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Pulmonary Langerhans' cell histiocytosis

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Pulmonary Langerhans' cell histiocytosis (PLCH) is an uncommon but important cause of interstitial lung disease, and it occurs predominantly in adult cigarette smokers [1]. PLCH belongs to the spectrum of Langerhans' cell histiocytosis (LCH), diseases characterized by uncontrolled proliferation and infiltration of various organs by Langerhans' cells [2,3]. Other clinical entities within this spectrum of LCH are seen in adults and children and vary in severity from mild disease that requires no therapy to severe disseminated forms with extensive organ involvement and high mortality [4–7]. Organ systems involved by LCH may include skin, bone, pituitary gland, lymph nodes, and lungs [1,4,6]. Although LCH is approximately three times more common in children than adults, pulmonary involvement is much more common in adults with LCH, in whom it frequently occurs as the sole organ involved with disease [1,8–10]. This article summarizes recent advances and current understanding of PLCH.

Epidemiologic features of pulmonary Langerhans' cell histiocytosis

PLCH afflicts predominantly whites and is uncommon in individuals of African or Asian descent. The disease occurs principally in young adults between the ages of 20 and 40 years, although it can present in other age groups [1,4,10]. The reported relative sex distribution of PLCH varies greatly among studies, with earlier studies suggesting a male preponderance and more recent studies reporting a slightly higher proportion of women [1,8–11]. These differences may reflect changing smoking habits of women.

The estimation of the prevalence and incidence of PLCH is difficult. A large surgical lung biopsy series of patients with interstitial lung disease identified PLCH in 5% of specimens [12]. Many patients with PLCH do not undergo a surgical lung biopsy for various reasons, however. In some patients the disease is never suspected, whereas others are diagnosed on the basis of radiologic features seen on high-resolution CT (HRCT) of the lungs. In a more recent study, PLCH was diagnosed in 91 of 1382 patients (6.6%) included in the Italian registry of interstitial lung diseases [13]. This report allowed the inclusion of patients whose diagnosis was established by clinical and radiologic studies without biopsy confirmation.

The principal epidemiologic factor associated with PLCH is cigarette smoking (Box 1). In multiple studies, most patients with PLCH used tobacco [1,9,10,14], in contrast to patients with LCH without pulmonary involvement in whom smoking is less prevalent [4]. Patients with PLCH are often heavy smokers and have a remarkably difficult time quitting smoking (unpublished observations). In addition to the observation that more than 90% of patients with PLCH smoke, other direct and indirect observations suggest a strong, although not absolute, link with cigarette smoking (see Box 1). Cigarette smoking was attributed to the onset of PLCH in two adults who had childhood LCH diagnosed 23 and 12 years, respectively, before the onset of their lung disease [15]. Smoking also may precipitate recurrence of disease in transplanted lungs of patients with PLCH [16]; con-

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Box 1. Evidence linking cigarette smoking and pulmonary Langerhans' cell histiocytosis

Experimental observations

Increased number of dendritic cell in lungs of mice exposed chronically to cigarette smoke [18]

Nonclonal proliferation of Langerhans' cells in PLCH lesions of smokers [42]

Epidemiologic observations

Most (> 90%) patients with PLCH are smokers [1,9,10,14]

Smoking precipitating PLCH many years after the onset of LCH in childhood [15]

Clinicopathologic observations

Increase in Langerhans' cell numbers in lungs of asymptomatic smokers [25]

Bronchiolocentric distribution of lung lesions [8,9]

Co-existence of PLCH and other smoking-related histologic patterns of lung injury [50]

Recurrence of disease in transplanted lungs of patients with PLCH upon resumption of smoking [16]

Regression of PLCH after smoking cessation [17]

versely, smoking cessation may result in objective improvement of disease [17]. These data, together with other clinical and animal studies, provide convincing evidence that cigarette smoking somehow predisposes to, or precipitates, PLCH [18].

Although the epidemiologic association between smoking and PLCH is strong, it is not absolute. We have seen occasional patients with biopsy-proven PLCH in whom there is no history of active, past, or second-hand smoking [1]. It is important to reemphasize that smoking is predominantly associated with isolated PLCH rather than multisystemic LCH, in which smoking is less prevalent. Nonsmokers with PLCH and multiorgan disease may represent a different disease entity than cases that involve isolated smoking-associated PLCH, despite similar radiologic and histopathologic features.

