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Suspected Pulmonary Langerhans Cell Histiocytosis Following Recurrent Treatment for Bronchitis: A Diagnostic Challenge

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Abstract

Background: Pulmonary Langerhans Cell Histiocytosis (PLCH) is an uncommon smoking-related diffuse cystic lung disease that predominantly affects young and middle-aged adults. Because its presenting symptoms frequently overlap with more prevalent respiratory disorders such as bronchitis, asthma and chronic obstructive pulmonary disease, diagnosis is often delayed. High-resolution computed tomography (HRCT) plays a pivotal role in diagnosis and may establish a confident diagnosis even when histopathological confirmation is unavailable.

Case Presentation: A 45-year-old woman with a history of cigarette smoking presented with a persistent non-productive cough of two years' duration that developed following relocation from New South Wales to Queensland. During this period, she received multiple courses of antibiotics for presumed recurrent bronchitis and atypical pneumonia without sustained clinical improvement. Occupational exposure to cleaning chemicals, angiotensin-converting enzyme inhibitor-induced cough and inhaled corticosteroid therapy complicated the diagnostic evaluation. Treatment with inhaled fluticasone/vilanterol resulted in symptomatic oral candidiasis without improvement in respiratory symptoms. Initial chest radiographs were unremarkable. Progressive diffuse reticular abnormalities subsequently developed, prompting HRCT, which demonstrated numerous upper-lobe predominant irregular thin-walled pulmonary cysts associated with centrilobular ground-glass nodules and relative sparing of the lung bases. These appearances were considered highly characteristic of Pulmonary Langerhans Cell Histiocytosis. Pulmonary function testing demonstrated a mild mixed obstructive-restrictive ventilatory defect with significantly impaired gas transfer. Bronchoscopy with bronchoalveolar lavage and biopsy was offered but declined by the patient.

Management and Outcome: Management consisted of intensive smoking cessation counselling, discontinuation of perindopril because of possible medication-related cough, withdrawal of inhaled corticosteroid therapy, and treatment of inhaled corticosteroid-associated oropharyngeal candidiasis with antifungal therapy. Three months following successful smoking cessation, the patient reported marked improvement in cough, pulmonary function remained stable, and repeat HRCT demonstrated no radiological progression.

Conclusion: This case illustrates the diagnostic complexity of chronic cough when multiple competing diagnoses coexist. Persistent respiratory symptoms despite appropriate treatment should prompt reconsideration of alternative diagnoses, particularly in smokers. HRCT remains the cornerstone of diagnosis in diffuse cystic lung disease and may permit a confident working diagnosis of Pulmonary Langerhans Cell Histiocytosis when imaging findings are characteristic and tissue confirmation is unavailable. Early recognition facilitates smoking cessation, longitudinal surveillance and prevention of irreversible pulmonary damage.

Clinical Message: Persistent chronic cough that fails to respond to standard therapy should prompt reconsideration of the diagnosis. In smokers, characteristic HRCT findings of upper-lobe predominant cystic and nodular lung disease should raise strong suspicion for Pulmonary Langerhans Cell Histiocytosis even when histopathological confirmation is unavailable.

Keywords: Pulmonary langerhans cell histiocytosis; High-resolution computed tomography; Antibiotics

Introduction

Pulmonary Langerhans Cell Histiocytosis (PLCH) is a rare smoking-associated diffuse cystic interstitial lung disease characterized by the accumulation of pathological Langerhans cells within the distal bronchioles and surrounding lung parenchyma. These specialised dendritic antigen-presenting cells express the surface markers CD1a, langerin (CD207), and S100 protein, and their abnormal proliferation results in bronchiolocentric granulomatous inflammation, progressive bronchiolar destruction, and the subsequent development of pulmonary nodules and cystic lesions. Although historically regarded as a purely inflammatory disorder, advances in molecular biology have transformed our understanding of PLCH, with increasing evidence suggesting that it represents a clonal myeloid neoplasm driven by activation of the mitogen-activated protein kinase (MAPK) signaling pathway in many patients. This evolving concept has important implications for disease classification and the future development of targeted therapies. PLCH belongs to the spectrum of Langerhans cell histiocytoses, a heterogeneous group of disorders characterised by tissue infiltration with pathological Langerhans cells. In adults, pulmonary involvement may occur as an isolated disease confined to the lungs or as part of multisystem Langerhans cell histiocytosis, although isolated pulmonary disease is considerably more common. PLCH accounts for less than 5% of diffuse parenchymal lung diseases and predominantly affects adults between 20 and 50 years of age. Unlike paediatric Langerhans cell histiocytosis, which commonly involves bone, skin, lymph nodes and the endocrine system, adult PLCH is usually restricted to the respiratory tract and demonstrates a striking association with cigarette smoking.

More than 90–95% of adults diagnosed with PLCH are current or former smokers, making cigarette smoking the single most important environmental risk factor identified to date. Although the precise mechanism by which tobacco smoke initiates disease remains incompletely understood, it is believed that cigarette smoke induces chronic activation of airway macrophages and dendritic cells, leading to excessive recruitment and proliferation of Langerhans cells around terminal and respiratory bronchioles. Tobacco smoke also stimulates the production of pro-inflammatory cytokines, including tumour necrosis factor-alpha (TNF-α), granulocyte-macrophage colony-stimulating factor (GM-CSF), transforming growth factor-beta (TGF-β), interleukin-1β (IL-1β), and interleukin-17 (IL-17), thereby promoting persistent inflammation and tissue remodelling. Continued exposure to cigarette smoke results in progressive bronchiolar injury, destruction of alveolar architecture, cyst formation and irreversible pulmonary fibrosis in susceptible individuals. Recent molecular studies have significantly advanced the understanding of PLCH pathogenesis. Somatic activating mutations involving components of the MAPK signalling cascade, particularly BRAF V600E, MAP2K1, NRAS, KRAS, and ARAF, have been identified in a substantial proportion of patients with pulmonary and multisystem Langerhans cell histiocytosis. These findings suggest that PLCH may represent an inflammatory neoplasm rather than solely a reactive inflammatory disorder. Identification of these molecular abnormalities has stimulated interest in targeted therapies, including BRAF inhibitors and MEK inhibitors, for patients with progressive or multisystem disease who fail conventional management. Although smoking cessation remains the cornerstone of treatment, these developments represent a significant advance in understanding disease biology and offer potential therapeutic options for selected patients.

