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Pulmonary Langerhans cell histiocytosis: A case series and literature review

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ABSTRACT

Pulmonary Langerhans cell histiocytosis (PLCH) is a rare diffuse parenchymal lung disease representing 3% of all interstitial lung diseases. PLCH occurs either as part of multi-system Langerhans cell histiocytosis (LCH) or an isolated disease of the lung. Isolated involvement of lungs is observed in approximately 50–70% of LCH cases and the age of onset peaks between 20 and 40 years without gender difference. Cigarette smoking is the only identified environmental risk factor. PLCH is characterized by Langerhans cell infiltrates that in general are in a bronchiolocentric distribution. Pulmonary lesions can occur after chronic systemic disease or are an initial sign of disease. The aims of this study are to (1) report five rare cases of PLCH in adults; (2) discuss the relationship of PLCH with interstitial lung fibrosis; (3) provide a concise review of PLCH epidemiology, pathophysiology, diagnosis, treatment, and prognosis to improve the knowledge of PLCH by pneumologists and internal medicine physicians.

Keywords: Lung transplantation, Pulmonary hypertension, Pulmonary Langerhans cell histiocytosis

INTRODUCTION

Pulmonary Langerhans cell histiocytosis (PLCH), a rare diffuse parenchymal lung disease, represents about 3% of all interstitial lung diseases (ILD). PLCH occurs as part of multisystem Langerhans cell histiocytosis (LCH) or as an isolated disease of the lung. PLCH is characterized by bronchiolocentric proliferation of CD1a-positive Langerhans cells (a type of histiocytes).[1-4]

PLCH is considered a neoplastic disorder, characterized by the infiltration of lungs by proliferating and often clonal bone marrow-derived histiocytic Langerhans cells with an accompanying inflammatory response and occasionally fibrosis that almost exclusively affects tobacco smokers 20–40 years of age.[5]

The course of the disease is not uniform. In some cases, single lesions with spontaneous regression simulating an abnormal inflammatory process occur, whereas in other cases, multiple lesions with infiltrative growth patterns like malignant tumors can appear with a mortality rate of up 50%.[6,7] Typical symptoms are dyspnea, non-productive cough, fatigue, chest pain, and spontaneous pneumothorax although the onset of presenting symptoms to diagnosis may take years.

The aims of the study are to (1) report five cases of PLCH in adult female smokers; (2) discuss the relationship of PLCH with interstitial lung fibrosis; and (3) provide a concise review of

epidemiology, pathophysiology, diagnosis, treatment, and prognosis of PLCH to improve the knowledge of PLCH by pneumologists and internal medicine physicians.

CASES SERIES

Case 1

A 31-year-old woman, smoker, ski instructor was referred for Internal Medicine consultation. Her presenting complaint was a 2-week history of cough, one episode of minor hemoptysis, and chest pain without dyspnea. Nil of note in clinical history. On physical examination, no enlarged cervical lymph nodes were palpable. On investigation, serological and coagulation tests were normal. Pulmonary function testing revealed reduced forced vital capacity (FVC) and normal forced expiratory volume in 1 s (FEV1). Diffusion capacity of the lung for carbon monoxide (DLCO) was 68% (normal ≥74%) indicating a restrictive pattern. All remaining airflow parameters were normal. Electrocardiogram (ECG) showed a sinus rhythm. Chest X-ray showed diffuse granular pattern in both lungs not allowing a definite diagnosis. High-resolution computed tomography (HRCT) showed multiple nodular cavities in the upper lobes of both lungs [Figure 1]. Bronchoscopy and transbronchial biopsy were performed during the endo-bronchial examination. Histopathology of the transbronchial specimen showed several eosinophils associated with Langerhans cells confirming the diagnosis of PLCH [Figure 2]. She was diagnosed with lung cancer 5 years later and was treated with carboplatin and paclitaxel.

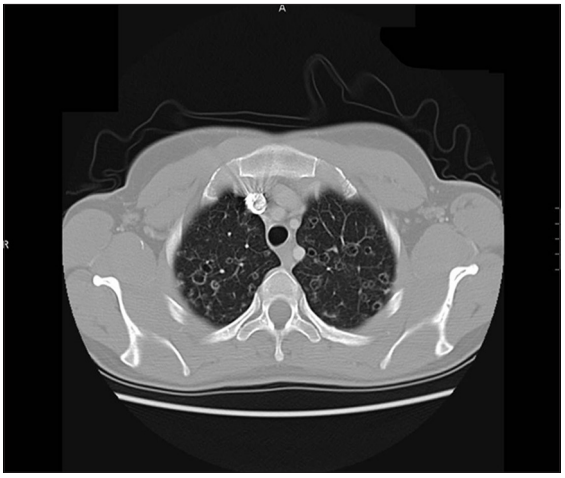

Figure 1: A 31-year-old smoker woman with a 2-week history of cough, one episode of minor hemoptysis, and chest pain without dyspnea. Histopathology of transbronchial biopsy specimen showed large numbers of eosinophils associated with Langerhans cells leading to the diagnosis of PLCH. HRCT shows several nodules in both lungs on the right upper lobes. Some nodules are solid, others present cavities, some have smooth margins, some have irregular or poorly defined margins. (PLCH: Pulmonary Langherans cells histiocytosis).