Because approximately 20% of adults in the United States smoke cigarettes, it is not clear why PLCH is relatively rare. This fact implies that other factors are required to cause this disease, in addition to smoking. There is an ongoing effort to identify additional host or environmental factors that may predispose to PLCH. The identification of LCH in siblings and first cousins from known or possibly consanguineous families, and reports of three affected parent-child pairs, have generated interest in genetic factors [19]. PLCH is almost always a sporadic disease, however, with only exceptional reports of familial clustering [20]. Although some studies have suggested a potential role for viral pathogens [21], others failed to reproduce these observations [22].

Pathogenesis

Dendritic cells are a heterogeneous population of potent antigen-presenting cells that are classified into distinct subsets according to location, surface phenotype, and functional properties [23]. Langerhans' cells are a specific population of dendritic cells that are distributed almost exclusively beneath the epithelium of the tracheobronchial tree, where they serve as a primary line of defense surveying the antigens constantly being deposited in the airway after inhalation [23,24]. After exposure to inhaled antigens that breach the airway epithelium, Langerhans' cells become activated and migrate to regional lymphoid tissues, where they stimulate lymphocyte proliferation in response to the antigenic exposure in the airway. In addition to having the capacity to stimulate inflammatory lymphocytic responses to harmful antigens (such as those expressed by infectious pathogens), Langerhans' cells also have a role in mediating tolerance toward harmless antigens. This latter function is essential, because unnecessary airway inflammation may ensue every time antigen is deposited in the airway. Unraveling the mechanisms by which Langerhans' cells coordinate airway immune responses after exposure to antigen is fundamental to understanding the pathogenesis of PLCH.

Although evident that cigarette smoke is the most important factor associated with the development of PLCH, the effect of smoking on Langerhans' and dendritic cell function is poorly understood. Smoking induces accumulation of Langerhans' cells in the lungs of asymptomatic smokers and patients with PLCH [25]. This finding suggests either that smoking alters the normal physiologic turnover of dendritic cells in the lung or may facilitate recruitment of precursors of Langerhans' cells into the lung. In this con-

text, certain cytokines, such as tumor necrosis factor-alpha, granulocyte-macrophage colony-stimulating factor (GM-CSF), and transforming growth factor-beta, may have an important role, because these cytokines are important for the development, recruitment, and function of dendritic cells [23,26,27]. Immunohistochemical techniques demonstrate that GM-CSF is abundant in the epithelium of bronchioles affected by the inflammatory lesions of PLCH [28]. Whether smoking induces the expression of GM-CSF in the airway epithelium is not known, although cigarette smoke extract has been shown to induce GM-CSF release from fibroblasts in vitro [29]. The pulmonary lesions of patients with PLCH also demonstrate abundant expression of transforming growth factor-beta, a cytokine that has important effects on dendritic cell function and participates in the process that leads to lung fibrosis and scarring [30]. It is possible that smoking may induce the production of tumor necrosis factor-alpha, GM-CSF, and transforming growth factor-beta by cells in the proximity of lung dendritic cells, particularly alveolar macrophages, airway epithelial cells and fibroblasts, which results in inappropriate and sustained production of these cytokines and facilitates the local expansion of Langerhans' cells in peribronchiolar regions. Subsequently, through an inability to upregulate chemokine receptors (such as CCR7) necessary for migration to lymph nodes, lung dendritic cells may persist in peribronchiolar regions in a suboptimally activated state [31]. Because of their reduced chemotactic potential, these pathologic Langerhans' cells persist inappropriately in the airways and may locally induce T-cell proliferation and the formation of inflammatory granulomatous lesions composed of Langerhans' cells, T cells, eosinophils, and plasma cells. Despite their reduced migratory capacity (based on the demonstration of reduced CCR7 expression in inflammatory LCH lesions), the pathologic Langerhans' cells seem to have potent lymphostimulatory capacity and the necessary costimulatory molecules to enable T-cell stimulation to occur at these sites of inflammation [32,33].

Several hypotheses have been proposed to explain mechanisms by which cigarette smoke leads to PLCH. One hypothesis suggests that cigarette smoke–induced secretion of bombesin-like peptides by neuroendocrine cells leads to induction of cytokine secretion by macrophages, proliferation of lung fibroblasts, and modulation of T-cell responses [34,35]. Other components of cigarette smoke, such as tobacco glycoprotein and circulating immune complexes to tobacco antigens, also have been implicated in the pathogenesis [36–38].

