

Current understanding and management of pulmonary Langerhans cell histiocytosis

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ABSTRACT

Pulmonary Langerhans cell histiocytosis (PLCH) is a diffuse lung disease that usually affects young adult smokers. PLCH affects different lung compartments; bronchiolar, interstitial and pulmonary vascular dysfunction may coexist to varying extents, resulting in diverse phenotypes. Analyses of PLCH tissues have identified activating mutations of specific mitogen-activated protein kinases (BRAF^{V600E} and others). The current consensus is that PLCH represents a myeloid neoplasm with inflammatory properties: the myeloid tumour cells exhibit surface CD1a expression and up to 50% of the cells harbour activating BRAF or other MAPK mutations. PLCH may be associated with multisystem disease. The detection of disease outside of the thorax is facilitated by whole body positron emission tomography. The natural history of PLCH is unpredictable. In some patients, disease may remit or stabilise following smoking cessation. Others develop progressive lung disease, often associated with evidence of airflow limitation and pulmonary vascular dysfunction. Due to the inability to accurately predict the natural history, it is important that all patients undergo longitudinal follow-up at least twice a year for the first few years following diagnosis. The treatment of PLCH is challenging and should be individualised. While there is no general consensus regarding the role of immunosuppression or chemotherapy in management, selected patients may experience improvement in lung function with therapy. Determination of BRAF^{V600E} or other mutations may assist with the development of an individualised approach to therapy. Patients with progressive disease should be referred to specialised centres and considered for a trial of pharmacotherapy or evaluated for transplantation.

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare disease of unknown aetiology, characterised by organ infiltration with specialised myeloid cells that share morphological and surface receptor markers with epidermal Langerhans cells (LCs).^{1,2} LCH belongs to the broader group of histiocytic disorders, comprising a diverse collection of diseases, whose common denominator is the accumulation of cells of the reticuloendothelial system in the tissues and organs concerned.²

LCH can affect patients of all ages. The Histiocyte Society classifies clinical forms of LCH according to the number and type of organs involved.² It distinguishes systemic LCH, combining varying degrees of bone, skin, hypothalamic–pituitary, lymph node, lung lesions, and more rarely central neurological lesions. Systemic LCH is associated with a worse

prognosis when so-called ‘risk organs’ are involved (liver, spleen, haematological involvement). This acute form of systemic LCH (previously called Letterer-Siwe syndrome) is predominantly observed in very young children.² Localised forms of LCH (previously called eosinophilic granuloma) often affect bone, skin and the lungs, and frequently have a more indolent course with the potential for spontaneous remission.² However, patients with an initially localised form of LCH can subsequently develop systemic LCH. Pulmonary involvement can be present in systemic forms of LCH, but more commonly pulmonary LCH (PLCH) occurs in young adult smokers and is usually isolated to the chest.³

EPIDEMIOLOGY

The prevalence of PLCH is unknown but may account for about 3–5% of all adult diffuse lung diseases. The precise prevalence of PLCH may be higher than estimated in earlier studies,⁴ because it may be asymptomatic, may spontaneously remit, and may be difficult to identify in very advanced forms. While infrequent in individuals of African origin, PLCH has been well described in Asian subjects.⁵ In adults, PLCH occurs predominantly in young smokers or ex-smokers (>90% of cases), with a peak incidence between the ages of 20 and 40 years.³ PLCH occurs with equal frequency in both genders.^{3,6} Other inhalation exposures may be relevant; for example, about 20% of patients of the French LCH registry are also cannabis users (personal observation).

PATHOGENESIS

There are four key elements concerning the pathogenesis of PLCH: (1) the mechanisms of accumulation of large numbers of CD1a+ cells in bronchiolocentric loosely formed granulomas; (2) the capacity of these granulomatous lesions to destroy and remodel surrounding tissues; (3) the reactive versus clonal/neoplastic nature of the disease; and (4) the role of smoking in adult PLCH.

Accumulation of CD1a+ cells

The accumulation of CD1a+ cells resulting in loosely formed granulomas around small airways likely results from recruitment of circulating peripheral blood myeloid haematopoietic precursor cells, which then differentiate in the tissues involved. Essential for this differentiation are growth factors (granulocyte macrophage colony stimulating factor: GM-CSF) and chemokines (CCL20 and CCL2) known to be expressed around PLCH lesions.^{7,8} Differentiation of precursor cells residing locally in



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the tissues involved is also possible. A proportion of granuloma cells express CD1a but not langerin (marker of LCs), indicating dendritic cells at various stages of differentiation. Local neoangiogenesis, signalling and cell adhesion molecules are involved in CD1a+ cell, T-cell and other inflammatory cell accumulation.⁹ The CD1a+ cells in PLCH granulomas do not bear markers of proliferation.^{10 11} In contrast, these cells appear to be less sensitive to apoptosis.¹²

Destructive nature of PLCH granulomas

A specific characteristic of PLCH granulomas is their capacity to destroy and remodel surrounding tissues.¹³ The lesional CD1a+ cells within granulomas have a different phenotype from the same cells under physiological conditions. Transcriptome studies of langerin-positive cells obtained from LCH granulomas show that these cells have a different transcriptomic profile from both epidermal LCs and normal dendritic cells.¹⁴ CD1a+ cells of PLCH granulomas express, to varying degrees, membrane maturation markers (especially co-stimulation molecules) similar to those present on the surface of dendritic cells after exposure to pathogens or activating cytokines.^{9 15}