Case 2

A 37-year-old woman, smoker, and catering manager was referred for Internal Medicine consultation for the onset of dry cough, dyspnea, and fatigue in the past 3 weeks. Nil of note in clinical history. On physical examination, no enlarged cervical lymph nodes were palpable. Allergy testing was negative. Chest X-ray showed granular pattern, bronchiectasis, and some cavities in middle lobes of the lungs. HRCT showed diffuse nodular cavities and bronchiectasis in the upper and middle lobes of both lungs [Figure 3]. Pulmonary function tests revealed DLCO 62%, a normal FEV1, and absence of mixed pattern. Transbronchial biopsy

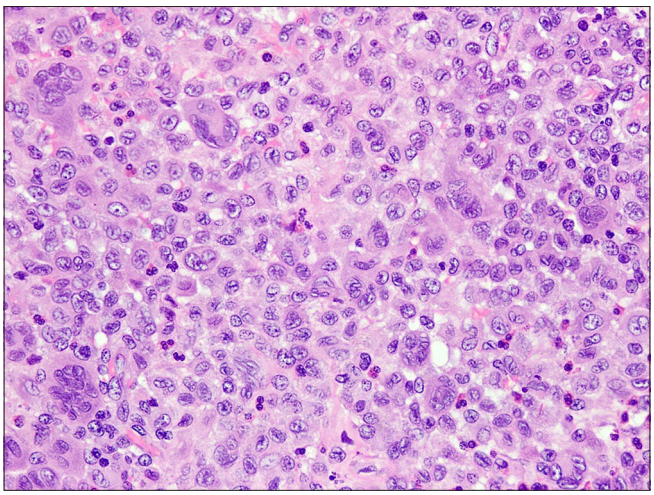

Figure 2: The sections show a proliferation of large cells with convoluted nuclei, containing grooves, and a moderate amount of pale, lightly eosinophilic cytoplasm. Several eosinophils and multinucleated histiocytes are seen. (Hematoxylin and eosin. Magnification, ×400).

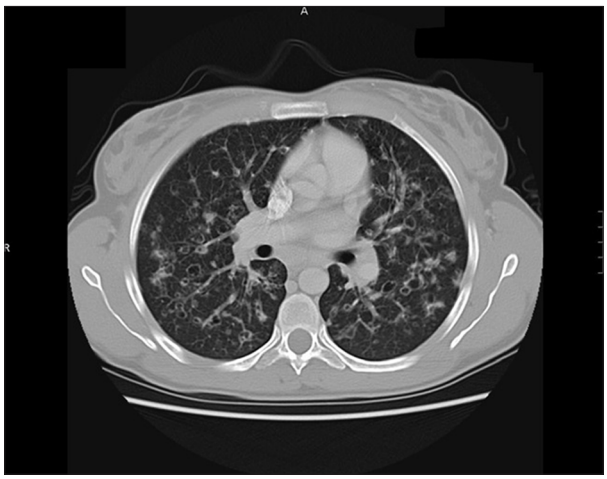

Figure 3: A 37-year-old smoker woman with a 3-week history of dry cough, dyspnea, and fatigue. HRCT shows many nodular cavitations and bronchiectases in both lungs and an increase of bronchial wall thickness interesting both lungs.

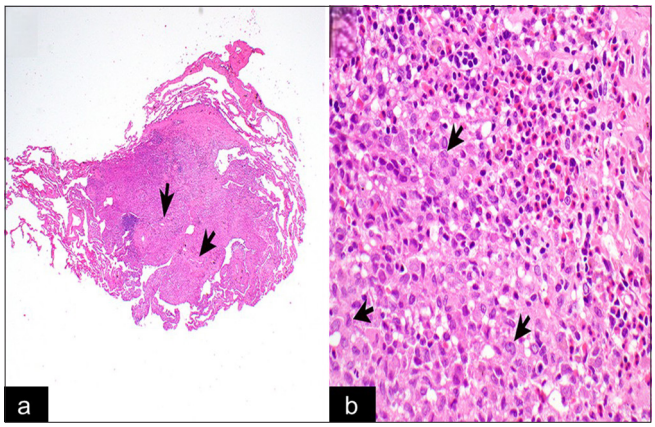

Figure 4: Histopathology of the transbronchial biopsy showed: (a) bronchiolocentric cellular infiltrate associated with cystic changes (arrows point towards pulmonary arteries) and (b) large epithelioid cells (arrows point towards Langerhans cells) with irregular nuclear borders, nuclear grooves, and conspicuous nucleoli intermixed with eosinophils (note clusters of eosinophils on the right upper hand side) leading to the diagnosis of PLCH. H&E, magnification (a) × 20 and (b) × 400. (PLCH: Pulmonary Langherans cells histiocytosis).

was performed. Histopathological findings demonstrated typical histologic features of PLCH with clusters of eosinophils [Figure 4a and b]. She was diagnosed with lung cancer and treated with carboplatin and paclitaxel. She passed away 10 years after her PLCH diagnosis.