The seminal report that monoclonal proliferation of Langerhans' cells occurs in childhood and adult forms of LCH stimulated discussion about LCH as a form of neoplasm [39–41]. In some patients with multisystemic LCH, the disease course is aggressive and systemic chemotherapy is indicated [7]. PLCH does not behave like a malignancy in most patients, however, and is much more likely to represent a reactive rather than neoplastic disorder. We propose that in contrast to LCH that involves other sites, PLCH is a reactive process usually incited by cigarette smoking in certain predisposed individuals. This hypothesis is supported by the observation that most lesions in PLCH are nonclonal, unlike the lesions of multisystemic LCH, which are almost uniformly caused by clonal proliferation [42].

Pathologic findings

The earliest histologic lesion of PLCH consists of proliferation of Langerhans' cells along small airways [8]. These early cellular lesions expand to form nodules 1 to 5 mm in diameter, although nodules as large as 1.5 cm have been observed. The characteristic lesion is composed of variable numbers of Langerhans' cells, plasma cells, lymphocytes, fibroblasts, and pigmented alveolar macrophages, which form a loosely aggregated granuloma. Eosinophils also may be seen in these lesions, hence the term ''eosinophilic granuloma.'' These granulomas are typically centered around distal bronchioles, where they infiltrate and destroy airway walls and are separated by areas of normal lung parenchyma [8].

An increase in the number of Langerhans' cells is the cardinal feature of the PLCH lesion. Although experienced pathologists traditionally have diagnosed PLCH by light microscopy, it is recommended that these cells be identified in suspected lesions by immunohistochemical methods. Langerhans' cells are typically identified by staining for the S-100 protein and the CD1a antigen [43]. Electron microscopy also allows definitive identification of Langerhans' cells through demonstration of specific intracytoplasmic organelles called Birbeck granules [44,45]. Birbeck granules are found in normal Langerhans' cells and are present in greater numbers in pathologic Langerhans' cells that populate the lesions of PLCH [33,44]. The function of these granules is not known, but it may be related to the antigen-presenting function of Langerhans' cells. A correlate of the presence of Birbeck granules is the expression of Langerin (also referred to as CD207), which may be demonstrated

by immunohistochemical staining [46]. Although useful as a research tool, electron microscopy is rarely used in our clinical practice for identification of Langerhans' cells.

The mere presence of Langerhans' cells is not diagnostic of PLCH, because accumulations of these cells have been described in other inflammatory and neoplastic pulmonary processes [47,48]. The histopathologic diagnosis of PLCH requires identification of typical morphologic features, together with demonstration of increased numbers of Langerhans' cells within the lesion. Because the folded nucleus and pale cytoplasm of the Langerhans' cell may be characteristic, expert pathologists may reliably render this diagnosis based solely on the morphologic examination of routine hematoxylin and eosin–stained tissue specimens without the need to use immunostaining [8,9].

It is believed that the lesions of PLCH progress from a cellular nodule to an intermediate cellular and fibrotic nodule and ultimately to an entirely fibrotic nodule. Macroscopically, the nodules are frequently stellate in configuration and may interconnect with adjacent nodules to yield a distinctive form of cicatricial change with adjacent airspace enlargement and eventually hyperinflation [8]. Cavitation of the nodules also may be appreciated histologically [8]. In later stages of the disease, the nodules become pauci-cellular, lack Langerhans' cells, and are predominantly fibrotic. In these situations, a presumed diagnosis of "burned out" PLCH may be made through identification of the typical shape and distribution of the fibrotic nodular lesions, termed "stellate scars."

In addition to the characteristic lesions, other histologic findings are commonly associated with PLCH. Because most patients are active smokers, respiratory bronchiolitis is invariably present [8,9,49]. Accumulation of pigmented macrophages in airspaces adjacent to PLCH lesions is also common and results in a so-called "desquamative interstitial pneumonia-like" reaction. Sometimes the degree of alveolar filling from this associated desquamative interstitial pneumonia-like reaction is extensive, which creates confusion regarding the primary underlying diagnosis [8–10,50]. The lesions of PLCH often extend into adjacent vascular structures, which causes a vasculopathy that may be partly responsible for the abnormal pulmonary hemodynamics that are increasingly recognized in these patients [51]. Because most patients are heavy smokers, it is not surprising that emphysema frequently coexists. In one study, histologic evidence of emphysema was present in all surgical biopsy specimens of PLCH [50].