Although bearing an activated surface phenotype, CD1a+ cells extracted from LCH granulomas appear to be functionally impaired.¹⁶ Thus, although T lymphocytes are abundant in LCH granulomas, it is unlikely that the observed tissue destruction is secondary to a local cytotoxic immune reaction. Furthermore, a considerable proportion of the T lymphocytes that infiltrate LCH granulomas are regulatory T lymphocytes.¹⁰ In contrast, various metalloproteinases have been identified in LCH granulomas and could account for LCH-induced tissue destruction.¹⁷ A role for interleukin-17 in tissue remodelling has been suggested by Coury *et al*,¹⁸ although other investigative teams have not confirmed those findings.¹⁹ More recently, activation of the Notch1 signalling pathway has been shown to be at least partly responsible for the specific profile of LCH cells.²⁰

PLCH: reactive, clonal or neoplastic?

Whether PLCH is a reactive or clonal process has been a subject of debate since this disease was first identified. The prevailing thinking until recently was that PLCH represents an inflammatory reactive disorder induced by cigarette smoke. In support of this contention were the observations that mitotic figures and recurrent cytogenetic abnormalities had not been observed in the CD1a+ cells of these lesions.¹¹ The 'spontaneous' resolution observed in certain PLCH cases – often following smoking cessation^{21 22} – as well as the detection of substantial infiltrating immune cells in PLCH granulomas,¹⁵ also were considered arguments favouring a non-clonal reactive immune granulomatous reaction. Conversely, the occasionally aggressive nature of the disease and the efficacy of chemotherapy in severe systemic forms of PLCH favoured a neoplastic mechanism. Discordant results have been reported concerning the clonal nature of CD1a+ cells in the different forms of LCH: a study of CD1a+ cells derived from extrapulmonary lesions of focal as well as systemic forms of LCH (the majority of the subjects were children) reported the clonal nature of these cells,²³ while a study conducted on lung biopsies from 13 women with PLCH using an alternative (and potentially less sensitive) molecular approach to determine clonality showed that 70% of the lesional CD1a+ cells were polyclonal in that small population of adults with PLCH.²⁴

The recent identification of recurrent genetic abnormalities involving cellular proliferative pathways in lesional CD1a+ cells obtained from systemic LCH,²⁵ as well as pulmonary LCH²⁶

tissues, provides the strongest argument to date in favour of the neoplastic hypothesis for LCH.^{27 28} The most prevalent genetic abnormality described in LCH is the BRAF^{V600E} mutation, which also occurs in various types of cancers, including malignant melanomas and almost all cases of hairy cell leukaemia²⁹ (and has also been reported in benign naevi).³⁰ Functionally, this BRAF^{V600E} mutation results in a modified kinase domain that is associated with constitutive activation of the mitogen-activated protein kinase (MAPK) pathway which plays a key role in cell differentiation and survival (figure 1). This mutation occurs in 35–50% of people with PLCH,²⁶ and at least 50% of those with systemic LCH granulomas.²⁵ Interestingly, Berres *et al*³¹ showed that in children with severe systemic forms of LCH, the presence of the BRAF^{V600E} mutation was not only present in tissue lesions (somatic mutation), but also in circulating and sometimes bone marrow precursors of dendritic cells that infiltrate LCH granulomas. Further evidence supporting a central role for this specific mutation in the pathogenesis of LCH comes from the recent report showing pathological lesions resembling systemic LCH in a murine model in which dendritic cells expressed the BRAF^{V600E} mutation.³¹

While approximately half of PLCH cases are associated with wild-type BRAF status, activation of the MAPK pathway – as determined by immunohistochemical localisation of phosphorylated MAPK pathway members – occurs in all cases.²⁵ This implies additional mechanisms for MAPK pathway activation in the absence of BRAF^{V600E} mutations. Indeed, MAP2K1 as well as activating NRAS^{Q61K/R} mutations have been reported.^{32–34} While in systemic LCH, BRAF and MAP2K1 mutations are mutually exclusive,³² NRAS mutations occurred concurrently with BRAF^{V600E} mutations in PLCH and both mutations were carried by different cell clones.³⁴ Importantly, NRAS^{Q61} mutations were not identified in non-pulmonary LCH lesions, and in a singular case occurred in pulmonary but not in skin lesions from the same patient.³⁴

The clinical significance of MAPK pathway mutations in PLCH is not fully appreciated. When first reported, patients with LCH lesions harbouring the BRAF^{V600E} mutation were younger than patients without somatic BRAF mutations, but no link was observed with disease phenotype.²⁵ In the study by Berres *et al*,³¹ the presence of somatic BRAF^{V600E} mutations was associated with increased risk of disease recurrence in paediatric systemic LCH, but did not influence survival. In contrast to Roden *et al*,²⁶ the study by Mourah *et al*,³⁴ did not find a correlation between smoking and the presence of BRAF or NRAS mutations. In that study, univariate analysis demonstrated an association between the presence of NRAS mutations in lung lesions and the risk of spontaneous progression of PLCH.³⁴ In children with LCH, the BRAF^{V600E} mutation is associated with high-risk disease and increased resistance to first-line therapy.²⁸ Further studies are needed to evaluate the impact of MAPK mutations and the clinical phenotype of LCH and to determine if these mutations are useful for disease stratification and outcome, particularly in adults.