The clinical manifestations of PLCH are frequently non-specific and contribute to delays in diagnosis. Chronic non-productive cough and exertional dyspnoea are the most common presenting symptoms, although fatigue, chest discomfort, constitutional symptoms and recurrent lower respiratory tract infections may also occur. Approximately 15–25% of patients initially present with spontaneous pneumothorax due to rupture of subpleural cysts, while a smaller proportion remain asymptomatic and are diagnosed following incidental abnormalities detected on chest imaging. As disease progresses, pulmonary function may deteriorate owing to increasing cystic destruction, airflow limitation, impaired gas transfer and pulmonary vascular involvement. Pulmonary hypertension is increasingly recognised as a major determinant of morbidity and mortality in advanced disease and may occur out of proportion to the degree of parenchymal destruction. The diagnosis of PLCH requires careful integration of clinical history, smoking exposure, radiological findings and, when necessary, histopathological examination. Routine laboratory investigations are often non-specific and are primarily useful for excluding alternative causes of diffuse parenchymal lung disease, including connective tissue disease-associated interstitial lung disease, systemic vasculitis and chronic infection. Pulmonary function testing typically demonstrates a variable physiological pattern. Early disease may be associated with normal spirometry, whereas more advanced disease

frequently exhibits airflow obstruction, restrictive physiology or a mixed ventilatory defect. A reduction in diffusing capacity for carbon monoxide (DLCO) is the most consistent physiological abnormality and often represents the earliest objective indicator of pulmonary involvement. High-resolution computed tomography (HRCT) has become the cornerstone of PLCH diagnosis and frequently obviates the need for surgical lung biopsy when characteristic findings are present. The radiological appearance reflects disease evolution. Early disease is characterised by poorly defined centrilobular nodules corresponding to active bronchiolocentric granulomatous inflammation. Progressive cavitation of these nodules leads to thick-walled cyst formation, which subsequently evolves into thin-walled irregular cysts of varying size and morphology. The coexistence of centrilobular nodules and bizarre-shaped cysts with a predominantly upper- and mid-lung distribution and relative sparing of the costophrenic angles is highly characteristic of PLCH and assists in differentiating it from other diffuse cystic lung diseases.

The differential diagnosis of diffuse cystic lung disease is broad and includes lymphangioleiomyomatosis (LAM), Birt-Hogg-Dubé syndrome (BHD), lymphocytic interstitial pneumonia (LIP), amyloidosis, light-chain deposition disease, advanced centrilobular emphysema and certain inherited cystic lung disorders. Distinguishing these entities relies upon integration of clinical characteristics with radiological features. Unlike PLCH, LAM typically demonstrates diffuse, uniformly distributed round cysts without associated nodules and predominantly affects women of reproductive age. BHD is characterised by basilar and subpleural cysts associated with fibrofolliculomas, renal tumours and a positive family history. LIP usually occurs in association with autoimmune disease and demonstrates diffuse ground-glass opacification and lower-lobe predominant cysts. Recognition of these distinguishing features is essential because management strategies and prognostic implications differ substantially. Although histopathological confirmation remains the diagnostic gold standard, biopsy is not always required. Bronchoscopic transbronchial biopsy has a relatively modest diagnostic yield due to the patchy distribution of lesions, while transbronchial cryobiopsy and surgical lung biopsy provide higher diagnostic accuracy but carry greater procedural risk. In contemporary respiratory practice, a confident working diagnosis may be established in patients with a compatible smoking history and classic HRCT findings after reasonable exclusion of alternative diagnoses, particularly when invasive investigations are contraindicated or declined by the patient. Smoking cessation remains the single most effective intervention in PLCH and is associated with disease stabilisation or partial regression in a substantial proportion of patients. Continued smoking is strongly associated with progressive cyst formation, accelerated decline in lung function, recurrent pneumothoraces and the development of pulmonary hypertension. Beyond smoking cessation, management is largely supportive and includes vaccination, optimisation of pulmonary function, pulmonary rehabilitation where appropriate and longitudinal surveillance with pulmonary function testing and HRCT. Systemic corticosteroids are no longer routinely recommended because of limited evidence of sustained benefit. Cytotoxic agents such as cladribine and cytarabine have been used in selected patients with progressive disease, while molecularly targeted therapies directed against BRAF or MEK have emerged as promising options for patients harbouring MAPK pathway mutations. Lung transplantation remains the definitive treatment for carefully selected patients with advanced respiratory failure, although disease recurrence has been described in individuals who continue to smoke following transplantation.

The present case illustrates several important diagnostic lessons. The patient's prolonged history of isolated chronic cough was repeatedly attributed to recurrent bronchitis, atypical pneumonia, occupational irritant exposure and medication-induced cough, resulting in a delay in recognising an uncommon smoking-related diffuse cystic lung disease. The eventual diagnosis became apparent only after HRCT demonstrated the characteristic combination of upper-lobe predominant irregular cysts and centrilobular nodules. Furthermore, this case demonstrates that clinically significant PLCH may occur in patients with a relatively modest cumulative smoking exposure and highlights the importance of maintaining a broad differential diagnosis when chronic cough fails to respond to standard therapy. It also underscores the pivotal role of HRCT in establishing a confident working diagnosis when histopathological confirmation is unavailable, enabling timely smoking cessation, appropriate surveillance and prevention of progressive irreversible lung injury [1-35].

Case Presentation

A 45-year-old woman was referred to the respiratory outpatient clinic for evaluation of a persistent non-productive cough that had been present for approximately two years. The cough began shortly after she relocated from New South Wales to Queensland and coincided with commencing employment as a commercial cleaner. Although initially intermittent, the cough gradually became persistent and troublesome, occurring throughout the day without an obvious diurnal variation. She denied sputum production, haemoptysis, wheeze, pleuritic chest pain or recurrent lower respiratory tract infections. The cough was not associated with meals or body position and was not accompanied by symptoms suggestive of gastro-oesophageal reflux disease or upper airway cough syndrome. She remained functionally independent and reported no significant limitation in exercise tolerance, although the persistent cough had become increasingly

disruptive to her daily activities and quality of life. During the preceding two years she sought medical attention on multiple occasions through both primary care and emergency services. She received several courses of oral antibiotics for presumed recurrent bronchitis, with only transient or no symptomatic improvement. On one emergency department presentation she was diagnosed with atypical pneumonia and acute sinusitis and was treated with further antimicrobial therapy. Despite these interventions, the cough persisted without meaningful clinical improvement. The lack of response to repeated antibiotic therapy prompted referral for specialist respiratory assessment. An important feature of the history was an unintentional weight loss of approximately 20 kg over the preceding two years. The patient attributed this to several factors, including increased physical activity associated with her new occupation, psychological stress related to relocation, and treatment with phentermine (Duromine) prescribed for weight reduction. Nevertheless, the magnitude of weight loss in conjunction with persistent respiratory symptoms appropriately raised concern for an underlying chronic pulmonary disorder, occult malignancy or chronic infection, necessitating comprehensive investigation. Her past medical history was significant only for hypertension, which was treated with a fixed-dose combination of perindopril and amlodipine (Reaptan). She had no previous diagnosis of asthma, chronic obstructive pulmonary disease, bronchiectasis or other chronic respiratory illness. She denied childhood asthma, allergic rhinitis, eczema or other atopic disorders. There was no history of recurrent pneumothorax, pulmonary embolism, tuberculosis, connective tissue disease or previous thoracic surgery.

The smoking history proved particularly relevant. The patient had commenced cigarette smoking at approximately 17 years of age, smoking an average of 8–10 cigarettes daily for approximately ten years before successfully quitting for 16 years. Four years before presentation she recommenced smoking and continued to smoke approximately 8–10 cigarettes daily until specialist review, giving an estimated cumulative smoking exposure of approximately 7–9 pack-years. Although relatively modest compared with many patients with smoking-related interstitial lung disease, this exposure was considered clinically significant given the recognised association between cigarette smoking and Pulmonary Langerhans Cell Histiocytosis (PLCH). She denied electronic cigarette use, vaping, cannabis smoking or exposure to illicit inhalational drugs.

