BMC Pulmonary Medicine

CASE REPORT

Open Access

Pulmonary langerhans cell histiocytosis secondary to Marijuana use: a case report and systematic review of the literature

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Abstract

Background Pulmonary Langerhans Cell Histiocytosis (PLCH) is a rare interstitial lung disease primarily affecting young to middle-aged smokers. While traditionally linked to tobacco use, there is growing evidence that cannabis use may contribute to PLCH.

Methods We present a case of a 52-year-old male with PLCH associated with heavy cannabis use. Diagnostic evaluations included CT scan of the chest and histopathological examination of a lung biopsy. In addition, a comprehensive review of the literature was conducted to identify and analyze similar cases of PLCH linked to cannabis use. Databases searched included PubMed and Google Scholar, following PRISMA guidelines.

Results The patient presented with dyspnea, cough and unintentional weight loss. The patient had a 20-year history of smoking approximately ten cannabis blunts per day. Despite normal initial chest X-ray findings, a CT scan of his chest revealed upper lobe predominant cystic changes and emphysema. Histopathology from a transbronchial biopsy confirmed the presence of Langerhans cells, consistent with PLCH. Literature review identified five additional case reports of PLCH associated with cannabis use, involving patients aged 16 to 59 years, with a mean age of 35.8 years. Common clinical presentations included cough, dyspnea, and chest pain, with radiographic findings of nodules and cysts. Treatment was primarily targeted towards smoking cessation, which led to clinical improvement in all cases.

Conclusions This case underscores the potential association between heavy cannabis use and the development of PLCH. With the increasing prevalence of cannabis consumption, it is essential to recognize cannabis as a possible risk factor for PLCH. Further research is needed to understand the pathophysiological mechanisms underlying cannabis-related PLCH. As cannabis use becomes more prevalent with changing legislation, understanding its impact on lung health and potential role in diseases like PLCH is increasingly important.

Keywords Cystic lung disease, Smoking, Marijuana, Interstitial lung disease, Tobacco use, Langerhans cells, Smoking cessation

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Background

Pulmonary Langerhans Cell Histiocytosis (PLCH) is a rare diffuse cystic lung disorder that primarily affects young to middle-aged smokers. This condition is characterized by the abnormal proliferation of Langerhans' cells and is often associated with mutations in the mitogen-activated protein kinase (MAPK) signaling pathway. Traditionally linked to cigarette smoking, recent evidence suggests that heavy cannabis use might also be a contributing factor [1, 2].

PLCH is part of the broader spectrum of Langerhans' Cell Histiocytosis (LCH), a group of disorders that can affect various organs, including the skin, lymph nodes, and lungs. While LCH is more commonly observed in children, pulmonary involvement is significantly more frequent in adults, with PLCH being a notable subset [3]. Management of PLCH is directed at smoking cessation and counseling patients on the negative health impact of tobacco use.

This case report presents a patient with PLCH associated with heavy cannabis use, a relatively underexplored etiology. The review of the literature aims to contextualize this case within the broader spectrum of PLCH research, focusing on the relationship between cannabis use and PLCH, and exploring diagnostic and management strategies based on current findings.

Case presentation

A 52-year-old African American male presented to the pulmonary medicine clinic for persistent symptoms of chronic cough and dyspnea of 6-month duration. In addition, he reported 21-pound unintentional weight loss. Past medical history included back pain without sciatica, bipolar disorder, gastroesophageal reflux disorder, hypertension, cervical stenosis status post C6-C7 cervical spinal fusion, as well as arthritis, primarily in both hips and wrists., etc. His medication regimen consisted of hydrocodone-acetaminophen, esomeprazole, amlodipine, ziprasidone, and trazodone. Of note this patient has history of incarceration for 14 years, and during that time he was unable to smoke cannabis. Following his release from prison he engaged in heavy cannabis use. He presented to pulmonary medicine 20 years after being incarcerated. During this 20-year period he reported smoking 10 blunts per day.