Clinical features of pulmonary Langerhans' cell histiocytosis

Patients with PLCH commonly present with nonspecific respiratory symptoms, such as cough and exertional dyspnea (Table 1) [1,9,10]. Approximately 25% of patients are asymptomatic at the time of presentation or have a mild "smokers cough." Spontaneous pneumothorax is the presenting symptom in approximately 10% to 15% of patients [1]. Constitutional symptoms of varying severity occur in up to one third of patients and may cause significant concern regarding the presence of an underlying malignancy, such as lymphoma. The physical examination, including auscultation of the lungs, is frequently normal, and digital clubbing is unusual [1]. In advanced stages of the disease, decreased breath sounds and prolonged expiration may be appreciated.

Because PLCH is primarily a bronchiolar disease with varying degrees of interstitial and pulmonary vascular involvement, complex and varied patterns of physiologic abnormalities have been described to occur, depending on when the test is performed during the course of the disease [1,14,52]. In the early stages, pulmonary function testing reveals normal results in a significant portion of patients despite the

Table 1
Demographics and clinical features of pulmonary Langerhans' cell histiocytosis

Feature	Findings	References
Peak age at presentation	third and fourth decades	[1,8–10,14]
Sex	Approximately 1:1	[1,10]
Smoking history	90%–95% of adults	[1,8–10,14]
Presenting symptoms (%)	Cough (50–68)	[1,9–11]
	Dyspnea (30–50)	[1,9–11]
	Fever, weight loss, sweats (20–30)	[1,5,6,9–11]
	Asymptomatic (25)	[1,10]
	Chest pain (10)	[1]
Pulmonary function tests (%)	Normal (10–42)	[1,52]
	Restrictive (23–52)	[1,9,10,52]
	Obstructive (22–59)	[1,9,10,52]
	Mixed (4–25)	[1,52]
Secondary complications (%)	Pneumothorax (10–20)	[1,10,11]
	Extrapulmonary disease (15)	[1,9–11]
	Pulmonary hypertension	[51,80]
	Respiratory failure	[1]
	Secondary malignancy	[1,82–85]

presence of abnormalities on chest radiographs (see Table 1) [1,9,52]. Approximately 75% of patients have some pulmonary function abnormality at the time of diagnosis, including obstructive, restrictive, and mixed patterns of impairment [35]. The most consistent physiologic abnormality overall is a reduced diffusing capacity for carbon monoxide, which is reported to occur in 60% to 85% of patients [1]. The reduced diffusing capacity for carbon monoxide is likely to be the consequence of involvement of the pulmonary vascular compartment and parenchymal disease. Obstructive change may be caused by bronchiolar obstruction that results from peribronchiolar inflammation and fibrosis in early disease, or coexistent emphysema in advanced PLCH. In advanced disease, severe obstruction and restriction have been reported to occur, although obstruction seems to be more commonly observed because of the presence of extensive cystic disease and coexistent emphysema. In some patients, severe restrictive physiology caused by extensive fibrotic changes is seen. Impaired exercise performance is common in these patients. One study found markedly reduced exercise capacity, as measured by either work achieved or oxygen use at peak exercise [52]. Exercise limitation correlated with measures of pulmonary vascular dysfunction rather than ventilatory limitation [52].

Radiologic features of pulmonary Langerhans' cell histiocytosis

The chest radiograph appearance is abnormal in most patients, and it often demonstrates micronodular or reticulonodular infiltrates in a symmetric and bilateral distribution with relative sparing of costophrenic angles [53]. Cystic changes may be apparent, commonly superimposed on a background of interstitial changes [53]. Lung volumes as assessed by a chest radiograph may be either normal or increased, a feature helpful in distinguishing PLCH from other interstitial lung diseases (with the exception of lymphangioleiomyomatosis) that are usually associated with reduced lung volumes [10,53]. Uncommon chest radiograph manifestations of PLCH include alveolar infiltrates, hilar or mediastinal adenopathy, prominent pulmonary arteries, pleural effusion, and presentation as a solitary pulmonary nodule without interstitial infiltrates [53–55]. Occasionally the chest radiograph may be normal [56].