Case 3

A 38-year-old woman, smoker with cough and dyspnea lasting for 6 months was referred for pulmonological consultation. There is no history of occupational exposure. Vital signs were within normal range, blood pressure 120/70 mmHg, pulse rate 72/min, respiratory rate 16 breaths/min, oxygen saturation 97% (room air), and body temperature 36.5°C. Fine crackles and wheezing were auscultated in both upper lung lobes; clinical examination was otherwise unremarkable. Laboratory tests revealed white blood cell count 7,000/μL, hemoglobin 14.5 g/dL, platelet count 220,000/μL, and C-reactive protein 0.80 mg/dL. Autoantibodies for connective tissue diseases or tumor markers were not detected. Pulmonary function tests revealed increased residual volume (RV) and normal DLCO values. Chest X-ray showed a granular pattern in the upper and middle fields of both lungs. HRCT showed multiple cystic lesions with thick walls predominantly in the upper lobes in association with peripheral bulla of emphysema [Figure 5a and b]. Bronchoalveolar lavage (BAL) from the right middle lobe (B5) revealed 4.0×10^5 cells/mL (96% macrophages and 4% lymphocytes) and 5.1% of CD1a-positive cells. Based on findings on HRCT and BAL, the patient was diagnosed with PLCH. The patient stopped smoking for 6 months.

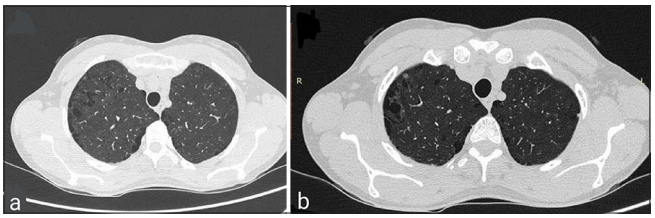

Figure 5: A 38-year-old smoker woman with a 6-month history of cough and dyspnea. Bronchoalveolar lavage from the right middle lobe revealed: 96% macrophages, 4% lymphocytes and 5.1% of CD1a –positive cells. HRCT shows: (a) multiple cystic lesions with thick walls predominantly in upper lobes of the lungs and (b) peripheral bullas of emphysema. Based on BAL and HRCT findings the patient was diagnosed with PLCH. (PLCH: Pulmonary Langherans cells histiocytosis).

Symptoms almost completely ameliorated and her quality-of-life improved after steroid treatment (prednisone tablets 25 mg day for 3 months followed by 5 mg weekly tapering).

Case 4

A 30-year-old woman, smoker, approximately 3 pack year history presented with a previous history of recurrent respiratory tract infections in childhood and recurrent acute bronchitis as an adult. She had experienced severe chest pains 2–3 years before diagnosis with no clear cause which was self-resolving. She had no dyspnea nor a history of pneumothorax. There are no significant past medical history, overseas travel history, or allergies. Medications were the combined oral contraceptive pill only. There is no known family history.

Pulmonary function tests demonstrated FEV1 3.54 (116%)/FVC 3.93 (111%) ratio of 0.90 and DLCO of 6.96 (77%). Chest X-ray and HRCT imaging indicated irregular cysts, mostly in the upper and mid zone with some of the cysts adjoining the pleura [Figure 6a and b]. Video-assisted thoracic surgery right upper and lower lobe biopsies show similar features in each: Multiple stellate scars present within the lung parenchyma showing bronchocentric accentuation. The air spaces around these scars showed cystic dilatation. The scars were composed of dense fibrous tissue with occasional eosinophils and scattered crenated histiocytes. A sprinkling of lymphocytes was also seen. Focally, there was a rim of pigmented alveolar macrophages around the scars. Immunohistochemistry for Langerin and S100 showed the presence of scattered Langerhans histiocytes in keeping with a diagnosis of LCH (fibrous type). Multidisciplinary team (MDT) discussion confirmed the diagnosis of PLCH on histology and imaging.

She stopped smoking at diagnosis and subsequently, there was no disease progression. Five years later, pulmonary function tests were stable: FEV1 3.36 (120%)/FVC 3.87 (119%) ratio