The initial evaluation by the primary care provider included both imaging and laboratory studies. A chest X-ray revealed no remarkable findings. A rheumatoid factor level was drawn due to the longstanding history of arthritis and concerns for a potential autoimmune disorder. The rheumatoid factor was found to be elevated, prompting a referral to rheumatology for further evaluation. Additional labs, including Quantiferon, erythrocyte sedimentation rate, C-reactive protein, Alpha-1 anti-trypsin, and anti-nuclear antibody titers, were within normal limits. The rheumatologist determined that the joint pain was largely due to osteoarthritis rather than an autoimmune process, but due to the unexplained weight loss, the decision was made to proceed with further CT imaging of the patient's chest. This scan revealed upper lobe predominant variable cystic changes and emphysema (Fig. 1). Based on the CT scan findings the patient was referred to Pulmonary Medicine. Bronchoscopy was offered to further evaluate abnormalities seen on chest.

Bronchoscopy, BAL, and right upper lobe transbronchial biopsy was performed. Samples were reviewed by an experienced chest pathologist. The specimen demonstrated lung parenchyma with interstitial fibrosis, as well as tiny segments of bronchial mucosa. There were pigmented alveolar macrophages noted within alveolar spaces. These macrophages had uniform nuclei without definite clefts or grooves (Fig. 2). There was no evidence of carcinoma. S100 immunohistochemical staining was performed which was negative. The samples were sent for further expert consultation at the University of Michigan, and further review revealed focal stellate fibrosis with paracicatrical air space enlargement consistent with fibrotic Langerhans Cell Histiocytosis. Based on the overall clinical picture in combination with these microscopic findings, a diagnosis of Pulmonary Langerhans Cell Histiocytosis was made. The pathologist further emphasized that in late fibrotic stage of Langerhans cell histiocytosis, where the diagnostic Langerhans cells disappear, the diagnostic value of special stains is invalidated.

The diagnosis was discussed with the patient, and he was sent for pulmonary function testing (PFT) which demonstrated decreased FEV1/FVC ratio and moderate diffusion capacity impairment (Table 1). Due to the classic association with heavy tobacco smoking, the patient's smoking history was again reviewed in depth and he reiterated that outside of his cannabis use, he had not been smoking or vaping tobacco products or any other drugs. The patient was instructed to cessate smoking and scheduled for monitoring PFTs. The patient was lost to follow-up and reestablished care with Pulmonology at a different center where follow up PFT about an year later was very similar (Table 2). The patient had significantly reduced his marijuana smoking and reported improvement in his cough and shortness of breath.

Systematic review

Methods

Literature Review The work has been expressed in line with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020 criteria [4]. We perused the PubMed and Google scholar databases using the medical subject headings (MeSH) "Pulmonary Langerhans' Cell Histiocytosis", "PLCH", "acute respira-