HRCT of the chest has become an essential tool in the evaluation of patients with suspected PLCH. The predominant findings on HRCT are nodules and cysts that involve predominantly upper lung zones with relative sparing of the lung bases (Fig. 1A) [57–59]. Relative sparing of lung bases is a useful discriminating feature from pulmonary lymphangioleiomyomatosis, another cystic lung disease that may mimic PLCH radiologically [59,60]. Cysts are often bizarre shaped, variable in size (although usually less than 20 mm in size), and typically have a thin (1 mm or less) wall [61]. In advanced PLCH, confluent cysts may form, which gives a radiologic appearance that may be difficult to distinguish from emphysema (Fig. 1B). Serial HRCT studies have shown that the lesions of PLCH evolve in the following sequence: nodules, cavitated nodules, cysts, and eventually confluent cysts [62]. In early disease, combinations of nodules and cysts are commonly seen, whereas in advanced disease cystic change and architectural distortion tend to predominate.

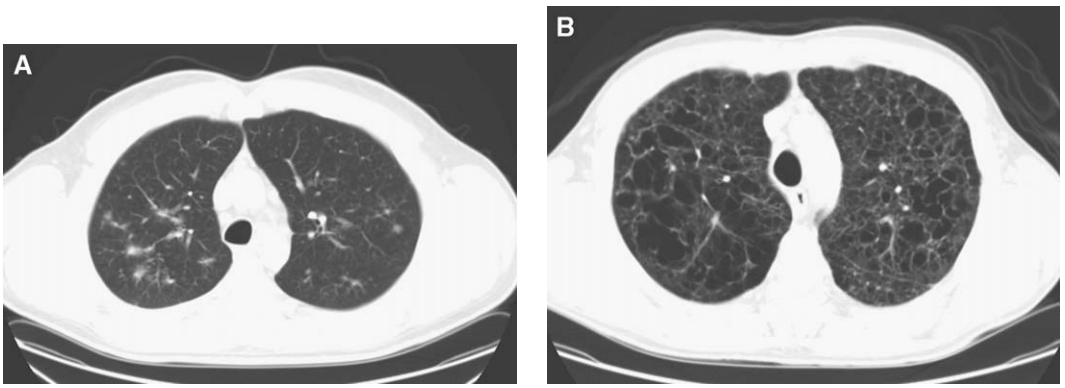

Fig. 1. (*A*) HRCT of a 39-year-old smoker with recent onset of PLCH demonstrates small scattered irregular nodules and tiny peripheral interstitial nodules more marked in the upper lungs. (*B*) HRCT of a 43-year-old heavy smoker with long-standing PLCH. The HRCT demonstrates extensive cystic changes, virtually replacing the normal lung parenchyma.

The distribution and pattern of lesions on HRCT are helpful diagnostically. The combination of cystic lesions associated with nodules (some of which are cavitated) results in a distinctive pattern that is nearly pathognomonic of PLCH. When the HRCT shows these characteristic features, it is possible to establish a presumptive diagnosis of PLCH in the appropriate clinical context. Although highly informative when present, this characteristic pattern is not encountered in all patients. The "typical" HRCT findings are most commonly seen in the earlier stages of disease, when combinations of nodular and cystic lesions are most likely to be seen [62]. In many other situations, nonspecific patterns may be encountered [50]. Ground-glass attenuation, adenopathy, and consolidation also have been reported to occur [50]. The combination of ground-glass infiltrates and nodules may be radiologically indistinguishable from hypersensitivity pneumonitis, whereas mediastinal adenopathy (appreciated in one third of cases on HRCT) may create diagnostic confusion with sarcoidosis [50]. In addition to diagnostic information, the HRCT is helpful in selecting appropriate sites for surgical lung biopsy, when needed.

