not only Langerhans cells but also various numbers of mixed inflammatory cells including eosinophils, T cells (especially FoxP3+ CD4+ regulatory cells),39 activated macrophages, and osteoclast-like multinucleated giant cells. Furthermore, pathologic Langerhans cells appear to have potent lymphostimulatory capacity and express abundant costimulatory molecules including CD40, CD80, and CD86.40,41 Matrix metalloproteinases (MMPs) produced by dendritic cells, Langerhans cells, and other infiltrating monocytoid cells in inflammatory nodules may play an important role in the airway remodeling and bronchiolar destruction given that MMP2 and MMP9 are strongly expressed in lesional dendritic cells, Langerhans cells, and macrophages.42,43

Given that more than 90% of patients with PLCH are current or former smokers, smoking has been implicated in the pathogenesis of PLCH, leading to several hypotheses. For instance, it has been shown that cigarette smoke can induce the production of cytokines that play a role in recruitment, differentiation, and activation of Langerhans cells and dendritic cells, including TNFα, granulocyte macrophage–colony stimulating factor (GM-CSF), TGFβ,
and CCL20.44–47 Moreover, dendritic cells incubated with cigarette smoke extract produced inflammatory mediators such as CXCL8 and prostaglandin E2 (PGE2).44 Furthermore, cigarette smoke suppresses lipopolysaccharide and CD40L-induced dendritic cell costimulatory molecule expression and cytokine secretion. In addition, cigarette smoking has been shown to stimulate the production of Bombesin-like peptides, which are chemotactic for monocytes, mitogenic for epithelial cells and fibroblasts, and stimulate cytokine secretion.49,50 An abundant expression of osteopontin in Langerhans cells from lesional tissue in PLCH has also been observed.51 Osteopontin has prochomatotic activity for Langerhans cells and dendritic cells, and macrophages and monocytes. Overexpression of osteopontin in rat lungs led to lesions analogous to human PLCH.52 Tobacco glycoprotein is found in tobacco and is an immunostimulant that induces lymphocyte differentiation and lymphokine production.53

Smoking may also alter the turnover of dendritic cells in the lung or facilitate recruitment of Langerhans cell and dendritic cell precursors. Increased Langerhans cells have also been found in other lung diseases of smokers, including COPD, certain ILDs, and lung carcinoma. Smoking might promote survival of Langerhans cells by increased expression of the antiapoptotic cytokine Bcl-XL, which has been shown to be overexpressed in biopsy specimens of patients with PLCH.54 Overall, it appears that effects of cigarette smoke on dendritic cell and Langerhans cell activation might be immunomodulatory.55 However, only a few smokers develop PLCH. Moreover, the clinical spectrum of PLCH seems diverse, with many patients having a favorable prognosis with or without smoking cessation and with a subset of patients with PLCH having a poor prognosis. A second hit by host factors has been postulated, for instance, exogenous factors/insult (virus) or failure of anti-inflammatory reaction.

It has long been debated whether PLCH is a reactive or neoplastic disease. Given the association with smoking for most patients, PLCH was originally thought to be a nonneoplastic disease associated with cigarette smoke. In contrast to PLCH, such a provoking agent was never identified in systemic LCH. Moreover, in systemic LCH, clonality was already described in 1994.56 Using X-linked polymorphic DNA probes for the human androgen receptor assay (HUMARA assay), Willman et al56 detected clonal cells in LCH lesions of 9 of 10 patients. The percentage of clonal cells closely approximated the percentage of CD1a+ Langerhans cells in each lesion. Moreover, no clonality was identified in the leukocytes of these patients, further supporting that the clonality found was indeed due to the lesional cells of LCH. Extreme constitutional lioniization precluded assessment of clonality in the 10th case. Willman et al56 concluded that the detection of clonal histiocytes in LCH indicates that this disease is probably a clonal neoplastic disorder. Studies by Yu et al57 and Gong et al58 confirmed clonal proliferation of lesional cells in LCH in all 6 cases tested. More recently, BRAF V600E mutations were identified in 38% to 57% of systemic LCH cases, suggesting that at least a subset of LCH might be myeloid neoplasm.59,60 Specifically, Badalian-Very et al59 identified the oncogenic BRAF V600E mutation in 35 of 61 (57%) cases. The mutation tended to appear in younger patients but was not associated with disease site or stage. In 2001 Yousem et al62 used the HUMARA approach to assess clonality in female patients with PLCH. Twenty-four nodules in 13 patients were tested; 7 nodules were clonal. These results were the first suggestion that at least some cases of PLCH might also be clonal. Recently, Yousem et al62 performed next-generation sequencing on 22 PLCH nodules from 5 patients and found BRAF V600E mutation in all nodules from 2 patients (40%) and no mutations in any nodule from the 3 other patients. Of the 2 cases in which BRAF mutations were identified, one case had 5, while the second case had 2 individual and distinct nodules that had an identical BRAF V600E mutation. All nodules were negative for 46 other cancer-related genes. This study further supported the possibility that at least a subset of PLCH might be clonal. This finding also led to the hypothesis that cigarette smoke might have a systemic effect, stimulating sensitized Langerhans cell precursors in the bone marrow. Once a mutational event occurs, the activated Langerhans cells would migrate selectively to the lung, where they would produce the clonal pulmonary nodular disease.62