Occupational history was explored in detail because symptom onset closely followed commencement of work as a commercial cleaner. She described regular exposure to a variety of cleaning agents, including bleach-based disinfectants, detergents and aerosolised chemical products. Although she did not identify any single exposure consistently precipitating symptoms, the temporal relationship raised the possibility of occupational irritant-induced cough. She denied exposure to asbestos, silica, coal dust, hard metal dust, birds, moulds, farming environments, hot tubs or other recognised causes of hypersensitivity pneumonitis or occupational interstitial lung disease. The patient lived independently and remained employed full-time. She consumed alcohol only occasionally, averaging three to four standard drinks per week, and denied recreational drug use. There had been no recent overseas travel, no exposure to tuberculosis, and no history of significant environmental or domestic inhalational exposures outside the workplace. Family history was unremarkable for interstitial lung disease, pulmonary fibrosis, spontaneous pneumothorax, connective tissue disease, renal malignancy or inherited cystic lung disorders such as Birt-Hogg-Dubé syndrome. A comprehensive review of systems failed to identify features suggestive of multisystem disease. She denied exertional dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, wheezing, chest tightness or exercise limitation. There was no history of fever, night sweats, recurrent sinus disease, recurrent infections or constitutional symptoms other than weight loss. She denied sicca symptoms, photosensitivity, oral ulceration, Raynaud phenomenon, inflammatory arthritis, proximal muscle weakness or skin rash that might suggest an underlying connective tissue disease. There were no symptoms suggestive of diabetes insipidus, neurological involvement or osseous pain that could indicate multisystem Langerhans cell histiocytosis.

Several therapeutic interventions had been attempted before specialist referral. In addition to repeated antibiotic therapy, inhaled fluticasone furoate/vilanterol (Breo Ellipta®) had been prescribed for presumed inflammatory airway disease. Despite appropriate use of the inhaler, she experienced no improvement in cough. Instead, she developed progressive oral discomfort with white plaques affecting the tongue and buccal mucosa, consistent with inhaled corticosteroid-associated oropharyngeal candidiasis. This adverse effect further reduced treatment adherence and reinforced the need to reconsider the original diagnosis. On examination, the patient appeared comfortable at rest and was not in respiratory distress. Vital signs were within normal limits, with normal oxygen saturation breathing room air. Her body mass index had decreased substantially compared with historical records, consistent with the reported weight loss. Oral examination demonstrated extensive removable white plaques involving the tongue and buccal mucosa, compatible with oropharyngeal candidiasis. There was no cervical or supraclavicular lymphadenopathy. Respiratory examination revealed symmetrical chest expansion with normal percussion note throughout both lung fields. Breath sounds were vesicular bilaterally without wheeze, crackles or inspiratory squeaks. No prolonged expiratory phase was appreciated. There was no digital clubbing, peripheral cyanosis or evidence of pulmonary hypertrophic osteoarthropathy. Cardiovascular examination was

normal without signs of pulmonary hypertension or right heart failure. Abdominal examination was unremarkable, with no hepatosplenomegaly or palpable masses. Dermatological examination revealed no fibrofolliculomas, xanthomatous lesions or cutaneous manifestations suggestive of systemic histiocytosis or Birt-Hogg-Dubé syndrome. Routine laboratory investigations, including complete blood count, renal and liver function tests, inflammatory markers and autoimmune serology, were all within normal reference limits. The absence of peripheral eosinophilia, elevated inflammatory markers or autoimmune antibodies reduced the likelihood of connective tissue disease-associated interstitial lung disease, systemic vasculitis or active inflammatory pulmonary disease. Rheumatoid factor, anti-cyclic citrullinated peptide antibodies, antinuclear antibodies, extractable nuclear antigen antibodies and antineutrophil cytoplasmic antibodies were all negative. Review of previous imaging demonstrated that a chest radiograph performed approximately ten months earlier had been interpreted as normal, with no focal consolidation or interstitial abnormality. However, because of persistent symptoms, repeat chest radiography was obtained and demonstrated new bilateral diffuse reticular opacities predominantly involving the mid and upper lung zones. Although these findings were non-specific, they raised suspicion for an evolving diffuse interstitial process and prompted further evaluation with high-resolution computed tomography (HRCT).

HRCT of the chest proved pivotal in establishing the diagnosis. Imaging demonstrated numerous irregular thin-walled pulmonary cysts distributed predominantly throughout the upper and mid lung zones, together with multiple centrilobular ground-glass nodules. The cysts were variable in size and morphology, several exhibiting bizarre and branching configurations characteristic of smoking-related cystic lung disease. Relative sparing of the lung bases and costophrenic angles was evident. No honeycombing, traction bronchiectasis, pleural effusion, mediastinal lymphadenopathy or suspicious pulmonary mass was identified. The radiological appearances were considered highly characteristic of Pulmonary Langerhans Cell Histiocytosis. Pulmonary function testing demonstrated a mild mixed ventilatory defect with both obstructive and restrictive features. Forced expiratory volume in one second (FEV_1) was mildly reduced to 68% predicted, while forced vital capacity (FVC) was 72% predicted, with preservation of the FEV_1/FVC ratio. Gas transfer was disproportionately impaired, with a diffusing capacity for carbon monoxide (DLCO) of 58% predicted and a reduced transfer coefficient (KCO), findings consistent with diffuse parenchymal lung disease involving the distal airspaces and pulmonary capillary interface. The reduction in DLCO correlated well with the extensive cystic abnormalities observed on HRCT. At this stage, the principal diagnostic consideration became diffuse cystic lung disease. Given the patient's age, smoking history and characteristic radiological pattern of upper-lobe predominant irregular cysts associated with centrilobular nodules, PLCH emerged as the leading diagnosis. Alternative diagnoses, including lymphangioleiomyomatosis, Birt-Hogg-Dubé syndrome, lymphocytic interstitial pneumonia and advanced smoking-related emphysema, were systematically considered but regarded as less likely on clinical and radiological grounds. To obtain histopathological confirmation, flexible bronchoscopy with bronchoalveolar lavage and transbronchial biopsy was discussed in detail. The potential benefits of tissue diagnosis, including immunohistochemical demonstration of CD1a- and langerin-positive Langerhans cells, were explained alongside the procedural risks of bleeding, pneumothorax and the recognised limitations of transbronchial biopsy due to the patchy distribution of disease. After careful consideration, the patient declined invasive investigation, expressing a preference for conservative management and radiological surveillance.

In view of the overall clinical picture, management was directed towards elimination of modifiable risk factors and optimisation of reversible contributors to chronic cough. Perindopril was discontinued because of its potential contribution to ACE inhibitor-induced cough and replaced with telmisartan/amlodipine. Inhaled corticosteroid therapy was ceased because of the absence of clinical benefit and the development of symptomatic oropharyngeal candidiasis, which was successfully treated with oral fluconazole and topical nystatin. Intensive smoking cessation counselling was provided, together with nicotine replacement therapy and referral to smoking cessation support services. The patient was reviewed three months later. She had successfully stopped smoking and reported a marked improvement in cough frequency and severity. Her weight had stabilised, exercise tolerance remained preserved and no new respiratory symptoms had developed. Repeat pulmonary function testing demonstrated stable spirometry and gas transfer without evidence of physiological deterioration. Follow-up HRCT showed no progression of the cystic or nodular abnormalities. Although histopathological confirmation was not obtained, the combination of a compatible smoking history, characteristic HRCT findings, exclusion of relevant alternative diagnoses and favourable clinical response following smoking cessation supported a confident working diagnosis of suspected Pulmonary Langerhans Cell Histiocytosis, with plans for continued long-term respiratory surveillance.