Role of smoking

Several lines of evidence support a role for cigarette smoking in the pathogenesis of adult PLCH. It is noteworthy that children with extrapulmonary LCH who subsequently develop PLCH during adolescence or adulthood are often smokers.³⁵ Although the precise mechanisms by which tobacco smoke is involved in the pathogenesis of PLCH remains incompletely understood, smoking-induced changes in the epithelium of

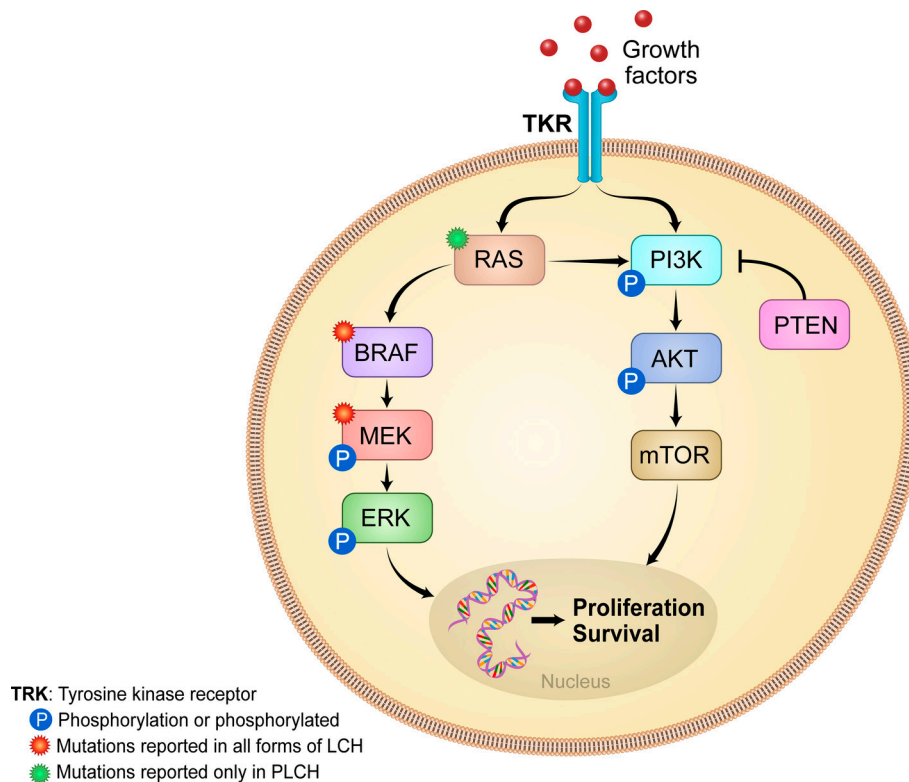


Figure 1 Cellular signals mediated by binding of growth factors to respective tyrosine kinase receptors (TKRs) activate downstream cellular signalling pathways such as the mitogen-activated protein kinase (MAPK) and other pathways. These pathways mediate a number of cellular responses, including cell proliferation and survival/death pathways. Constitutively active mutated BRAF and MEK variants have been reported to occur in both systemic Langerhans cell histiocytosis (LCH) and pulmonary LCH (PLCH), while active RAS mutations have only been described in PLCH.

distal bronchioles are likely involved.^{36 37} Smoking induces accumulation of CD1a+ cells in the lungs in healthy smokers, in various diseases and in murine models.³⁸ Smoking stimulates local production of cytokines, which are important for the recruitment, differentiation and activation of dendritic cells, especially tumour necrosis factor α (TNF α), granulocyte macrophage colony-stimulating factor (GM-CSF), transforming growth factor β (TGF β) and chemokine CCL20, which are also expressed in PLCH lesions.^{7 36–38} Tobacco smoke also promotes the survival of dendritic cells via anti-apoptotic mechanisms.^{12 39} Osteopontin appears to play a role in PLCH, as large quantities of osteopontin are present in the bronchoalveolar lavage (BAL) of patients with PLCH compared with control smokers.⁴⁰ This glycoprotein, the secretion of which is increased by nicotine, exerts chemoattractant effects on monocytes/macrophages and dendritic cells.⁴⁰ In a rat model, osteopontin overexpression induces lesions similar to those of PLCH.⁴⁰ Whether cigarette smoke can directly induce mutations in the MAPK pathway has not been demonstrated, but it is possible that smoking is the necessary stimulus that enables the recruitment and persistence of myeloid cell clones harbouring MAPK mutations in the lung of smokers with PLCH. What drives the inflammatory and granulomatous like nature of the nodular lesions that characterise PLCH remains unknown: potentially cigarette smoke injury to distal lung epithelial structures together with the induction of myeloid cell clones harbouring mutated MAPKs may be the critical events that set the stage for the development of the nodular early lesions. Chilosi *et al*⁴¹ recently proposed oncogene-induced senescence as a mechanism by which cell cycle arrest and inflammation may be perpetuated in PLCH. Utilising an immunohistochemical approach to detected BRAF^{V600E}, the authors showed