Bronchoscopy and lung biopsy

Definitive diagnosis of PLCH requires histologic demonstration of typical lesions that contain Langerhans' cells in lung tissue, which may be accomplished by either transbronchoscopic lung biopsy or surgical lung biopsy. Bronchoscopy with transbronchoscopic lung biopsy has a relatively low diagnostic yield in the range of 10% to 40% [1,9,49]. The diagnostic use of transbronchoscopic lung biopsy is limited because of the patchy distribution of nodular lesions in PLCH and the small amounts of tissue obtained. In addition to transbronchoscopic lung biopsy, analysis of bronchoalveolar lavage fluid (BAL) also has a small, but appreciable, diagnostic yield [63,64]. An increase in BAL $CD1a^{+}$ cells (Langerhans' cells) of more than 5% occurs almost exclusively in PLCH [64–66]. Unfortunately, only a

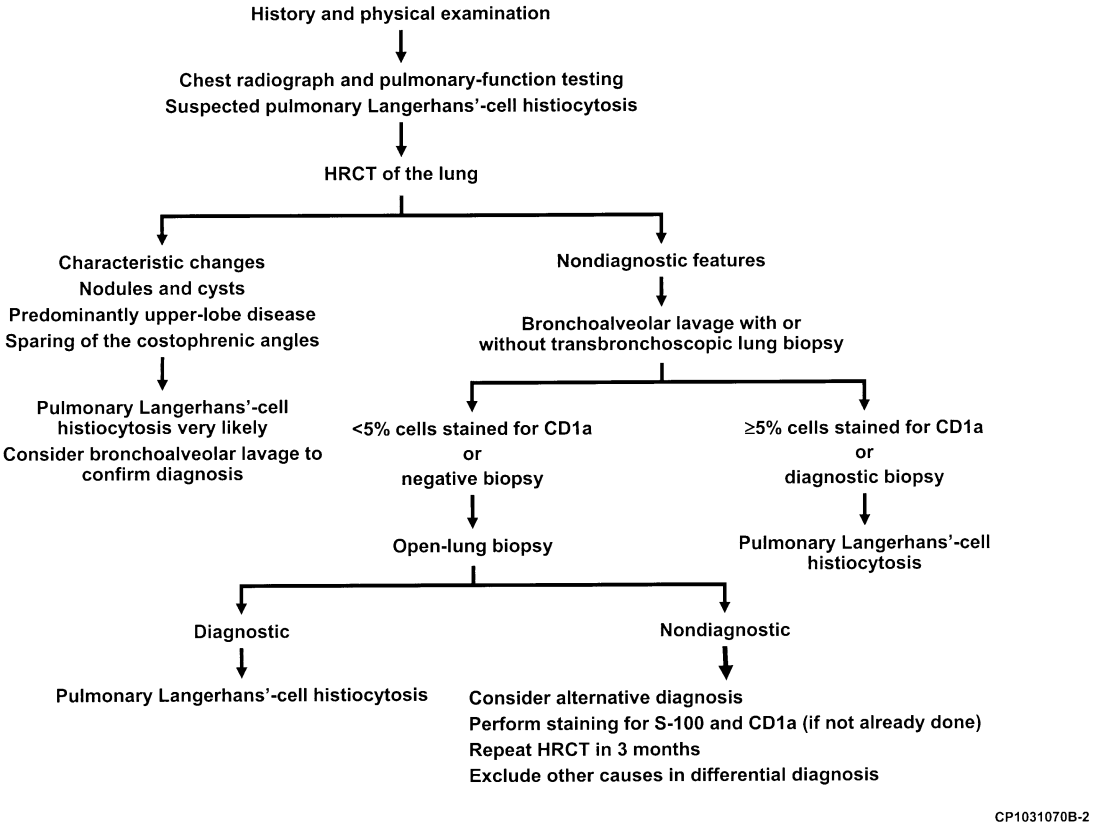

Fig. 2. Proposed diagnostic algorithm for the evaluation of patients with suspected PLCH. (*From* Vassallo R, Ryu JH, Colby TV, Hartman T, Limper AH. Pulmonary Langerhans' cell histiocytosis. N Engl J Med 2000;342:1969–78; with permission.)

modest elevation of $CD1a^+$ cells in the range of 1% to 5% is present in the BAL of many patients with PLCH. Active smokers without PLCH also may have mildly elevated CD1a cell counts in the BAL [25]. Although the finding of more than 5% $CD1a^+$ cells in the BAL has high specificity for PLCH, the use of this test in clinical practice is limited by relatively low sensitivity (unpublished observations) [67]. Despite these limitations, we generally recommend bronchoscopy and BAL for most patients with suspected PLCH, because PLCH or another form of interstitial lung disease (eg, sarcoidosis or hypersensitivity\ pneumonitis) sometimes can be diagnosed with this method, which avoids a surgical procedure.