Investigations and Diagnostic Reasoning

The diagnostic evaluation was undertaken systematically to identify the cause of the patient's persistent cough, significant weight loss and newly recognised diffuse interstitial abnormalities on chest imaging. Given the prolonged symptom duration and failure to respond to conventional therapy, investigations were

directed towards excluding chronic infection, malignancy, connective tissue disease-associated interstitial lung disease, vasculitis and other causes of diffuse cystic lung disease.

Baseline laboratory investigations demonstrated no evidence of systemic inflammation, haematological abnormality or end-organ dysfunction (Table 1).

Laboratory Investigations

Table 1: *Most recent pathology investigation results.*

Full blood count		
Observations	**Value**	**Ref Ranges**
Haemoglobin	124	115 – 160
WCC	8.3	4.0 – 11.0
Platelets	244	140 – 400
Haematocrit	0.36	0.33 – 0.47
MCH	29.3	27.5 – 33.0
Red Cell Count	4.23	3.80 – 5.20
MCV	86	80 – 100
Neutrophils	5.02	2.0 – 8.0
Lymphocytes	2.57	1.0 – 4.0
Monocytes	0.46	0.1 – 1.0
Eosinophils	0.14	<0.60
Basophils	0.07	<0.20
Liver function tests		
Observations	**Value**	**Ref Ranges**
Protein (Total)	68	60 – 80
Albumin	36	35 – 50
Globulin	32	25 – 45
Bilirubin (total)	5	<20
Alkaline phosphatase	81	30 – 110
Gamma-GT	24	<38
Alanine transaminase	15	<34
Aspartate transaminase	12	<31
Urea, electrolytes and creatinine		
Observations	**Value**	**Ref Ranges**
Sodium	141	135 – 145
Potassium	4.4	3.5 – 5.2
Chloride	111	95 – 110
Bicarbonate	27	22 – 32
Anion gap	3	4 – 13
Lactate dehydrogenase	184	120 – 250
Calcium	2.29	2.10 – 2.60
Phosphate	1.32	0.75 – 1.50
Magnesium	0.87	0.7 – 1.10
Urea	5.2	2.1 – 7.1
Creatinine	104	45 – 90
Urate	0.36	0.15 – 0.45
Glucose random	6.0	3.0 – 7.8
CRP		
Observations		**Ref Ranges**

17		<5mg/L
Autoantibodies		
Observations		**Status**
Anti-Nuclear Abs (ANA)		Negative
ENA Abs		
ANCA		
Observations		**Status**
Classical ANCA (C-ANCA)		Negative
Perinuclear ANCA (p-ANCA)		Negative
Rheumatology studies		
Observations	**Value**	**Ref Ranges**
Rheumatoid factor (RF)	<20	<20
CCP Abs	<5	<5
Metabolics		
Observations	**Value**	**Ref Ranges**
Angiotensin Converting Enzyme (MASS)	175	37 – 211
Protein Chemistry		
Observations	**Value**	**Ref Ranges**
IgA	2.6	1.0 – 4.0
IgG	11.2	7.0 – 16.0
IgM	0.8	0.4 – 2.3
Alpha – 1 – Antitrypsin Genotype	1.68	0.90 – 2.0

Haemoglobin, white cell count and platelet count were within normal reference ranges, making chronic infection, occult haematological malignancy and significant inflammatory disease less likely. The absence of eosinophilia reduced the likelihood of eosinophilic lung disease or allergic bronchopulmonary disorders. Renal function, liver function tests and serum electrolytes were entirely normal. Serum albumin and total protein concentrations were preserved, indicating satisfactory nutritional status despite the reported weight loss. Lactate dehydrogenase, although non-specific, was also within the normal range and did not suggest an aggressive inflammatory or malignant process. Inflammatory markers demonstrated only a mild elevation in C-reactive protein (Table 1). While this finding is non-specific and may reflect a range of inflammatory or infectious processes, the absence of systemic symptoms, normal haematological indices, negative autoimmune serology and lack of radiological features suggestive of active infection reduced the likelihood of a significant infective or systemic inflammatory disorder requiring antimicrobial or immunosuppressive therapy. Although a mildly elevated CRP does not exclude chronic interstitial lung disease, the overall laboratory profile was not suggestive of an alternative inflammatory aetiology for the patient's pulmonary abnormalities. Given the radiological suspicion of diffuse parenchymal lung disease, an autoimmune screen was performed to exclude connective tissue disease-associated interstitial lung disease. Antinuclear antibodies (ANA), extractable nuclear antigen antibodies (ENA), rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (anti-CCP), cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) and perinuclear ANCA (p-ANCA) were all negative. In the absence of clinical features suggestive of systemic autoimmune disease, these findings substantially reduced the likelihood of connective tissue disease, rheumatoid lung disease or ANCA-associated vasculitis as the underlying cause of the patient's pulmonary abnormalities. Overall, the laboratory evaluation did not identify an alternative systemic disorder and supported further investigation with advanced thoracic imaging.

Chest Radiography

The evolution of the patient's chest radiographs illustrates an important feature of Pulmonary Langerhans Cell Histiocytosis. A chest radiograph performed approximately ten months before specialist assessment demonstrated no significant abnormality. This finding is consistent with early PLCH, in which conventional radiography may remain normal despite active bronchiolocentric disease. Repeat chest radiography obtained because of persistent symptoms demonstrated new diffuse bilateral reticular opacities with a predominately mid- and upper-zone distribution. Although these abnormalities were non-specific, their interval development suggested progression of an underlying diffuse parenchymal lung process rather than recurrent acute bronchitis or pneumonia. Importantly, no focal consolidation, pleural effusion or pulmonary mass was identified. The progression from a normal radiograph to diffuse reticular

change despite repeated empirical treatment highlights the limitations of plain radiography in early diffuse cystic lung disease and emphasises the importance of proceeding to HRCT when symptoms remain unexplained (Figure 1).



Figure 1: *Chest x-ray demonstrating new diffuse reticular opacities throughout both lungs with a mid- to upper-zone predominance. The appearances were considered suspicious for an evolving diffuse interstitial lung process.*

High-Resolution Computed Tomography

High-resolution computed tomography represented the pivotal diagnostic investigation. HRCT demonstrated numerous bilateral thin-walled pulmonary cysts of variable size and morphology involving predominantly the upper and middle lung zones. Several cysts demonstrated irregular, bilobed and branching ("bizarre") configurations rather than the uniformly round morphology typically observed in other cystic lung diseases. Multiple small centrilobular ground-glass nodules were present throughout the affected lung, reflecting active bronchiolocentric inflammatory lesions. Relative preservation of the lung bases and costophrenic recesses was evident.

Importantly, several radiological features argued strongly in favour of Pulmonary Langerhans Cell Histiocytosis:

- Upper-lobe and mid-lung predominance.
- Relative sparing of the lung bases.
- Coexistence of centrilobular nodules and cysts.
- Irregular thin-walled cysts with bizarre morphology.
- Absence of diffuse uniform cysts.
- No significant mediastinal lymphadenopathy.
- No pleural effusion.
- No honeycombing.
- No traction bronchiectasis.
- No dominant pulmonary mass.