immunoreactivity in 12 of 19 PLCH biopsies.⁴¹ Interestingly, a high proportion of the CD1a+ cells in those cases showed expression of p16^{INK4a} and p21^{CIP1/WAF1} (markers of senescence), suggesting that PLCH may be a senescence-related neoplasm.⁴¹ In PLCH, it is possible that either the BRAF^{V600E} – or an alternative MAPK mutation – can lead to activation of senescence pathways in CD1a+ myeloid cells that go on to infiltrate the lung. It is also possible that cellular senescence – potentially driven by cigarette smoke exposure – may induce the senescence-associated secretory phenotype which is recognised as a chronic proinflammatory stimulus. This in turn may act as the ‘driver’ of the inflammatory cell recruitment and inflammation noted in the PLCH nodular lesions. While cigarette smoke is clearly associated with PLCH, it is noteworthy that in Ercheim-Chester Disease (ECD) – the other histiocytic disorder in which somatic BRAF and MAPK mutations are very prevalent² – is more frequently observed in non-smokers.⁴²

The rarity of PLCH relative to the prevalence of smoking in the general population suggests the presence of predisposing factors in patients who develop this disease. Another exogenous factor, for example viral infection, is another potential cofactor involved in the pathogenesis of PLCH in genetically predisposed patients. Various studies designed to detect the pathogens responsible have generally been inconclusive.

CLINICAL PRESENTATION

Adult PLCH is generally diagnosed in three main settings^{3 5 43}:

1. Onset of respiratory symptoms (usually cough and dyspnoea) in about two-thirds of patients. Constitutional symptoms

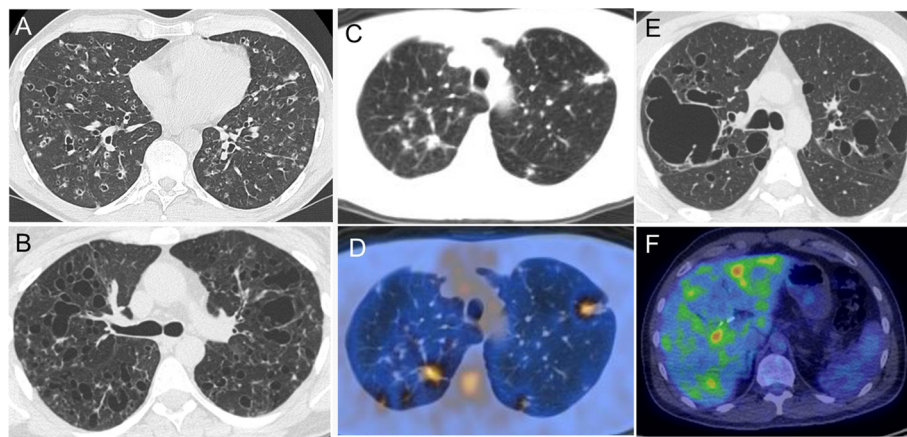


Figure 2 (A) Representative high-resolution chest CT image from a patient with biopsy-proven pulmonary Langerhans cell histiocytosis (PLCH) demonstrating a combination of small nodules, cavitory nodules and lung cysts. (B) Representative chest CT image from a patient with advanced biopsy-proven PLCH demonstrating cystic lung lesions of varying sizes and appearance. Nodular change is not apparent. (C and D) Corresponding chest CT and positron emission tomography (PET) images from a patient with biopsy-proven PLCH showing nodular lesions on the chest CT which are hypermetabolic on the PET. (E) Representative chest CT image from a patient with biopsy-proven systemic Langerhans cell histiocytosis with pulmonary, liver and bone involvement. The chest CT image demonstrates cystic changes with formation of a bullous like abnormality in the right upper lobe. (F) Representative PET image showing hypermetabolic liver lesions from the same patient whose chest CT is shown in panel E.

(fever, malaise, sweats and weight loss) are described in 15–20% of cases.

2. Acute presentation with a spontaneous pneumothorax in about 15–20% of cases. Spontaneous pneumothorax can occur at any time during the course of disease; it may be bilateral and recurrent.
3. As an incidental finding on routine chest X-ray in 5–25% of cases.

Haemoptysis occurs rarely and justifies the search for possible complications (infectious bronchitis, lung cancer, rarely aspergillus colonisation of a cystic cavity) or an alternative diagnosis. Adult PLCH is generally isolated. When present, extrathoracic lesions usually involve bone, the hypothalamic–pituitary axis (polyuria–polydipsia syndrome due to diabetes insipidus) and more rarely the skin.³ Physical examination is generally normal, except in advanced stages or when associated with extrathoracic involvement.