Surgical lung biopsy (either by thoracotomy or thoracoscopic lung biopsy) remains the ''gold standard'' method with the greatest diagnostic yield, principally because of the relatively large portion of tissue obtained during the procedure. Surgical lung biopsy still may be subject to sampling error, however, because the lesions of PLCH are focal and of varying ages. HRCT is useful in directing a surgeon to optimal biopsy sites.

Diagnostic algorithm

Our clinical approach to patients with suspected PLCH is outlined in Fig. 2. A complete history and physical examination are essential in all patients with interstitial lung disease. Although the presenting symptoms and physical examination are commonly nonspecific, the lack of a current or prior cigarette-smoking history renders the diagnosis of PLCH unlikely. Similarly, although chest radiography and pulmonary function testing may yield nonspecific findings, certain clues may suggest PLCH. For instance, PLCH should be suspected in any adult cigarette smoker who presents with bilateral interstitial lung infiltrates that spare the costophrenic angles. The history of spontaneous or recurrent pneumothorax should further heighten consideration of PLCH. We recommend that HRCT be performed in all patients in whom the diagnosis of PLCH is entertained. The diagnosis of PLCH is nearly certain when characteristic findings of nodular and cystic abnormalities are present with relative basilar sparing and the appropriate clinical context. Although a biopsy is needed to establish definitively the diagnosis of PLCH, this may not be required or necessary, particularly in mildly symptomatic patients with typical radiologic findings in whom no specific therapy is contemplated (other than smoking cessation). When the HRCT is nondiagnostic, further evaluation with bronchoscopy or surgical lung biopsy is indicated. A significant portion of patients, particularly patients who have unusual findings on HRCT or in whom aggressive therapy is contemplated, may require surgical lung biopsy for definitive diagnosis. In patients with documented extrapulmonary LCH (such as skin or bone), the diagnosis can be established if HRCT shows features consistent with PLCH.

Management of pulmonary Langerhans' cell histiocytosis

Factors that should be considered when treating adults with PLCH include personal smoking history, the extent and rate of progression in lung function impairment, presence of other organ involvement with LCH, and presence of constitutional symptoms. Considering the irrefutable association of PLCH with tobacco use, the first therapeutic intervention that should be pursued in all smokers is smoking cessation. Although prospective data on the effect of smoking cessation are lacking, smoking cessation seems to result in stabilization of symptoms, may lead to objective radiologic and physiologic improvement, and limits the potential for further decline in lung function in patients with PLCH [17,68]. In our practice, we repeatedly emphasize the association of PLCH with smoking (referring to PLCH as a specific smoking-related interstitial lung disease), prescribe nicotine replacement and bupropion therapy, and refer patients to nicotine dependence counselors to maximize the chance of success. Despite this relatively aggressive approach, the smoking cessation rate in our clinical practice has been disappointingly low.

For patients with persistent pulmonary or constitutional symptoms or patients who demonstrate progressive decline in lung function, corticosteroid therapy is often used. The choice of corticosteroids as the primary pharmacologic therapy for PLCH is founded on anecdotal reports and expert opinion rather than prospective studies [10,14,69]. Retrospective case series suggest that corticosteroid therapy in PLCH is associated with stabilization of disease and symptomatic improvement [8,10,14]. These data are difficult to evaluate because they lack a control for the effect of smoking cessation. A recent report suggested that corticosteroid therapy might be of benefit in symptomatic PLCH complicated by pulmonary hypertension [70].

There are no specific guidelines as to when corticosteroid therapy should be used in PLCH. In our practice we do not recommend pharmacologic treatment of patients with normal pulmonary function

(although we recommend smoking cessation if applicable). For patients with progressive disease (as determined by serial pulmonary function testing and imaging studies), we recommend a trial of prednisone treatment at a dose of 0.5 mg/kg body weight. Patients are counseled on potential side effects of oral corticosteroids and are informed of the lack of definitive data regarding the efficacy of corticosteroid therapy, particularly in the context of continued tobacco exposure.