This radiological pattern is regarded as highly characteristic of PLCH and, when combined with an appropriate smoking history, may allow a confident clinical diagnosis without the need for surgical lung biopsy. The HRCT findings also reflected different stages of disease evolution. The coexistence of centrilobular nodules and cystic lesions suggests ongoing active bronchiolar inflammation together with established bronchiolar destruction. This mixed appearance is typical of intermediate-stage disease and distinguishes PLCH from end-stage fibrotic cystic lung disorders (Figure 2).

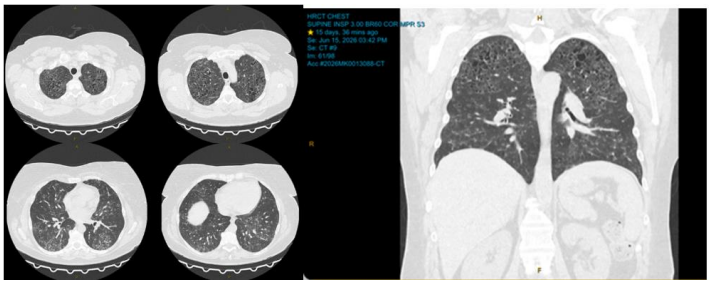


Figure 2: *High resolution CT scan demonstrating diffuse cystic and nodular lung disease characterised by numerous thin-walled cysts and ground-glass centrilobular nodules with relative sparing of the lung bases. The radiological impression was diffuse cystic lung disease with high confidence for Pulmonary Langerhans Cell Histiocytosis (PLCH).*

Pulmonary Function Testing

Comprehensive pulmonary function testing demonstrated physiological abnormalities consistent with diffuse smoking-related cystic lung disease (Table 2).

Table 2: *Full lung function test.*

Observations	Result	% Predicted
FEV1		68%
FVC		72%
FEV1/FVC		
DLCO		58%
KCO		

Spirometry revealed a mild mixed ventilatory defect with both obstructive and restrictive features. Forced expiratory volume in one second (FEV_1) was reduced to 68% predicted, while forced vital capacity (FVC) measured 72% predicted. The preserved FEV_1/FVC ratio suggested that airflow obstruction alone could not explain the physiological impairment. The most striking abnormality was a significantly reduced diffusing capacity for carbon monoxide (DLCO), measured at 58% predicted, together with a reduced transfer coefficient (KCO). Reduction in DLCO is recognised as the most sensitive physiological abnormality in PLCH and reflects destruction of the alveolar-capillary membrane secondary to bronchiolar inflammation, cyst formation and loss of functional pulmonary capillary surface area. The combination of mildly impaired spirometry with disproportionately reduced gas transfer correlated closely with the extensive cystic abnormalities demonstrated on HRCT and further supported the diagnosis of diffuse cystic lung disease.

Histopathological Assessment

Histological confirmation was discussed with the patient.

Flexible bronchoscopy with bronchoalveolar lavage and transbronchial biopsy was offered to obtain tissue for histopathological examination. The patient received detailed counselling regarding the potential diagnostic value of demonstrating characteristic CD1a-positive and langerin (CD207)-positive Langerhans cells within bronchiolocentric granulomatous lesions. However, the limitations of bronchoscopic biopsy were also explained. PLCH lesions are patchy in distribution, resulting in relatively modest diagnostic yields from conventional transbronchial biopsy. Surgical lung biopsy provides greater diagnostic accuracy but is associated with increased procedural morbidity, while transbronchial cryobiopsy remains an emerging technique with variable availability. After considering the risks and benefits, the patient declined invasive tissue sampling and elected to proceed with conservative management and radiological surveillance.

Differential Diagnosis

Diffuse cystic lung disease encompasses a diverse group of disorders with overlapping clinical and radiological features. A systematic differential diagnosis was therefore undertaken.

Pulmonary Langerhans Cell Histiocytosis

PLCH was considered the most likely diagnosis because of the combination of cigarette smoking, upper-lobe predominant irregular cysts, associated centrilobular nodules and relative sparing of the lung bases. The coexistence of nodules and cysts is particularly characteristic and strongly favoured PLCH over alternative cystic lung diseases.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) was considered because it predominantly affects women of similar age. However, the HRCT findings were not typical. LAM usually demonstrates numerous thin-walled round cysts of relatively uniform size distributed diffusely throughout both lungs, including the lung bases, without associated nodules. Furthermore, the patient had no history of recurrent pneumothorax, chylous pleural effusion, renal angiomyolipomas or features of tuberous sclerosis complex.

Birt-Hogg-Dubé Syndrome

Birt-Hogg-Dubé syndrome was considered unlikely because there was no family history of spontaneous pneumothorax or renal malignancy, no characteristic skin fibrofolliculomas and no basal or paramediastinal predominance of cysts. The radiological distribution was inconsistent with this inherited disorder.

Lymphocytic Interstitial Pneumonia

Lymphocytic interstitial pneumonia was also considered. However, the absence of autoimmune disease, sicca symptoms, hypergammaglobulinaemia, diffuse ground-glass opacification and lower-lobe predominant cysts argued strongly against this diagnosis.

Smoking-Related Emphysema

Although cigarette smoking is associated with emphysema, emphysematous destruction generally lacks visible cyst walls and is not accompanied by centrilobular nodules. The bizarre cyst morphology observed on HRCT was not consistent with centrilobular emphysema.

Chronic Hypersensitivity Pneumonitis

The temporal relationship between symptom onset and occupational exposure initially raised concern for hypersensitivity pneumonitis. However, the patient lacked compatible clinical features, autoimmune serology was negative, and HRCT did not demonstrate mosaic attenuation, significant air trapping or diffuse ground-glass infiltrates typical of chronic hypersensitivity pneumonitis.

Pulmonary Malignancy

Significant weight loss prompted careful exclusion of malignancy. However, HRCT demonstrated no pulmonary mass, suspicious lymphadenopathy or metastatic disease. The diffuse cystic and nodular pattern was much more consistent with smoking-related diffuse cystic lung disease than primary lung carcinoma.

Establishing the Working Diagnosis

Although histopathological confirmation was not obtained, the diagnosis of suspected Pulmonary Langerhans Cell Histiocytosis was considered highly probable based upon the convergence of multiple clinical, physiological and radiological findings.

These included:

- A current cigarette smoker with an established smoking history.
- Persistent chronic non-productive cough refractory to conventional therapy.
- Characteristic HRCT demonstrating upper-lobe predominant irregular cysts associated with centrilobular nodules.
- Relative sparing of the lung bases.
- Reduced diffusing capacity consistent with diffuse cystic lung disease.
- Exclusion of autoimmune, infective and malignant causes.
- Clinical improvement following smoking cessation.

In accordance with contemporary international practice, these findings were considered sufficient to establish a confident working diagnosis of Pulmonary Langerhans Cell Histiocytosis despite the absence of histopathological confirmation.

Discussion

Pulmonary Langerhans Cell Histiocytosis (PLCH) is an uncommon smoking-related diffuse cystic lung disease that remains diagnostically challenging because of its heterogeneous clinical presentation and overlap with more common respiratory disorders. This case illustrates several important clinical lessons. First, chronic cough that fails to respond to conventional therapy should prompt reconsideration of the initial diagnosis. Second, multiple plausible explanations for persistent respiratory symptoms may coexist and delay recognition of an uncommon interstitial lung disease. Finally, characteristic HRCT findings, interpreted in the appropriate clinical context, may establish a confident working diagnosis even when histopathological confirmation is unavailable.