CHEST IMAGING

Chest X-ray often shows bilateral, and generally symmetric, reticulo-micronodular changes, in which cysts may sometimes be identified, predominantly involving the upper and middle lung fields.⁴⁴ Occasionally, chest radiography may reveal a pneumothorax, or rarely, a lytic lesion of a rib. Pleural effusion and mediastinal lymphadenopathy are very uncommon. In rare cases, the chest X-ray is normal.⁴⁴

Chest high-resolution computed tomography (HRCT) characteristically demonstrates a combination of nodules, cavitating nodules measuring 1–10 mm in diameter and thick-walled or thin-walled cysts (figure 2).^{45–48} Cysts vary in size and may coalesce to form irregular shapes (figure 2). Abnormalities are predominantly located in the upper and middle lung fields with relative sparing of the lung bases. The types of lung lesions vary with disease duration. In early disease, nodules and cavitated nodules are more numerous than lung cysts, while more advanced disease is often cystic in appearance.⁴⁷ Significantly enlarged mediastinal lymph nodes are rarely observed. In some cases there are extensive ground glass opacities due to the concomitant presence of other smoking-related interstitial lung disease (ILD).⁴⁹

Quantitative assessment of cystic lung disease on HRCT also correlates with pulmonary function parameters.⁵⁰

The role of positron emission tomography (PET)-CT in the assessment of isolated PLCH is not well defined. Pulmonary nodules can be hypermetabolic, in which case they cannot be distinguished from malignant disease (figure 2).⁵¹ Thick-walled cysts can sometimes also demonstrate high metabolic uptake.⁵¹ The presence of an isolated hypermetabolic pulmonary nodule in a patient who smokes may be due to PLCH, but should raise suspicion for a superimposed lung cancer which needs to be carefully excluded depending on the clinical context. Whether PET-CT is predictive of the natural disease course or response of PLCH to treatment remains to be determined.⁵²

PULMONARY FUNCTION TESTS

Pulmonary function abnormalities vary according to the extent of cystic involvement and disease duration. The most common abnormality is reduction of diffusing capacity of the lungs for carbon monoxide (DLCO) (observed in 80–90% of cases).³ In addition, the pulmonary function test often demonstrates reduction in vital capacity (VC), normal or increased residual volume (RV), preserved total lung capacity (TLC) and increased or normal RV/TLC ratio (air trapping).⁵³ An obstructive ventilatory defect is observed in approximately a third to half of all patients, while restrictive ventilatory defect (defined by a TLC <80% predicted) is present in a minority (usually <20%).^{3, 54} Mixed restrictive and obstructive abnormalities may also be seen in about a third of patients. A proportion of patients will have normal lung volumes and spirometry with an isolated reduction in diffusing capacity to carbon monoxide. In a recent study, 10% of patients with obstructive physiology demonstrated reversibility following short-acting β_2 -agonist therapy.⁵⁴ The severity of airflow limitation on lung function testing correlates with the extent of cystic lesions on HRCT.⁵⁵

BRONCHOSCOPY AND BRONCHOALVEOLAR LAVAGE

Bronchoscopy is macroscopically normal or reveals non-specific smoking-related abnormalities. Bronchial mucosal biopsies

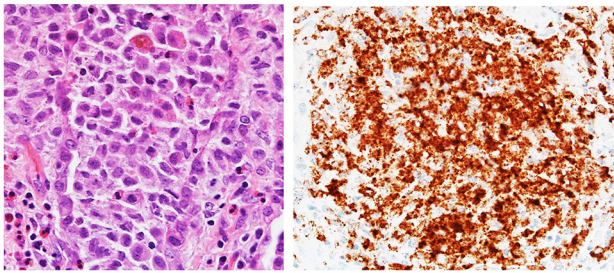


Figure 3 Light microscopic features of cellular pulmonary Langerhans cell histiocytosis is shown in the left-hand panel. The cellular infiltrate includes cells that morphologically resemble Langerhans cells and are characterised by delicate and folded nuclei. Scattered eosinophils are present (hematoxylin and eosin, $\times 400$). The right-hand panel demonstrates cellular staining with a BRAF-V600E antibody on a separate biopsy specimen, showing marked positivity for the BRAF-V600E antigen in cells (magnification $\times 400$).

do not contribute to the diagnosis of PLCH, but may be useful to exclude other diseases. Transbronchial lung biopsies have variable diagnostic yields (15–40%) due to the focal nature of lesions.^{56–57} Cryobiopsy is associated with an increased diagnostic yield due to the larger samples acquired.⁵⁸ BAL may be useful to support the diagnosis of PLCH by showing an increase in the number of CD1a+ cells.⁵⁹ The presence of at least 5% of CD1a+ cells in BAL has only been reported in PLCH, but is observed in only a minority of cases.^{57–60} BAL is therefore rarely diagnostic of PLCH in adults.

LUNG PATHOLOGY

The histological hallmark of PLCH is accumulation of CD1a+ cells organised into loosely formed granulomas, preferentially located in, and destroying the wall of distal bronchioles.⁶¹ On light microscopy, LCs may be identified by their convoluted nucleus, pale, slightly eosinophilic cytoplasm, and an irregular indented nucleus (figure 3). On immunohistochemical examination, they express CD1a and langerin (CD207). Langerin has replaced the search for Birbeck granules on electron microscopy, which is now rarely performed. In contrast, cytoplasmic expression of protein S100 is non-specific. Immunohistochemical detection of BRAF^{V600E} expression is a simple and effective method to screen for this mutation when the diagnosis is confirmed by tissue biopsy (figure 3).