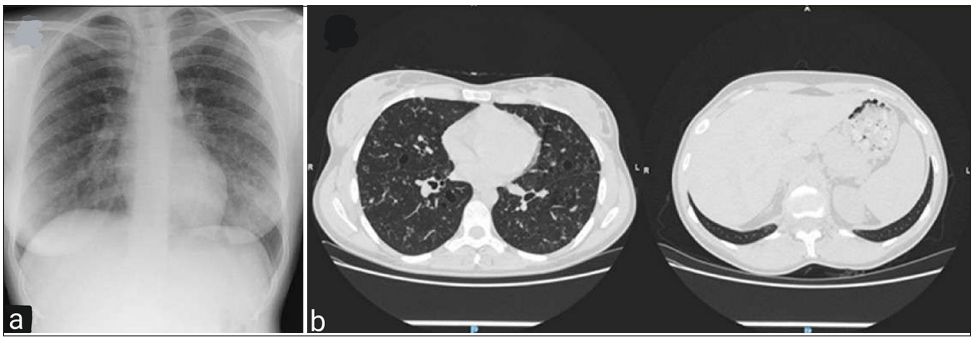

Figure 6: A 30-year-old smoker woman with a previous history of recurrent respiratory tract infections. Lung biopsies showed multiple fibrous stellate scars with bronchocentric accentuation, airspace cystic dilatation and a rim of pigmented alveolar macrophages and Langerhans histiocytes. (a) Chest X-ray and (b) HRCT imaging indicate nodules and irregular cysts, mostly in the upper and mid zone with some of the cysts adjoining the pleura. Based on histopathological and imaging findings the diagnosis of Langerhans cell histiocytosis (fibrous type) was made.

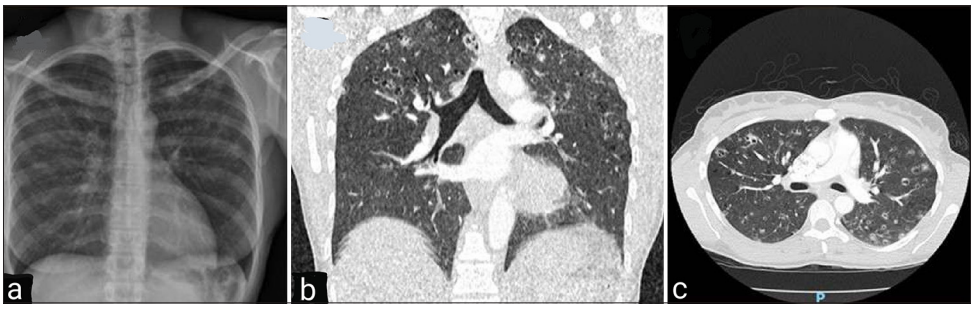

Figure 7: A 37-year-old smoker woman presented with acute chest pain. (a) Chest X-ray demonstrates widespread small cystic areas throughout both lungs with surrounding minor consolidation. HRCT (b) coronal and (c) axial imaging of both lungs indicate rounded cystic and solid lesions with an apical and mid zone predominance. Pulmonary emboli and mediastinal or hilar lymphadenopathy were not present. These imaging characteristics lead to Histiocytosis X diagnosis.

0.87; DLCO 6.15 (72%); carbon monoxide transfer coefficient (KCO) 1.27 (74%); total lung capacity (TLC) 5.53 (111%); and RV1.78 RV (111%). She remained asymptomatic with no occurrence of pneumothorax.

Case 5

A 37-year-old woman, smoker with 15 pack year history, and clerical worker presented to the acute medical unit with chest pain. A computed tomography (CT) pulmonary angiogram was performed to exclude pulmonary embolism (PE). Previous medical history recorded asthma as a young adult and epilepsy. No family history is noted. On examination, no clubbing and chest auscultation was normal. Pulmonary functions tests recorded FEV1 2.02 (79%)/FVC 2.62 (89%) ratio 0.77; DLCO 5.29 (66%); and Kco 1.34 (74%). ECG was normal.

Radiological findings demonstrated widespread small cystic areas throughout both lungs with surrounding minor consolidation. The appearances are in keeping with infective cystic lesions in the lungs. Subsequent HRCT imaging reported no filling defects identified within the pulmonary arteries to suggest the presence of any pulmonary emboli. There was no mediastinal or hilar lymphadenopathy. Throughout both lungs, with an apical and mid-zone predominance, there were unusual, rounded lesions, most of which appeared cystic, but some appear solid in nature. These imaging characteristics most likely represented histiocytosis X. Diagnosis was confirmed by MDT discussion, imaging [Figure 7a-c], and histopathology [Figure 8]. She continued to smoke 10 cigarettes/day and became pregnant 5-year post-diagnosis. Her pulmonary function tests before this were FEV1 1.79 (82%); FVC 2.5 (95%); and DLCO 5.5 (74%). She delivered preterm at 31 weeks although neither mother nor baby experienced enduring significant medical issues. She went on to be diagnosed with right upper lobe lung cancer 11 years later – T4 N1/2 M1b squamous cell lung cancer. Programmed death ligand 1 was 30% positive, and neurotrophic tyrosine receptor kinase (NTRK) was 70% positive. She was treated with carboplatin, paclitaxel, and pembrolizumab, then maintenance pembrolizumab. Finally, patient was treated with palliative gemcitabine and radiotherapy and she passed away 11 years after her PLCH diagnosis.

In all five reported cases, the lungs were the only organs involved by LCH and echocardiography was negative for pulmonary

Table 1: Comparative table of clinical characteristics.