Diagnostic delay in PLCH

Delayed diagnosis is well recognised in PLCH. Patients frequently present with non-specific respiratory symptoms including chronic cough, exertional dyspnoea, fatigue and chest discomfort, all of which overlap considerably with common respiratory disorders such as asthma, chronic bronchitis and chronic obstructive pulmonary disease (COPD). Consequently, many patients undergo repeated empirical treatment before appropriate imaging is performed. Our patient experienced a persistent dry cough for approximately two years before the diagnosis was considered. During this period, she received multiple courses of antibiotics for presumed recurrent bronchitis and atypical pneumonia without meaningful improvement. She was also treated with inhaled corticosteroid/long-acting β_2-agonist therapy because inflammatory airway disease was suspected. The absence of clinical response to these interventions represented an important clue that the underlying diagnosis had not been established. This case reinforces a fundamental principle in respiratory medicine: failure to respond to appropriate evidence-based therapy should always prompt reassessment of the diagnosis rather than repeated escalation of the same treatment. In patients with chronic cough persisting beyond eight weeks, particularly smokers, clinicians should maintain a broad differential diagnosis that includes diffuse parenchymal lung diseases in addition to more common airway disorders.

Chronic cough as the presenting manifestation

Chronic cough is one of the commonest reasons for referral to respiratory physicians, yet PLCH remains an uncommon cause. Most diagnostic algorithms focus initially on upper airway cough syndrome, asthma, eosinophilic bronchitis, gastro-oesophageal reflux disease and ACE inhibitor therapy because these conditions account for the majority of presentations. Our patient presented almost exclusively with cough and had little physiological impairment or exertional dyspnoea despite extensive radiological abnormalities. Such clinicoradiological dissociation has been described in PLCH and reflects the variable distribution of bronchiolocentric lesions. Patients may demonstrate extensive cystic change on HRCT while remaining relatively asymptomatic, whereas others develop significant functional limitation with less extensive radiographic abnormalities. The cough associated with PLCH is believed to result from inflammation centred on terminal and respiratory bronchioles. Accumulation of pathological Langerhans cells, macrophages and activated inflammatory cells within the bronchiolar walls stimulates local cytokine production, airway irritation and cough receptor activation. Progressive bronchiolar destruction subsequently leads to cyst formation and impairment of pulmonary mechanics. The absence of wheeze, reversible airflow obstruction or eosinophilia in this patient further reduced the likelihood of asthma as the primary diagnosis. Similarly, the persistence of cough despite repeated antibiotic therapy argued strongly against recurrent bacterial bronchitis.

Smoking and disease pathogenesis

The relationship between cigarette smoking and PLCH is one of the strongest environmental associations recognised in respiratory medicine. More than 90–95% of adults diagnosed with PLCH are current or former smokers, and smoking cessation remains the only intervention consistently associated with disease stabilisation. Although our patient's cumulative smoking exposure was modest compared with many published cohorts, her history remained highly significant. She had smoked during early adulthood, achieved prolonged abstinence and subsequently recommenced smoking several years before symptom onset. The temporal association between resumed cigarette smoking and development of respiratory symptoms is consistent with the recognised pathophysiology of PLCH. Cigarette smoke promotes recruitment of dendritic cells and macrophages into distal airways while stimulating release of tumour necrosis factor-alpha (TNF-α), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-1β, interleukin-17 and transforming growth factor-beta (TGF-β). These mediators enhance survival and activation of pathological Langerhans cells, leading to bronchiolocentric granulomatous inflammation and progressive bronchiolar destruction. In recent years, molecular studies have substantially altered the understanding of PLCH. Somatic activating mutations involving components of the MAPK signalling pathway—including BRAF V600E, MAP2K1, KRAS, NRAS and ARAF—have been identified in a significant proportion of patients. These findings support the concept that PLCH represents a clonal myeloid neoplasm occurring within a pro-inflammatory microenvironment created by cigarette smoke rather than a purely reactive inflammatory condition. This paradigm shift has important therapeutic implications because

targeted inhibition of the MAPK pathway has demonstrated promising results in selected patients with multisystem or progressive disease.

Radiological diagnosis

High-resolution computed tomography was the pivotal investigation in the present case and ultimately established the diagnosis. HRCT has transformed the evaluation of diffuse cystic lung disease and frequently obviates the need for surgical lung biopsy when characteristic features are present. The imaging findings in our patient were highly characteristic of PLCH, demonstrating irregular thin-walled cysts of varying size and morphology predominantly involving the upper and middle lung zones together with multiple centrilobular nodules and relative sparing of the lung bases. This combination is considered virtually pathognomonic in an appropriate clinical setting. The radiological appearance of PLCH reflects disease evolution. Early lesions consist of poorly defined bronchiolocentric nodules representing focal collections of pathological Langerhans cells. Progressive destruction of bronchiolar walls results in cavitation of these nodules and subsequent formation of thick-walled cysts. As inflammation subsides, the cyst walls become thinner and progressively assume bizarre, branching or cloverleaf configurations. Eventually, advanced disease may be characterised predominantly by irregular cysts with little residual nodularity. Recognition of these evolutionary stages is clinically important because patients with mixed nodular and cystic disease may still have active inflammatory lesions that are potentially responsive to smoking cessation. In contrast, extensive thin-walled cystic destruction generally represents irreversible structural damage. Unlike chest radiography, which may remain normal during early disease, HRCT provides excellent spatial resolution of bronchiolocentric abnormalities and has become the imaging modality of choice for suspected diffuse cystic lung disease. In our patient, the transition from an initially normal chest radiograph to abnormal HRCT illustrates the limited sensitivity of conventional radiography and supports current recommendations favouring HRCT in patients with persistent unexplained respiratory symptoms.

Differential diagnosis of diffuse cystic lung disease

Diffuse cystic lung disease encompasses a heterogeneous group of disorders that require careful clinical and radiological differentiation. In women of this age, the principal differential diagnoses include lymphangioleiomyomatosis (LAM), Birt-Hogg-Dubé syndrome (BHD), lymphocytic interstitial pneumonia (LIP), smoking-related emphysema and chronic hypersensitivity pneumonitis. LAM was considered because it typically affects women of reproductive age. However, the uniformly round cysts characteristic of LAM, diffuse lung involvement including the costophrenic recesses, and the absence of associated centrilobular nodules differed substantially from the HRCT findings observed in our patient. Furthermore, there was no history of renal angiomyolipomas, tuberous sclerosis complex or recurrent chylous pleural effusions. Birt-Hogg-Dubé syndrome was considered unlikely because of the absence of a family history of spontaneous pneumothorax, renal neoplasia or characteristic fibrofolliculomas. The HRCT distribution also favoured PLCH, with upper-lobe rather than lower-lobe or paramediastinal cyst predominance. Similarly, lymphocytic interstitial pneumonia was not supported because the patient lacked autoimmune disease, hypergammaglobulinemia, lower-lobe predominant cysts or diffuse ground-glass opacification. Smoking-related emphysema was also considered but was discounted because emphysema produces regions of low attenuation without definable cyst walls and is not associated with centrilobular inflammatory nodules. The systematic exclusion of these alternative diagnoses strengthened the clinical confidence in the diagnosis of PLCH despite the absence of histopathological confirmation.