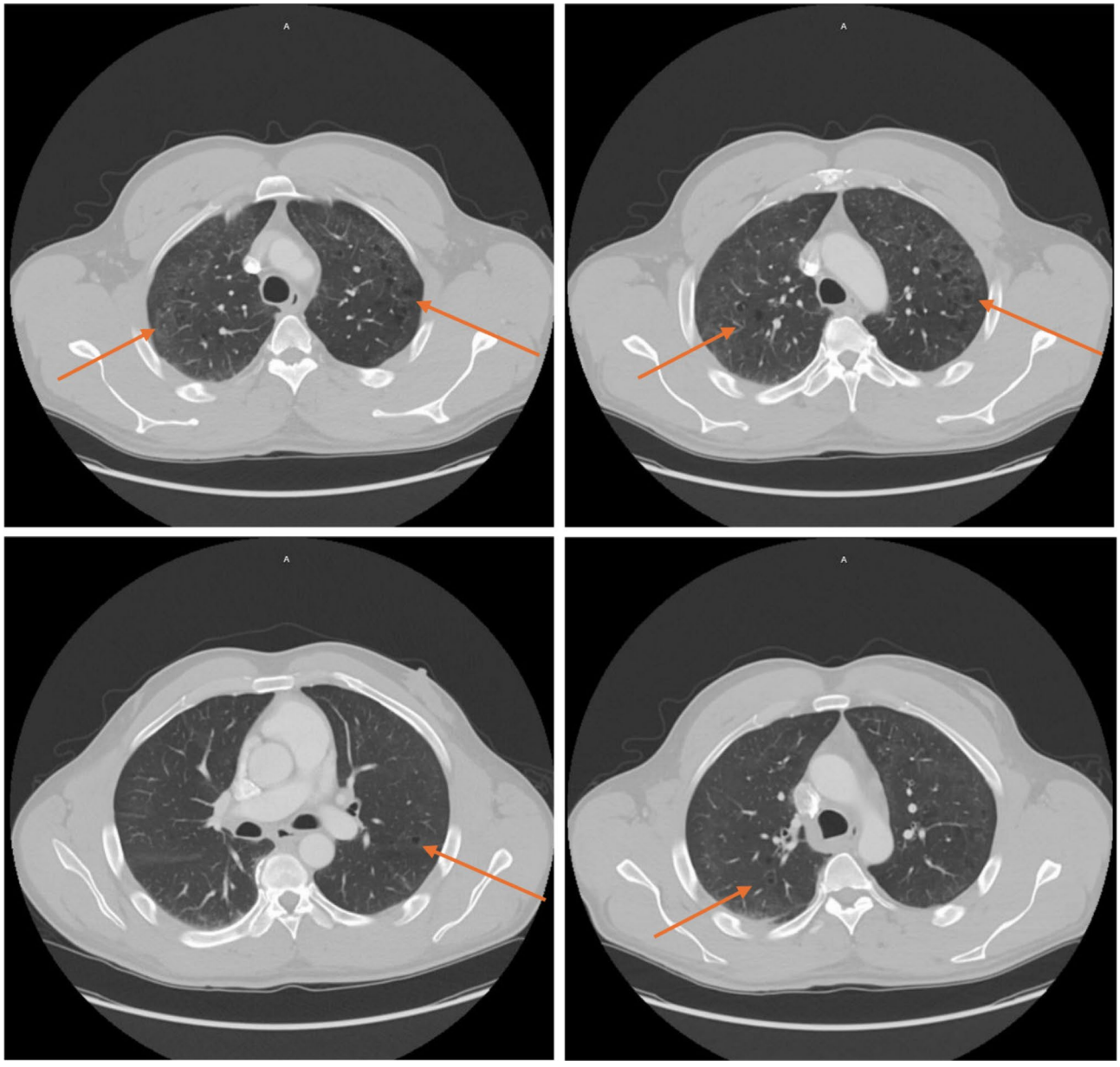

Fig. 1 CT chest showing diffuse cystic changes in the lungs bilaterally with the arrow pointing at the variable cysts

tory distress syndrome", "Marijuana Smoking", or "Cannabis Smoking".

Inclusion criteria and study selection Two reviewers (IZ) and (RT) completed the title, abstract, and full-text screening in duplicate and independently. To settle disagreements between authors on the selection of studies, duplicate records were eliminated, and a third reviewer (AS) was contacted. Languages other than English were not allowed for articles. The current review includes case reports, case series, correspondence articles, and editorials. Studies that reported aggregate-level data (that is. retrospective cohorts) or unique empirical data on patients with PLCH because of marijuana or cannabis consumption were excluded. The combined search strategy identified 31 potential publications, 24 on Google Scholar and 7 on PubMed [Fig. 3]. These publications included review articles, cross sectional studies, cohorts and case reports. After screening and removing duplicate studies, a total of 12 case reports were found, out of which 5 were shortlisted which fulfilled the inclusion criteria.