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5
	Female	Female	Female	Female	Female
Age (year)	31	37	38	30	37
Pulmonary function test	Yes	Yes	Yes	Yes	Yes
Smoking history	Yes	Yes	Yes	Yes	Yes
Imaging features	Chest X-ray, HRCT	Chest X-ray, HRCT	Chest X-ray, HRCT	Chest X-ray, HRCT	Chest X-ray, HRCT
Histological findings	Histopathology	Histopathology	BAL	Histopathology	Histopathology
Treatments	Steroids, Chemotherapy	Steroids, Chemotherapy	Steroids	Steroids	Chemotherapy
Outcomes	5 years	10 years	20 years	20 years	11 years

HRCT: High-resolution computed tomography

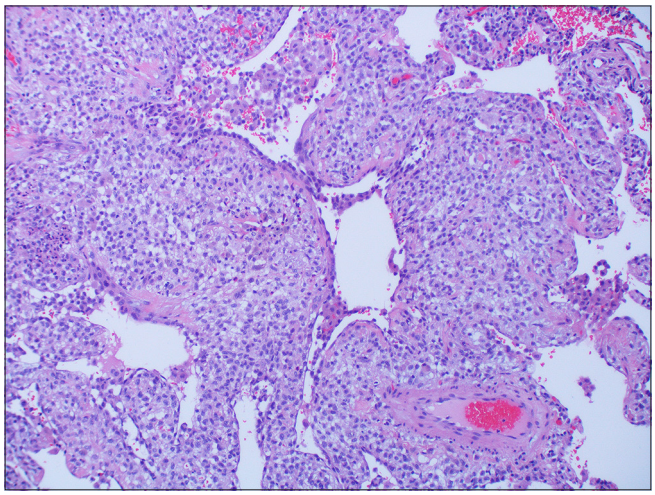

Figure 8: The alveolar walls are markedly expanded by a cellular infiltrate consisting mostly of large mononuclear cells which are Langerhans histiocytes. A few eosinophils can be seen at this relatively low magnification. Hematoxylin and eosin. Magnification ×200.

hypertension (PH). All cases are women in their third decade with a smoking history and presented with a history of cough or chest pain**.** Clinical characteristics of patients are summarized in Table 1. Notably, pulmonary tuberculosis diagnosis was excluded in all cases by purified-protein derivative skin test. Connective tissue disorder profile was not performed as patients did not show suggestive symptoms.

DISCUSSION

The prevalence of PLCH is estimated to be 3–5% of ILD patients; however, many cases may go undiagnosed and the lack of global epidemiological data means that the incidence is precisely determined. More than 90% of PLCH patients are cigarette smokers, therefore, its frequency depends on the prevalence of cigarette smoking in the population.[8]

Recently, the England National LCH Registry reported on 658 patients including 324 children of whom 53 were infants aged <1 year. The registry provided for the 1st time epidemiological data on the incidence, prevalence, and survival of LCH during the period of 2013–2019.[9] Age-standardized incidence rate (ASR) of LCH was 1.60 per million persons/year, with children having a higher incidence than adults (4.46 and 1.06, respectively). ASR was significantly higher in males than in females (1.79 vs. 1.41, $P < 0.01$). In children, LCH was localized in bone (128 cases), bone marrow (73 cases), and lungs (2 cases). In adults, LCH was detected in bone (37 cases), bone marrow (79 cases), and lungs (60 cases). Of note, PLCH was significantly more present in urban than in non-urban areas ($P = 0.02$). One-year and 5-year overall survival (OS) were 99% and 86% for children and 90% and 72% for adults, respectively. One- and 5-year OS was 99% for the youngest group (aged <15 years), compared to 1-year OS of 77% and 5-year OS of 33% for the oldest group (aged ≥60 years). Further, 1-year and 5-year OS were 95% and 86% for females and 94% and 85% for males, respectively. In summary, the England registry is the largest population-based study to date providing epidemiological LCH data. The main findings of the registry include high incidence of LCH in young age and male sex, better survival in children than in adults, and higher ASR for people living in the most deprived areas compared to those in the least deprived areas, 24% and 6%, respectively.[9] LCH association with environmental and other unknown factors requires further investigation.[9]

Isolated involvement of lungs is observed in approximately 50–70% of LCH cases and the age of onset peaks between 20 and 40 years without gender difference.[10,11] Pulmonary lesions can occur after chronic systemic disease or are an initial sign of disease.[6]

In agreement with Hazim *et al.*,[12] our PLCH cases have a very low risk of progression to multisystem disease. Interestingly, all patients were young women and smokers.

Symptoms, smoking habits, and HRCT should be considered the gold standard for the diagnosis of PLCH.

Systemic LCH can involve bones, lungs, skin, pituitary, lymph nodes, liver, spleen, bone marrow, gastrointestinal tract, thyroid, and central nervous system. Pulmonary lesions occur in 20% of systemic LCH and lymph node involvement is present in 30% of cases. Diabetes insipidus is a possible severe complication in advanced LCH. Fluorodeoxyglucose-positron emission tomography scanning is required to evaluate the pituitary gland as magnetic resonance imaging and CT scan are not useful.[13] Patients with involvement of the lungs by LCH either as PLCH or as part of systemic LCH are at high risk of developing life-threatening complications such as pneumothorax and recurrent pulmonary infections. Pulmonary function testing persists as a useful approach to evaluate airflow alterations in asymptomatic patients with lung involvement.