Histopathological Considerations

Histopathological examination remains the reference standard for the diagnosis of Pulmonary Langerhans Cell Histiocytosis (PLCH), particularly when clinical or radiological findings are atypical. Characteristic lesions consist of bronchiolocentric granulomatous infiltrates composed of pathological Langerhans cells admixed with eosinophils, macrophages, lymphocytes, plasma cells and occasional multinucleated giant cells. Progressive bronchiolar destruction eventually leads to fibrosis and cyst formation, accounting for the characteristic radiological evolution observed on HRCT. Immunohistochemistry plays a central role in confirming the diagnosis. Langerhans cells characteristically express CD1a, langerin (CD207) and S100 protein, while electron microscopy demonstrates Birbeck granules, rod-shaped intracytoplasmic organelles that are considered ultrastructural hallmarks of Langerhans cells. Among these markers, langerin is regarded as the most specific because it is directly associated with Birbeck granule formation. Despite the diagnostic value of histopathology, obtaining tissue is not always necessary or appropriate. Conventional transbronchial biopsies frequently have limited diagnostic yield because PLCH lesions are patchy and predominantly centred on distal bronchioles. Surgical lung biopsy offers greater diagnostic accuracy but carries higher procedural risks, including pneumothorax, prolonged air leak and postoperative pain. Transbronchial cryobiopsy has emerged as an alternative with improved tissue acquisition; however, its role in PLCH remains incompletely defined and depends on local expertise. In the present case, bronchoscopy with bronchoalveolar lavage and transbronchial biopsy was discussed in detail. The patient declined invasive investigation

after understanding the potential benefits and risks. Given the highly characteristic HRCT appearance, compatible smoking history, exclusion of major alternative diagnoses and subsequent clinical improvement following smoking cessation, a working diagnosis of suspected PLCH was considered clinically appropriate. This approach aligns with contemporary respiratory practice, in which biopsy may reasonably be deferred when imaging findings are classic and invasive procedures are unlikely to alter management.

Pulmonary Function Abnormalities

Pulmonary function testing in PLCH is variable and reflects the heterogeneous distribution of bronchiolar inflammation and cystic destruction. Spirometry may be normal in early disease, whereas more advanced stages demonstrate obstructive, restrictive or mixed ventilatory defects. This physiological variability distinguishes PLCH from many other interstitial lung diseases, in which restriction typically predominates. The most consistent physiological abnormality reported across published cohorts is a reduction in the diffusing capacity for carbon monoxide (DLCO), often preceding significant changes in spirometry. Reduced DLCO reflects destruction of the alveolar-capillary interface, loss of functional pulmonary vascular bed and impaired gas exchange resulting from bronchiolar remodelling and cyst formation.

Smoking Cessation as the Cornerstone of Management

Smoking cessation remains the most effective and universally recommended treatment for PLCH. Numerous observational studies have demonstrated disease stabilisation and, in some patients, partial regression of pulmonary nodules following complete smoking cessation. Continued tobacco exposure, in contrast, is associated with progressive cyst formation, accelerated decline in lung function, recurrent pneumothoraces and increased risk of pulmonary hypertension. The mechanisms underlying clinical improvement following smoking cessation are thought to involve reduced activation of dendritic cells and alveolar macrophages, diminished production of pro-inflammatory cytokines and interruption of the inflammatory cascade responsible for bronchiolar injury. Although established cystic destruction is generally irreversible, cessation of smoking may halt progression of active inflammatory lesions and preserve remaining lung function. A notable feature of the present case was the significant improvement in cough within three months of successful smoking cessation. This favourable clinical response further supports the proposed diagnosis and reinforces the importance of early recognition of smoking-related diffuse cystic lung disease before irreversible structural damage develops.

Pharmacological Therapy

Unlike many inflammatory interstitial lung diseases, there is currently no universally accepted pharmacological treatment for isolated PLCH. Historically, systemic corticosteroids were widely prescribed because of the inflammatory nature of the disease. However, contemporary evidence supporting sustained benefit is limited, and routine corticosteroid therapy is no longer recommended in the absence of progressive inflammatory disease or extrapulmonary involvement. Immunosuppressive and cytotoxic agents including cladribine, cytarabine and, less commonly, methotrexate, have been used in selected patients with progressive pulmonary disease, multisystem involvement or recurrent disease despite smoking cessation. Although encouraging responses have been reported in small observational studies, robust prospective clinical trial data remain limited. Perhaps the most significant therapeutic advance has been the recognition of activating mutations within the MAPK signalling pathway. Identification of BRAF V600E, MAP2K1 and related mutations has led to successful use of BRAF inhibitors (such as vemurafenib and dabrafenib) and MEK inhibitors (including trametinib and cobimetinib) in selected patients with refractory or multisystem Langerhans cell histiocytosis. While these agents are not routinely indicated for isolated stable pulmonary disease, they represent an important emerging therapeutic option and exemplify the transition towards precision medicine in histiocytic disorders.

Long-Term Monitoring and Prognosis

The clinical course of PLCH is highly variable. Some patients experience prolonged stability following smoking cessation, whereas others develop progressive cystic destruction leading to chronic respiratory failure. Several factors have been associated with poorer prognosis, including continued smoking, severe airflow obstruction, markedly reduced DLCO, extensive cystic destruction on HRCT, recurrent pneumothoraces and development of pulmonary hypertension. Pulmonary hypertension is increasingly recognised as a major determinant of mortality in advanced PLCH and may develop independently of the degree of parenchymal destruction. The underlying mechanisms are multifactorial and include pulmonary vascular remodelling, endothelial dysfunction and hypoxic vasoconstriction. Because pulmonary hypertension may initially be clinically silent, periodic echocardiographic assessment should be considered in patients with worsening dyspnoea, declining exercise tolerance or progressive impairment of gas transfer. Long-term surveillance should include serial pulmonary function testing, repeat HRCT when clinically indicated, smoking abstinence reinforcement, vaccination against influenza and pneumococcal disease, and prompt evaluation of new respiratory symptoms. Patients should also be counselled regarding the increased risk of spontaneous pneumothorax and advised to seek immediate medical attention should acute pleuritic chest pain or

sudden dyspnoea occur. For patients progressing to end-stage respiratory failure despite optimal management, lung transplantation remains an effective treatment option. However, disease recurrence has been reported following transplantation, particularly among individuals who resume smoking, emphasising the lifelong importance of smoking cessation.

Comparison with Published Literature

The present case shares many of the characteristic clinical and radiological features reported in contemporary PLCH cohorts, including chronic cough, cigarette smoking, upper-lobe predominant cystic lung disease and impaired gas transfer. However, several aspects distinguish this case from previously published reports. First, the patient's cumulative smoking exposure was relatively modest compared with that reported in many case series, suggesting that substantial disease may occur even after limited tobacco exposure in susceptible individuals. Second, chronic cough represented the predominant presenting symptom despite extensive radiological abnormalities and only mild physiological impairment. Finally, multiple competing diagnoses—including recurrent bronchitis, atypical pneumonia, occupational chemical exposure, ACE inhibitor-associated cough and inhaled corticosteroid-associated oral candidiasis—contributed to diagnostic uncertainty and delayed recognition of PLCH. These features highlight the importance of maintaining a high index of suspicion for diffuse cystic lung disease in smokers with persistent respiratory symptoms, even when alternative explanations appear plausible.