Data extraction Two separate reviewers extracted the data twice, and a third reviewer's input helped to reconcile any differences. The initial author, age and sex, patient

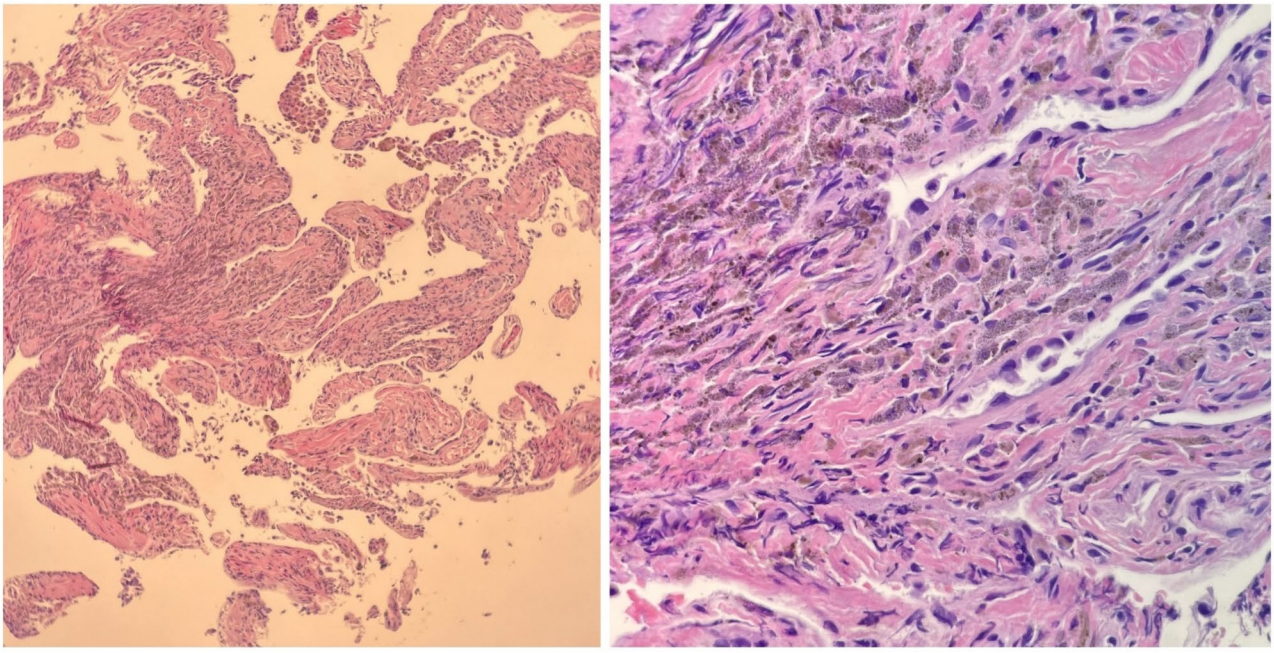

Fig. 2 A combination of emphysema and patchy mild paucicellular fibrosis characteristic of so-called smoking-related interstitial fibrosis. Against this backdrop, a single piece shows fibrosis with a more stellate configuration, the central focus comprising conventional pigmented (smoking-related) histiocytes and dense collagen fibrosis. This stellate nodule is accompanied by an equally distinctive pattern of paracicatricial airspace enlargement ("scar emphysema"). This combination of features is characteristic of the late fibrotic stage of Langerhans cell histiocytosis, a stage in which diagnostic Langerhans cells have disappeared thus negating the diagnostic value of special stains

Table 1 Pulmonary function test at the time of diagnosis

	Reference	Pre-bronchodilator
FVC/liters	5.08	5.96 (117%)
FEV1/liters	4.03	3.93 (97%)
FEV1 to FVC ratio/%	80	66
DLCO/ mL/min/mmHg	32.5	18.5 (57%)

PFT obtained at the time of diagnosis

Table 2 Repeat pulmonary function test one year later

	Reference	Pre-bronchodilator
FVC/liters	5.21	5.93 (114%)
FEV1/liters	4.12	4.02 (98%)
FEV1 to FVC ratio/%	79	68
DLCO/ mL/min/mmHg	32.5	21.48 (66%)

PFT at one year follow-up

characteristics, functional tests, morphological findings, diagnosis, laboratory parameters, course of treatment, and prognosis were among the data that were extracted.