HRCT scanning remains an important tool in the diagnosis of PLCH. Pulmonary lesions include centrilobular nodules, nodules with or without a central cavity, and thick-walled cysts of various shapes that may convolute forming the so-called clover leaves. These lesions usually spare costophrenic angles.[12]

The primary lesions of PLCH are loose clusters of Langerhans cells that are characteristically polygonal with pale cytoplasm and folded/grooved/convoluted nuclei that often harbor conspicuous nucleoli together with eosinophils, macrophages, T-lymphocytes, and sometimes neutrophils [Figure 4a and b]. The clusters of Langerhans cells surround the bronchioles and alveolar ducts. Occasionally, these aggregates will be replaced by fibrosis that forms stellate-like bronchiolocentric scars. The background lung, in general, shows smoking-related changes in the form of clusters of pigmented (smoker) macrophages and emphysema. Langerhans cells express S-100 protein, CD1a, and Langerin. A characteristic ultrastructural hallmark of Langerhans cells is Birbeck granules. Birbeck granules are very difficult to identify in the spleen, liver, and gastrointestinal tract.[14,15] However, ultrastructural analysis is not performed for the diagnosis of LCH given the characteristic morphologic and immunophenotypical features of LCH.

While PLCH is associated with cigarette smoking in most patients, the identification of *B-Raf encoding (BRAF) V600E* mutations and other mutations specifically in the mitogen-activated protein kinases (MAPK) pathway are suggestive of a subset of PLCH being neoplastic rather than reactive in nature. The *BRAF* gene found on chromosome seven encodes a protein called *BRAF*. A *BRAF* mutation is a spontaneous change in the *BRAF* gene that makes it work incorrectly, the most common type being the *BRAF V600E* mutation. The name V600E defines the nature and location of the mutation. The number 600E refers to the location of mutation, amino acid number 600 inside the protein. *BRAF* mutations can cause cancers alone or in combination with additional mutations. PLCH lesions involve persistent MAPK pathway activation, characterized by BRAF V600E mutation and additional driver somatic genomic alterations including MAP2K1 mutations/deletions and BRAF deletions. These genomic insights offer promising targeted therapeutic opportunities. Vemurafenib, a *BRAF* kinase inhibitor, is reported as an effective treatment in patients with LCH.[16-19]

Smoking seems to facilitate the recruitment of MAPK-activated circulating myeloid precursors to the lung. PLCH survival >10 years is favorable in 90% of cases. Progressive respiratory failure and lung cancer are causes of death. However, some patients develop severe pneumonia complications within 5 years after diagnosis.[20] Further discussions and case reviews of these complications would be very helpful for the PLHC community.

While the pathogenesis of PLCH is not fully understood, the likelihood of its association with smoking-induced injury is accepted. Smoking tobacco exhibits anti-apoptotic mechanisms that enhance dendritic cell survival, while P16 acts as a critical cell cycle regulator by suppressing cyclin D/cyclin-dependent kinase (CDK) activity, inhibiting cellular proliferation. In a southwestern China population, the overexpression of P16 protein was thought to be related to the regulation of the cell cycle, resulting in the pathogenesis of PLCH and P16 was proposed as a potential diagnostic biomarker for PLCH.[20] This case series also reported that a meaningful correlation between P16 activity and the progression of PLCH was not observed. Previously, a loss of senescence control rather than overexpression of P16 was thought to be associated with clinical aggressiveness of PLCH, as in melanoma.[20]

The pathogenesis of PLCH is also likely related to airway inflammation[20] and in long-standing PLCH patients, superimposed emphysema is observed. It has been hypothesized that there might be a link between PLCH and Alpha 1 antitrypsin deficiency (AATD) as both share mechanisms of proteolytic tissue damage. Further, AATD is an inflammatory condition due to the reduced AAT capacity to modulate inflammatory cytokines, and PLCH is similarly an inflammatory condition.[20] Contemporary analysis of a large dataset refutes this hypothesis reporting a lack of correlation between AAT level and pulmonary function or CT scores in PLCH establishing no clinical link between these two conditions.[20]

Progression of PLCH can lead to the destruction of pulmonary parenchyma with fibrosis, as well as to the development of pulmonary hypertension (PH). Oxygen treatment is recommended in a small group of patients with stable ventilation parameters and PH. In addition, PH may respond to phosphodiesterase and endothelin receptor inhibitors as well as to prostacyclin. However, these drugs are not accepted as standard treatment and should be delivered in experienced centers.[21-23]

The cause of pulmonary vascular remodeling in PLCH leading to PH development is unclear. One hypothesis is that various cytokines including interleukin 1, interleukin 6, and transforming growth factor β combined with growth factors such as platelet-derived growth factor may induce vascular cell growth and pulmonary vascular remodeling. Notably, Langerhans cells may release these mediators.[24-27]