PLCH granulomas are focal, poorly demarcated, separated by zones of healthy tissue, and are centred on distal bronchioles (terminal and respiratory), accompanying arterioles and sometimes adjacent venules.⁶¹ The appearance of PLCH granulomas depends on the stage of the disease, and lesions of different ages are often present on the same lung biopsy. New lesions are localised in the distal bronchiolar wall, which appears to be initially infiltrated by variable numbers of LCs and lymphocytes, monocytes/macrophages and subsequently inflammatory cells, especially eosinophils and more rarely giant cells.⁶¹

Destruction of bronchiolar epithelium occurs early during the disease process, making it difficult to confirm the bronchiolo-centric distribution of the lesions (presence of a residual ring of smooth muscle cells) on a single tissue section. Examination of serial sections with three-dimensional reconstructions demonstrated that PLCH lesions progress in the form of a granulomatous cuff along the bronchiole.⁶² Cystic lesions are due to destruction of the bronchiolar wall and progressive dilatation of the bronchiolar lumen.

With progression of the lesions, the number of CD1a+ cells decreases, while inflammatory cells persist, associated with lymphoid aggregates, which are subsequently replaced by either fibrosis in the form of a characteristic stellate scar, or contiguous and confluent cystic cavities, surrounded by a fibrous ring.⁶¹ Interestingly, correlations between CT features and pulmonary histopathology have shown that LCH granulomas may still be observed in diffuse cystic forms and that inflammatory cells may persist even inside thin-walled cysts.⁶³

In areas not involved by the disease process, lung architecture is preserved, but non-specific smoking-related lesions (respiratory bronchiolitis, intra-alveolar accumulation of pigmented macrophages, lymphoid cells) are often present. In some cases, the predominant features may be suggestive of respiratory bronchiolitis ILD or desquamative interstitial pneumonia, but underlying specific LCH granulomas should be sought by comprehensive examination of biopsy samples, including immunohistochemistry.⁴⁹

The differential diagnosis includes other histiocytic and eosinophilic lung diseases, as well as desquamative interstitial pneumonia, hypersensitivity pneumonitis and idiopathic interstitial pneumonias.⁶¹ ECD is associated with histiocytic infiltration, but the histiocytes in ECD lack CD1a staining, and are characterised by foamy cytoplasm on light microscopy.⁶¹ As observed in PLCH, the histiocytic infiltrates in ECD may be located around small airways, but the primary distribution of the inflammatory ECD infiltrates in the lung occur in lymphangitic and sub-pleural distribution, resulting in expansion of interlobular septa (figure 4).⁴² The predilection for ECD infiltrates to involve these regions of the lung correlates with the imaging findings on chest CT which are completely different from those observed with PLCH (figure 4).

DIAGNOSTIC APPROACH

The definitive diagnosis of PLCH requires lung biopsy, either by bronchoscopic or surgical biopsy. Imaging of the lung by HRCT has reduced the need for surgical lung biopsy, particularly when combinations of nodular and cystic changes are present in the appropriate clinical context (young adult smoker). The indication for lung biopsy must be determined in each individual case with careful evaluation of risks and potential benefits of the procedure to the patient. The diagnostic approach is essentially guided by the clinical context and chest CT findings.^{64–65}

MANAGEMENT

Due to the irrefutable link between PLCH and smoking, the first component of any therapeutic regimen is smoking cessation.^{21–54–66} In a recent prospective study, persistence in smoking was one of the factors associated with longitudinal decline in lung function, while smoking cessation for at least 6 months was associated with reduced longitudinal lung function decline.⁵⁴ Smoking cessation is the only intervention necessary in a substantial proportion of patients, and individualised smoking cessation strategies should be used to address this powerful addictive behaviour. The effects of smoking cessation on extra-pulmonary manifestations are not well defined.

Pharmacological treatment with corticosteroids or chemotherapeutic agents should be considered in patients with severe or progressive disease despite smoking cessation (table 1). Oral corticosteroids (prednisone 0.5–1.0 mg/kg daily) are often prescribed in patients with progressive disease, even though the efficacy of corticosteroids in stabilising or inducing disease remission remains unclear. All of the studies describing corticosteroid