Quality assessment

Using the critical appraisal tool for case reports developed by the Joanna Briggs Institute, we evaluated the quality of all included studies [5]. A numerical score was assigned to each qualitative response. After settling differences, the assessment was completed by two impartial evaluators, and a final score was determined. A comprehensive quality evaluation can be found in the attached file. A measurement tool for assessment of multiple systematic reviews (AMSTAR) 2 criteria were used to evaluate the quality of our systematic review [6]. The AMSTAR 2 level of compliance was determined to be "low." Meta-analysis of the data could not be performed because the analyses only comprised 5 case reports.

Statistical analysis

Extracted data were input into a spreadsheet. While continuous data were presented in mean form, categorical variables were reported using frequency and percentage.

Results

The search strategy found 5 studies [1, 2, 7–9] that met our inclusion criteria and were included in the systematic review (Table 3). These studies were case reports that focused on a single instance. The Joanna Briggs Institute critical appraisal tools assessments had a mean score of 7 out of a possible 8 points, with scores ranging from 6 to 8 (table S1, supplementary file). Among the 5 cases, 3 were males. The age ranged from 16 to 59 years, with a mean age of 35.8 years. Notably, patients with PLCH because of smoking marijuana or cannabis started the disease at a younger age than those who smoked tobacco. Out of the five patients, only one engaged in high-risk sexual behavior (without precautions and having multiple partners). He reflects to be a case of PJP along with PLCH [7].