Steroids are the elective treatment of choice for PLCH, which, if ineffective, may be combined with weekly infusions of vinblastine, especially in systemic disease.[28,29] Lung transplantation is the last option for PLCH patients in an advanced stage with respiratory failure and PH but is rarely required. The prognosis of patients with PLCH who have undergone lung transplantation is comparable with other ILDs with a 1-year and 5-year OS of 75% and 50%, respectively. Patients with multi-system PLCH and lung involvement have a worse prognosis after transplantation and recurrence is approximately 20%.[30-32]

Differential diagnosis of nodular lesions on HRCT includes neoplasm, sarcoidosis, hypersensitivity pneumonitis, and infections. HRCT with or without lung biopsy is required to distinguish PLCH from its differential diagnosis such as sarcoidosis associated with pulmonary emphysema, tuberculosis, lymphangioleiomyomatosis, and multiple pulmonary metastases. Notably, the occurrence of PLCH with lung cancer is extremely rare and where it does occur PLCH tends to precede the occurrence of lung cancer and there is an association with cigarette smoking.

The presence of nodular cavities and an increase in alveolar-bronchial wall thickness associated with a typical history can allow for a diagnosis of PLCH. In the remaining cases, pulmonary biopsy is required for the diagnosis.[33,34]

The five cases we present are females with a history of or active smoking behavior in their 30's. All are presented to different healthcare professionals and there is no deficiency in establishing the diagnosis. Sadly, one case resulted in a fatality due to a secondary onset of lung cancer. While further mechanistic studies are needed to identify an appropriate and reliable biomarker, as clinicians, we must also focus our efforts on smoking cessation and consider outreach work with social and educational partners to promote smoking avoidance. This includes more contemporary practices of vaping given that while, to date, "rare" cases of nicotine vaping and cannabis smoking have been reported.

CONCLUSION

PLCH is a rare and diffuse parenchymal lung disease that represents about 3% of all causes of ILD. Epidemiology, pathophysiology, diagnosis, treatment, and prognosis have been described with the aim of improving the knowledge of PLCH and its differential diagnosis for pulmonologists and internal medicine physicians. We report on five PLCH cases from our respective centers which alongside our concise literature review offers better knowledge of this poorly known disease for the general pulmonologist.

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REFERENCES

1. Shaw B, Borchers M, Zander D, Gupta N. Pulmonary Langerhans cell histiocytosis. Sem Respir Crit Care Med 2020;41:269-79.
2. Qanneta R, Raventos-Estelle A. Pulmonary Langerhans-cell histiocytosis. N Engl J Med 2022;387:2449.
3. Vassallo R, Ryu JH, Schroeder DR, Decker PA, Limper AH. Clinical outcomes of pulmonary Langerhans'-cell histiocytosis in adults. N Engl J Med 2002;346:484-90.
4. Goyal G, Tazi A, Go RS, Rech KL, Picarsic JL, Vassallo R, *et al*. International expert consensus recommendations for the diagnosis and treatment of Langerhans cell histiocytosis in adults. Blood 2022;139:2601-21.
5. Tillotson CV, Anjum F, Patel BC. Langherans cells histiocytosis. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2024.
6. Radzikowska E. Update on pulmonary Langerhans cell histiocytosis. Front Med 2021;7:582581.
7. Goldsmith AJ, Myssiorek D, Valderrama E. Unifocal Langerhans' cell histiocytosis (eosinophilic granuloma) of the petrous apex. Arch Otolaryngol Head Neck Surg 1993;119:113-6.
8. Vassallo R, Limper AH, Ryu JH. In: Schwarz MI, King TE Jr., editors. Interstitial lung disease. 5th ed. Shelton, CT, USA: People's Medical Publishing House; 2011. p. 961.
9. Liu H, Stiller CA, Crooks CJ, Rous B, Bythell M, Broggio J, *et al*. Incidence, prevalence and survival in patients with Langerhans cell histiocytosis: A national registry study from England, 2013-2019. Br J Haematol 2022;199:728-38.
10. Aricò M, Girschikofsky M, Généreau T, Klersky C, McClain K, Grois N, *et al*. Langerhans cell histiocytosis in adults. Report from the International registry of the histiocyte society. Eur J Cancer 2003;39:2341-8.
11. Vassallo R, Limper AH. Pulmonary Langerhans; cell histiocytosis. Semin Respir Crit Care Med 2002;23:93-101.
12. Hazim AZ, Ruan GJ, Hu M, Ravindran A, Rech KL, Young JR, *et al*. Langerhans cell histiocytosis with lung involvement in isolation and multisystem disease: Staging, natural history, and comparative survival. Am J Hematol 2021;96:1604-10.