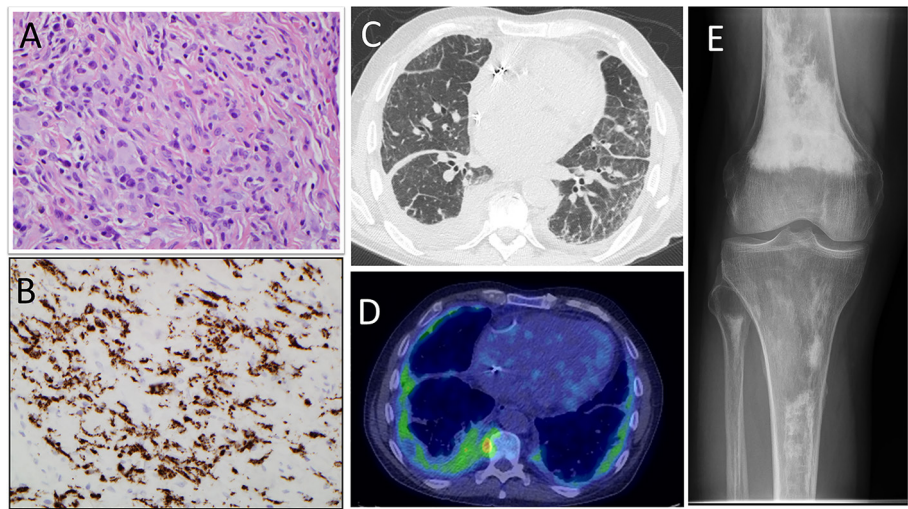


Figure 4 Histopathological and imaging findings in a 76-year-old man with Erdheim Chester disease (ECD). (A) Representative image from a surgical lung biopsy showing infiltration of the lung by foamy histiocytes, lymphocytes and scattered giant cells. The infiltrate involves visceral pleura and interlobular septa. (B) Immunohistochemical stain on lung biopsy showing positive staining for CD68 (not shown are CD1a and S100 which were negative, in contrast to pulmonary Langerhans cell histiocytosis (PLCH)). (C) Representative chest CT image showing diffuse, smooth thickening of the interlobular septa, circumferential pleural thickening with areas of loculated fluid and a small amount of pericardial fluid or thickening. In contrast to PLCH, ECD is not associated with cystic change and there is no sparing of the lung bases. (D) Representative positron emission tomography image from the lower thoracic region showing intense FDG avid pleural and parenchymal lung abnormalities with effusions, extending into the fissures, and involving the mediastinal region. (E) Plain radiography of the right lower femur and tibia showing characteristic bony changes associated with ECD: areas of increased density and sclerosis are present in the distal femur, proximal tibia and proximal fibula.

use in PLCH were retrospective and failed to control for the effect of smoking cessation.^{3 67} Whether a trial with oral corticosteroids should be attempted at all in PLCH is a matter of debate, but should only be considered in patients with progressive disease. Inhaled corticosteroids and bronchodilator therapy may provide benefit for patients with co-existent reactive airway disease.

Vinblastine, the main chemotherapeutic agent used in management of systemic LCH, has limited efficacy in PLCH (unpublished observations). Cladribine (also known as 2-chlorodeoxyadenosine), a synthetic purine nucleoside analogue which is cytotoxic for lymphocyte and monocyte cells, may induce disease remission when used as a single drug in selected patients.^{68–71} Importantly, cladribine has been anecdotally demonstrated to improve lung function and induce reduction in cystic size, suggesting that even patients with predominantly

cystic disease (previously believed to be advanced or burnt-out disease) may benefit from therapy.^{68 72} The role of cladribine in the treatment of symptomatic forms of PLCH with impaired pulmonary function is currently under evaluation in a phase II clinical trial (<http://clinicaltrials.gov/NCT01473797>).

The identification of BRAF^{V600E} in both LCH and PLCH has led to the use of targeted therapy with inhibitors of mutated BRAF that were originally developed for melanoma and other malignancies.⁷³ A recent study reported on 122 patients with BRAF^{V600E} mutation-positive non-melanoma cancer, of which, 18 were affected by ECD/LCH.⁷⁴ Treatment with a BRAF inhibitor resulted in stabilisation of disease in the majority (eight) while five showed a partial response, and in one patient a complete resolution was observed; none experienced disease progression during treatment.⁷⁴

| Table 1 Therapies and medical interventions for PLCH | |
|--|--|
| | Clinical context |
| Smoking cessation | Mandatory for all cigarette smokers. Avoidance of all second-hand smoke exposure highly recommended |
| Corticosteroids | |
| Inhaled | Patients with concomitant COPD or airflow limitation |
| Oral | Limited role in most clinical contexts: may have role for treatment of some multisystem forms of disease |
| Oxygen | Patients with hypoxemia (O ₂ sat<89%) at rest or with activity, particularly in individuals with pulmonary hypertension |
| Pulmonary hypertension therapies | No clear consensus regarding use. Systemic vasodilator therapy should only be considered in selected patients with pulmonary hypertension following right heart catheterisation and vasodilator challenge. Inhaled prostacyclin may be more beneficial in this context, but data regarding safety and efficacy are lacking |
| Cladribine (2-CDA) | Consider for patients with abnormal lung function, if disease progression occurs despite smoking cessation, and in patients with multisystem disease |
| Cytarabine | Reported efficacy in anecdotal reports and series of patients with multi-system Langerhans cell histiocytosis and pulmonary involvement |
| Vinblastine | Limited evidence for efficacy |
| Lung transplantation | Consideration in any patients with advanced and/or progressive disease in spite of smoking cessation or medical therapy |

Pulmonary hypertension is a common complication in PLCH.^{75–77} When present, hypoxemia should be treated with supplemental oxygen. The role of vasodilator therapy for the treatment of pulmonary hypertension in PLCH is not well established. In the study by Le Pavec,⁷⁷ 14 out of 29 patients with PLCH received pulmonary hypertension treatment which included an endothelin receptor antagonist, a phosphodiesterase five inhibitor, or inhaled Iloprost. This study showed that pulmonary arterial hypertension therapies improve haemodynamics without worsening gas exchange or induction of pulmonary oedema.⁷⁷ Other small case series or isolated case reports have documented substantial improvement in dyspnoea scores and haemodynamic parameters,⁷⁸ but the role of pulmonary arterial hypertension therapy in PLCH remains debatable and should only be pursued in medical facilities that have expertise in advanced lung diseases and pulmonary vascular management.⁷⁷

Management of extra-pulmonary manifestations is required in approximately 10–20% of adults with PLCH.³ The management of diabetes insipidus, endocrine, skin and bone involvement often require a multidisciplinary approach with other specialists experienced in the management of LCH.