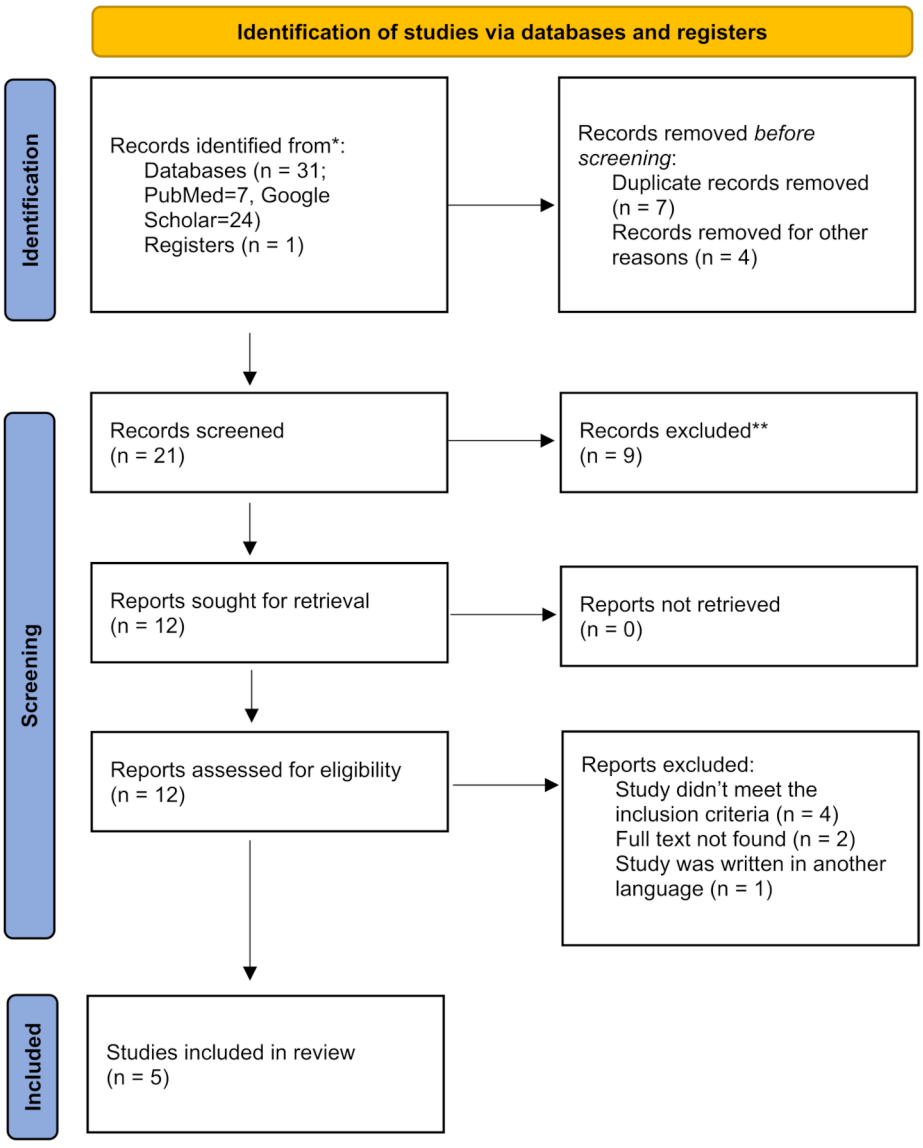

Fig. 3 Flowchart depicting the inclusion process for studies related to PLCH and marijuana use

Metabolic syndrome with hyperlipidemia and fibromyalgia affected 1 of the 5 patients [9]. The time of presentation after onset of cough ranges from few weeks to one year. All patients had a history of tobacco smoking except for one who smoked Marijuana alone. All clinical manifestations, including fever, dyspnea, and active cough, were similar. The majority of the diagnosis was based on biopsy and radiographic results, as well as laboratory results and the patient's lack of response to conventional pneumonia treatment. The prognosis was good as all the patients improved after management. Magnesium sulphate, nebulized bronchodilators, and IV hydrocortisone were among the treatments employed. Insertion of bilateral chest tubes and pairing Video-Assisted Thoracic Surgery (VATS) with affected lobe talc pleurodesis and resection in addition to quitting smoking were additional treatments pursued in severe cases.

The findings of the literature review are depicted in Table 3.

Discussion

This case report and review of the literature highlights a rare presentation of PLCH in a patient with significant history of heavy cannabis use. Although traditionally associated with tobacco smoking, this case raises concerns about the potential role of cannabis smoking in the development of PLCH. PLCH is known to account for 3–5% of all adult diffuse lung disorders, with a peak incidence in young smokers or ex-smokers between the ages of 20 and 40, and affecting both sexes equally [10, 11].