13. Lourenco J, Ferreira C, Marado D. Adult pulmonary Langerhans cell histiocytosis revealed by central diabetes insipidus: A case report and literature review. Mol Clin Oncol 2020;13:30.
14. Roden AC, Yi ES. Pulmonary Langerhans cell histiocytosis an update from the pathologists' perspective. Arch Pathol Lab Med 2016;140:230-40.
15. Tazi A, Bonay M, Grandsaigne M, Battesti JP, Hance AJ, Soler P. Surface phenotype of Langerhans' cells and lymphocytes in granulomatous lesions from patients with pulmonary histiocytosis X. Am Rev Respir Dis 1993;147:1531-6.
16. Roden AC, Hu X, Kip S, Parrilla Castellar ER, Rumilla KM, Vrana JA, *et al*. BRAF V600E expression in Langerhans cell histiocytosis: clinical and immunohistochemical study on 25 pulmonary and 54 extrapulmonary cases. Am J Surg Pathol 2014;38:548-51.
17. Jouenne F, Chevret S, Bugnet E, Clappier E, Lorillon G, Meignin V, *et al*. Genetic landscape of adult Langerhans cell histiocytosis with lung involvement. Eur Respir J 2020;55:1901190.
18. Diamond EL, Subbiah V, Lockhart AC, Blay JY, Puzanov I, Chau I, *et al*. Vemurafenib for BRAF V600-mutant Erdheim-Chester disease and Langerhans cell histiocytosis: Analysis of data from the histology-independent, phase 2, open-label VE-BASKET study. JAMA Oncol 2018;4:384-8.
19. Acosta-Medina AA, Kemps PG, Zondag TC, Abeykoon JP, Forma-Borst J, Steenwijk EC, *et al*. BRAF V600E is associated with higher incidence of second cancers in adults with Langerhans cell histiocytosis. Blood 2023;142:1570-5.
20. Jouenne F, Benattia A, Tazi A. Pulmonary Langerhans cell histiocytosis - an update on pathogenesis and treatment. Curr Opin Pulm Med 2023;29:451-8.
21. Le Pavec J, Lorillon G, Jaïs X, Tcherakian C, Feuillet S, Dorfmüller P, *et al*. Pulmonary Langerhans cell histiocytosis-associated pulmonary hypertension: clinical characteristics and impact of pulmonary arterial hypertension therapies. Chest 2012;142:1150-7.
22. May A, Kane G, Yi E, Frantz R, Vassallo R. Dramatic and sustained responsiveness of pulmonary Langerhans cell histiocytosis-associated pulmonary hypertension to vasodilator therapy. Respir Med Case Rep 2014;14:13-5.
23. Nemoto K, Oh-Ishi S, Inui T, Nakazawa M, Hyodo K, Nakajima M, *et al*. Long-term improvement during tadalafil therapy in a patient with pulmonary hypertension secondary to pulmonary Langerhans cell histiocytosis. Respir Med Case Rep 2016;18:54-7.
24. Botney MD, Bahadori L, Gold LI. Vascular remodeling in primary pulmonary hypertension: potential role for transforming growth factor-β. Am J Pathol 1994;144:286-95.
25. Humbert M, Monti G, Brenot F, Sitbon O, Portier A, Grangeot-Keros L, *et al*. Increased interleukin-1 and interleukin-6 serum concentration in severe primary pulmonary hypertension. Am J Respir Crit Care Med 1995;151:1628-31.
26. Humbert M, Monti G, Fartoukh M, Magnan A, Brenot F, Rain B, *et al*. Platelet-derived growth factor expression in primary pulmonary hypertension: Comparison of HIV seropositive and HIV seronegative patients. Eur Respir J 1998;11:554-9.
27. Asakura S, Colby TV, Limper AH. Tissue localization of transforming growth factor-β1 in pulmonary eosinophilic granuloma. Am J Respir Crit Care Med 1996;154:1525-30.
28. Girschikofsky M, Arico M, Castillo D, Chu A, Doberauer C, Fichter J, *et al*. Management of adult patients with Langerhans cell histiocytosis: Recommendations from an expert panel on behalf of Euro-Histio-Net. Orphanet J Rare Dis 2013;8:72.
29. Elia D, Torre O, Cassandro R, Caminati A, Harari S. Pulmonary Langerhans cell histiocytosis: A comprehensive analysis of 40 patients and literature review. Eur J Int Med 2015;26:351-6.
30. Dauriat G, Mal H, Thabut G, Mornex JF, Bertocchi M, Tronc F, *et al*. Lung transplantation for pulmonary Langerhans' cell histiocytosis: A multicenter analysis. Transplantation 2006;81:746-50.
31. Boehler A. Lung transplantation for cystic lung diseases: Lymphangio-leiomyomatosis, histiocytosis X, and sarcoidosis. Sem Resp Crit Care Med 2001;22:509-15.
32. Goyal G, Acosta-Medina AA, Abeykoon JP, Dai C, Ravindran A, Vassallo R, *et al*. Long-term outcomes among adults with Langerhans cell histiocytosis. Blood Adv 2023;7:6568-78.
33. Vassallo R, Ryu JH, Colby TV, Hartman T, Limper AH. Pulmonary Langerhans'-cell histiocytosis. N Engl J Med 2000;342:1969-78.
34. Vassallo R, Ryu JH. Pulmonary Langerhans' cell histiocytosis. Clin Chest Med 2004;25:561-71.

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