In patients with advanced PLCH, lung transplantation should be considered. Overall, survival data following transplantation are relatively good: 76.9% 1-year, 63.6% 2-year, 57.2% 5-year and 53.7% 10-year survival.⁷⁹ Disease relapse in the transplanted lungs has been described, particularly for patients with preoperative extra-pulmonary manifestations and in those who resumed smoking following transplantation.⁷⁹

Recommended initial evaluation and longitudinal follow-up

A limited but careful medical assessment must be performed following the diagnosis. In some patients a more extensive evaluation with advanced imaging modalities (including PET) may be clinically indicated. The primary goal of this clinical assessment is to determine the degree of functional and pulmonary impairment, assess for complications like pulmonary hypertension, and evaluate for extra-pulmonary manifestations.⁸⁰ This clinical assessment should include a comprehensive history and physical examination with particular attention to ENT, dental, cardiac, pulmonary and lymph node systems. At the time of initial diagnosis, all patients should undergo a complete blood count analysis, serum electrolytes, liver function studies, and urine osmolality testing. In selected patients, particularly when extra-pulmonary disease is suspected because of focal symptoms (bone pain in multiple sites) or constitutional symptoms (weight loss, fevers, sweats, extreme fatigue), imaging with a PET scan may provide evaluation of disease extent (staging) with high sensitivity.⁵²

The natural history of PLCH may be unpredictable. It is recommended that all patients undergo follow-up every 3–4 months for the first year after diagnosis, with pulmonary function testing (including diffusing capacity measurement) and other diagnostic studies as clinically indicated. Further follow-up should be a shared decision between the medical provider and the patient. It seems reasonable that all patients undergo annual follow-up with pulmonary function testing for a minimum of 5 years following diagnosis. The role of repeat chest CT imaging during follow-up is not well established and its use in longitudinal follow-up is a decision that has to be made on a case-by-case basis.

Prognosis and long-term perspectives

The natural history and the prognosis of PLCH are not very well defined. In one retrospective study involving 102 adults with biopsy-proven PLCH, the median survival was 12.5 years, significantly shorter than that expected for persons of the same sex and age ($p < 0.001$).³ A number of studies have now shown that physiological markers of airflow limitation such as a lower FEV₁, lower FEV₁/FVC ratio and higher RV/TLC ratio are predictive of worse outcomes.^{3,54} While a proportion of patients (more than half) develop stable disease with little or no progression over time, a third to a half of patients will develop impaired pulmonary function over time.⁵⁵ During follow-up, a significant number of patients with impaired pulmonary function developed obstructive lung disease (about 40%), while rarely patients with restrictive lung disease at diagnosis no longer show this defect later in the course of the disease due to progressive increase of the RV.⁵⁵

In a recent multicentre study designed to evaluate the incidence of early, marked deterioration (defined as $\geq 15\%$) of pulmonary function parameters in recently diagnosed forms of PLCH, 2-year follow-up data showed that 40% of patients experienced early decline of pulmonary function parameters, mainly FEV₁ and DLCO, after a median follow-up of 1 year after diagnosis.⁵⁴ Interestingly, sequential chest CT scans showed that only about 10% of patients demonstrated significant progression of the extent of pulmonary cystic lesions over the same period.⁵⁴

In some patients, despite regression of the disease, pulmonary function continues to deteriorate as a result of smoking-related COPD. Similarly, cardiovascular complications are not uncommon in these patients. Pregnancy does not appear to modify the course of PLCH, but certain precautions are required (caesarean section) in women with diffuse cystic lesions and impaired pulmonary function due to the risk of pneumothorax during labour. Cases of exacerbation of diabetes insipidus have been reported during pregnancy, and de novo diabetes insipidus may also be observed after delivery.

A retrospective study based on 29 patients with pulmonary hypertension confirmed by right cardiac catheterisation, showed that pulmonary hypertension may occur during the course of known LCH (an average of 10 years after the diagnosis) or may be discovered concomitantly.⁷⁷ In these patients with a mean pulmonary artery pressure (PAP) of 45 mmHg, the New York Heart Association stage of dyspnoea was the only prognostic factor of mortality. In these patients, pulmonary hypertension is due to vasculopathy involving small to medium calibre arteries (intimal fibrosis, medial hypertrophy) and septal veins and venules (intimal fibrosis, partial muscularisation).

Secondary haematological malignancies occur at a higher rate than expected in adults with PLCH.³ In addition to the association with lymphoma, particularly Hodgkin's lymphoma, an increased incidence of primary lung cancer (related to ongoing smoking in these patients), and various other types of malignant tumours, has also been reported.⁸¹

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