Clinical Lessons

Several important lessons emerge from this case.

Persistent cough that fails to respond to repeated empirical therapy should prompt reconsideration of the underlying diagnosis rather than repeated prescription of antibiotics or inhaled therapies. High-resolution computed tomography should be performed early in the evaluation of smokers with persistent unexplained respiratory symptoms when chest radiography is non-diagnostic. The coexistence of upper-lobe predominant irregular cysts and centrilobular nodules on HRCT is highly suggestive of PLCH and, in the appropriate clinical context, may permit a confident diagnosis without histological confirmation. Smoking cessation remains the most effective therapeutic intervention and should be prioritised immediately following diagnosis. Finally, multidisciplinary assessment integrating clinical history, radiology, pulmonary physiology and pathology remain the optimal approach for evaluating diffuse cystic lung disease.

Limitations

The principal limitation of this report is the absence of histopathological confirmation. Although tissue diagnosis remains the reference standard, the patient declined invasive investigation after detailed discussion of the potential benefits and procedural risks. Nevertheless, the combination of characteristic HRCT findings, compatible smoking history, exclusion of relevant differential diagnoses and subsequent clinical improvement following smoking cessation provides strong support for the working diagnosis. Another limitation is the relatively short follow-up period. Longer-term surveillance with serial pulmonary function testing and interval HRCT will be important to determine disease stability and monitor for the development of complications, including pulmonary hypertension and recurrent pneumothorax.

This case highlights the diagnostic challenges posed by Pulmonary Langerhans Cell Histiocytosis and emphasises the importance of maintaining a broad differential diagnosis in smokers presenting with persistent chronic cough. Failure of conventional therapy should prompt reassessment and consideration of uncommon smoking-related interstitial lung diseases. High-resolution computed tomography remains the cornerstone of diagnosis and, when interpreted in conjunction with a compatible clinical history, may establish a confident working diagnosis even in the absence of histopathological confirmation. Early recognition is clinically important because smoking cessation remains the single intervention consistently associated with disease stabilisation. Continued surveillance with pulmonary function testing and appropriate imaging is essential to identify disease progression, monitor for pulmonary hypertension and optimise long-term outcomes. This case further demonstrates that clinically significant PLCH may occur in individuals with relatively modest cumulative smoking exposure and underscores the need for heightened clinical awareness of this rare but important smoking-related diffuse cystic lung disease.

Learning points

- Pulmonary Langerhans Cell Histiocytosis (PLCH) should be considered in current or former smokers presenting with persistent chronic cough, particularly when symptoms fail to respond to conventional therapy.
- Repeated empirical treatment with antibiotics or inhaled corticosteroids without objective clinical improvement should prompt reassessment of the diagnosis rather than continuation of the same treatment strategy.
- High-resolution computed tomography (HRCT) is the imaging modality of choice for suspected diffuse cystic lung disease and is substantially more sensitive than chest radiography.

- The combination of upper-lobe predominant irregular cysts, centrilobular nodules and relative sparing of the lung bases is highly characteristic of PLCH and may permit a confident clinical diagnosis in the appropriate setting.
- Reduced diffusing capacity (DLCO) is often the earliest physiological abnormality and should be carefully monitored during follow-up.
- Histopathological confirmation remains the diagnostic gold standard; however, biopsy may not be necessary when HRCT findings are typical, smoking history is compatible, and alternative diagnoses have been reasonably excluded.
- Smoking cessation remains the cornerstone of management and is the only intervention consistently associated with disease stabilisation and improved long-term outcomes.
- Long-term surveillance with pulmonary function testing, smoking abstinence reinforcement and interval imaging is essential because disease progression, pulmonary hypertension and spontaneous pneumothorax may occur despite initial clinical stability.

Clinical Pearls

This case highlights several practical messages for clinicians.

- First, chronic cough should never be assumed to represent recurrent bronchitis simply because the patient is a smoker. When symptoms persist despite guideline-directed therapy, clinicians should revisit the differential diagnosis and actively search for alternative causes.
- Second, PLCH may occur in patients with a relatively modest smoking history. Although most published series involve heavier smokers, cumulative smoking exposure alone should not determine whether PLCH is considered.
- Third, HRCT is indispensable in the evaluation of unexplained chronic respiratory symptoms. Characteristic imaging patterns frequently establish the diagnosis before invasive investigations become necessary.
- Finally, multidisciplinary collaboration between respiratory physicians, thoracic radiologists and pulmonary pathologists remains fundamental in achieving an accurate diagnosis of diffuse cystic lung disease.

Patient Perspective

“For almost two years I believed I simply had repeated chest infections. Every time I was treated with antibiotics, I expected the cough to improve, but it always came back. I became worried after losing so much weight and was frustrated that nobody could explain why I was still coughing. Learning that the scans showed a rare smoking-related lung disease was unexpected, but finally gave me an explanation. Stopping smoking was difficult, but it has made a significant difference. My cough has improved greatly and I now understand how important regular follow-up is for protecting my lung health.”

The patient reviewed and approved this statement prior to publication. (Only include this section if the patient has genuinely reviewed and approved it, as required by some journals.)

Conclusion

Pulmonary Langerhans Cell Histiocytosis remains an uncommon but important smoking-related diffuse cystic lung disease that may present with isolated chronic cough and minimal physiological impairment. This case demonstrates how multiple competing diagnoses—including recurrent bronchitis, atypical pneumonia, occupational irritant exposure, ACE inhibitor-associated cough and inhaled corticosteroid-related complications—may delay recognition of the underlying disease. The case emphasises that persistent respiratory symptoms unresponsive to standard therapy should prompt reconsideration of the diagnosis and early performance of high-resolution computed tomography. The characteristic coexistence of upper-lobe predominant irregular cysts and centrilobular nodules in a smoker provides strong diagnostic evidence for PLCH and may allow a confident working diagnosis even when histopathological confirmation is unavailable. Successful smoking cessation resulted in marked symptomatic improvement and radiological stability, reinforcing its central role in disease management. Early recognition of PLCH enables appropriate counselling, smoking cessation, longitudinal surveillance and timely identification of complications such as pulmonary hypertension and spontaneous pneumothorax, ultimately improving long-term patient outcomes.

Future Directions

Advances in molecular pathology have fundamentally changed our understanding of PLCH. Identification of recurrent MAPK pathway mutations has reclassified the disease as a clonal myeloid neoplasm with inflammatory features rather than a purely reactive disorder. This has opened new therapeutic avenues, particularly for patients with progressive or multisystem disease.

Future research should focus on:

- Defining biomarkers that predict disease progression and treatment response.
- Determining the optimal role of transbronchial cryobiopsy in establishing diagnosis.
- Evaluating long-term outcomes following smoking cessation in contemporary patient cohorts.
- Assessing the efficacy and safety of targeted therapies, including BRAF and MEK inhibitors, in isolated pulmonary disease.

- Developing evidence-based surveillance protocols incorporating pulmonary function testing, HRCT and assessment for pulmonary hypertension.

Further multicentre prospective studies are required to improve understanding of disease pathogenesis, identify prognostic factors and optimise management strategies for this uncommon disorder.

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