Roden et al63 identified BRAF V600E expression in 7 of 25 PLCH cases (28%) and 19 of 54 systemic LCH cases (35%). Interestingly, in PLCH cases, BRAF expression was associated with higher cumulative tobacco exposure. In systemic LCH cases, the amount of tobacco exposure did not appear to play a role in BRAF expression. BRAF expression correlated with BRAF V600E mutation status in most cases with only 4.4% of the cases being discordant. Two (of 3) discordant cases consisted of bone biopsy specimens that were positive for BRAF V600E mutation by polymerase chain reaction but negative by immunohistochemistry; 1 biopsy specimen of PLCH was wild type by polymerase chain reaction and showed BRAF expression by immunohistochemistry. This discrepancy might at least in part have been due to fixation/decalcification of the bone biopsy specimens. Nonetheless, this study confirmed that at least a subset of PLCH might be clonal processes. BRAF is a member of the MAPKinase signaling pathway, which is activated through the engagement of the epidermal growth factor receptor, eventually resulting in stimulation of cell proliferation, differentiation, migration, and senescence/apoptosis. BRAF mutations have been identified in malignant (melanoma, colonic adenocarcinoma, lung adenocarcinoma, papillary thyroid carcinoma) and benign (nevi) tumors. Recurrent BRAF mutations in systemic LCH and PLCH indicate that the disease may respond to MAPKinase pathway inhibitors.

**PROGNOSIS**

The disease can be progressive, stable, or resolving; however, the outcome of PLCH is unpredictable even after smoking cessation. The overall survival for PLCH is good with most reports showing a 5-year survival estimate of 73% or more.2,31 In a review of clinical outcomes of 102 adult patients with PLCH, the median survival of 12.5 years from the time of diagnosis was shorter than for age-matched controls in the general population.2 Estimated 5- and 10-year survival rates were 74% and 64%, respectively. Thirty-three patients died during follow-up; almost half of the deaths were attributed to respiratory failure. The other major cause of death was malignancy, primarily of hematologic or epithelial origin. In another study of 29 patients with PLCH and PHT, the 1-, 3-, and 5-year survival estimates were 96%, 92%, and 73%, respectively.31 Factors associated with poor outcome are summarized in Table 5.
SUMMARY

Pulmonary Langerhans cell histiocytosis, a nodular and eventually cystic lung disease of the upper and mid lung zones, is a disorder of cells with Langerhans cell phenotype. PLCH appears to be distinct from systemic LCH and occurs almost exclusively in smokers. Although in some patients a surgical lung biopsy is necessary to establish the diagnosis, many cases can be diagnosed on a transbronchial biopsy, or, if clinical and radiologic findings are typical, tissue might not be necessary for diagnosis. PLCH is commonly associated with pulmonary hypertension that may be independent of the severity of PLCH. The pathogenesis of PLCH is still debated but might be related to host and smoking-related immunomodulatory processes. The recent finding of BRAF V600E mutation and BRAF V600E protein expression indicates that at least a subset of PLCH might represent a clonal process. These findings also suggest that therapies targeting the MAPKinase pathway may potentially be useful for therapy-refractory patients with PLCH. However, additional studies are needed to identify prognostic factors of PLCH and improved treatments for refractory PLCH cases.

References