Regardless of whether patients receive treatment, all patients with PLCH should be followed up at 3- to 6-month intervals with pulmonary function testing. Screening echocardiography for pulmonary hypertension also should be considered in all dyspneic patients, particularly persons with dyspnea that is out of proportion to the degree of abnormality on pulmonary function testing. Right heart catheterization should be performed when an echocardiogram suggests significant pulmonary hypertension to confirm the presence and severity of pulmonary hypertension and assess the response to vasodilator therapy. Empiric trials of vasodilators should not be attempted in these patients, because catastrophic vascular responses may occur after intravenous vasodilator challenge in patients with occult pulmonary veno-occlusive disease, which can be associated with PLCH [71]. Although a previous case report suggested that pulmonary hypertension may respond to corticosteroid therapy [70], we have not observed this in our practice (unpublished observations).

Various chemotherapeutic agents, such as 2-chlorodeoxyadenosine [7,72–74], vinblastine [4], methotrexate [75], cyclophosphamide [6], etoposide [75], and etanercept [76], have been tried in patients with progressive PLCH (or multisystemic LCH) that is unresponsive to corticosteroid therapy or patients with progressive multisystemic involvement. Because of limited data on efficacy and potential adverse effects, these drugs should be reserved for patients with progressive disease. 2-Chlorodeoxyadenosine deserves special mention among these therapeutic agents. There are several case reports and small case series of adult patients who responded favorably to 2-chlorodeoxyadenosine despite having multisystemic progressive disease [7,72–74]. Few of the patients reported in these case series had pulmonary involvement, however, and none had isolated PLCH. Patients with isolated PLCH who are seen by pulmonologists may have a different disease than patients with multisystemic LCH, who are usually managed by hematologists or oncologists. The effect of 2-chlorodeoxyadenosine on PLCH remains unclear. The use of this agent is a potential option in the treatment of patients with progressive PLCH that is unresponsive to other therapeutic measures, however.

Pneumothorax is a well-recognized complication of PLCH and is observed in 10% to 20% of patients during the course of disease [1,10]. In a recent study, the recurrence rate was more than 50% when pneumothorax was managed with observation or chest tube alone and 0% with surgery and pleurodesis, which indicates that surgical pleurodesis may be the preferred therapy for the management of pneumothorax that occurs in patients with PLCH [77]. Patients with progressive PLCH associated with severe respiratory impairment and limited life expectancy should be evaluated for lung transplantation [78,79]. It is imperative that patients stop smoking before lung transplantation, because PLCH may recur in the transplanted lung if smoking is resumed [16,80].

Prognosis and long-term outcomes

There are no prospective data on the long-term outcomes of adults with PLCH. Retrospective studies and anecdotal experience suggest that asymptomatic or minimally symptomatic patients have a relatively good prognosis with stabilization or spontaneous improvement, especially with cessation of cigarette smoking [8,10]. A subgroup of PLCH patients develops progressive lung disease, however, which leads to severe respiratory impairment and premature mortality from respiratory failure [1]. Similarly, some patients may develop severe pulmonary hypertension and cor pulmonale [81]. The frequency of respiratory failure, pulmonary hypertension, and cor pulmonale related to PLCH is not clearly known. Ideally, these patients should be identified early in the course of disease and be targeted for aggressive smoking cessation and other therapies that may alter favorably the course of PLCH. Currently, we do not have good clinical markers to identify patients who are at risk for progressive disease. Retrospective studies have identified various factors associated with adverse clinical outcome, including extremes of age, multisystemic involvement, prolonged constitutional disturbance, extensive cysts and honeycombing on chest radiograph, markedly reduced diffusing capacity, low forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio, corticosteroid therapy at time of follow-up, and a high residual volume/total lung capacity (RV/TLC) ratio [1,82]. Based on these observations, we recommend serial pulmonary function testing every 3 months in the first year after diagnosis to identify patients who are likely to develop progressive disease. We recommend that all

patients with progressive decline in pulmonary function tests undergo aggressive attempts at smoking cessation and be considered for a trial of corticosteroid therapy. In these patients, echocardiography should be performed to assess for the presence and severity of pulmonary hypertension as a contributing factor in the progression of disease.

In addition to being at risk for developing pulmonary complications, adult patients with PLCH seem to have an increased risk of developing malignant neoplasms [1,83]. Lymphoma, myeloproliferative disorders, and various epithelial cancers have been described to occur at higher frequency in patients with PLCH [1,84–86]. Although it is possible that the increased incidence of neoplasms is caused by cumulative tobacco exposure rather than the PLCH itself, this explanation seems unlikely, because an increased incidence of cancer also has been reported in other forms of LCH [85].

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