Table 3 A summary of the published case reports on PLCH in marijuana users

Author	Age and sex	Patient characteristic	Morphological Findings	Functional Test	Diagnosis	Laboratory Parameters	Treatment	Prognosis
Sophie Buckley [1]	36 y/o Male	Significant Tobacco and Cannabis user. Presented with Acute respiratory Distress. Onset: Dyspnea 1 year prior to respiratory arrest.	CXR: bilateral pneumothoraces, pulmonary parenchymal disease. HRCT Thorax: extensive bilateral cystic lung disease with a large right sided persistent pneumothorax.	Audible Wheeze and Silent chest on auscultation.	Bilateral spontaneous pneumothoraces secondary to PLCH.	pH of 7.0, pCO2 of 15.7 kPa, and a pO2 of 4.5 kPa	IV hydrocortisone, magnesium sulfate, nebulized bronchodilators. Bilateral chest tubes. Bilateral VATS with talc pleurodesis and right upper/lower lobe wedge resection. Smoking cessation.	Persistent left sided pneumothorax on discharge. No residual dyspnoea.
Ronald Cassada [2]	24 y/o Female	Smoked 1–2 joints of marijuana per day. No tobacco smoking. Presented with dyspnea, chest pain, and dry cough. Onset: 1 month prior	CXR: large sided right pneumothorax with shift of the mediastinum to the left. Left lung was notable for interstitial infiltrates. HRCT Thorax: bilateral diffuse cystic lung disease, multiple sub-centimeter thin-walled cyst without perceptible wall.	Bronchoscopy revealed diffuse nodularity along with multiple cysts. A right lower lobe bulla with exophytic cyst was seen. H&E stain revealed nodule distillate of various sizes, focal histiocytic infiltrates, and cystic changes of the surrounding alveoli with eosinophilic cytoplasm's reniform nuclei.	PLCH with mediastinal shift and pulmonary infiltrates.	Heart rate 125, respiratory rate 30, O2 sat 86%. l CD1 a positive Langerhans' cells. S100 protein, CD1a, vimentin, HLA-DR, and placental alkaline phosphatase reactive with Langerhans cells.	Bilateral chest tubes. VATs surgery. Smoking cessation.	Unavailable.
Lauren Mias. [3]	59 y/o Male	Marijuana smoker of 10 chalices per day for over 40 years. 9 lifetime sexual partners and stopped condom use. Onset: 7 months prior.	CXR: Lungs were hyperinflated with multiple cysts of roughly uniform size and wall thickness.	Mild respiratory distress. generalized wasting and digital clubbing. Central trachea, hyper-resonant percussion, no added sounds. There was a thick, milky urethral discharge.	PLCH, cystic lung disease, and HIV positive PJP.	FEV1 was 60% predicted; FVC was 51% predicted. FEV1/FVC was 119% predicted. BP 107/78, pulse 104/min, temperature 37.3 C, respiratory rate 24/min, SpO2 90%.	Bilateral chest tubes. Smoking cessation.	No improvement post-BD.
Angela Onorato, M.D [4]	16 y/o Male	Productive, progressive cough which was exacerbated by activity and worse in the morning. Shortness of breath. Unintentional 30-pound weight loss over the previous 8 months	CXR: Initially right pneumothorax and 1 week later bilateral pneumothoraces. CT Chest shows innumerable thin-walled cysts throughout the lung parenchyma bilaterally, distributed primarily in subpleural areas and lower lobes.	Macroscopic examination of the wedge biopsy demonstrated subpleural cystic spaces. Biopsy showed collections of large cells that were positive for CD1a immunohistochemical stain. Cells containing abundant eosinophilic cytoplasm, irregular convoluted nuclei, and grooves.	isolated PLCH	FEV1: 107% predicted. FVC: 116% predicted. FEV1/FVC ratio: 80. DLCO 91% predicted.	Smoking cessation only	gradual improvement of the cystic lesions. good exercise tolerance. weight increased back. FEV1, FVC, FEV1/FVC and DLCO normal.

Table 3 (continued)

Author	Age and sex	Patient characteristic	Morphological Findings	Functional Test	Diagnosis	Laboratory Parameters	Treatment	Prognosis
Winston McCormick, BS. [5]	44 y/o Female	Left chest wall pain that radiated to her back. Hyperlipidemia and fibromyalgia.	CT scan thorax revealed exostosis on the sixth rib of the left hemithorax and an incidental, small, right-sided ground-glass nodule in the right upper lobe.	Right lung needle biopsy revealed alveolar septal thickening with associated atypical pneumocyte proliferation, stellate-shaped areas in periphery of the lungs containing sparse cellular proliferation and abundant eosinophils.	Respiratory bronchiolitis, smoking-related interstitial fibrosis along with PLCH.	PFT unremarkable.	wedge resection of the right upper, middle and lower lobes.	no residual disease.

PLCH pathogenesis involves dendritic cells with mutations in genes related to the MAPK pathway. Smoking, whether tobacco or cannabis, leads to the accumulation of inflammatory cells in the lungs, which release cytokines such as transforming growth factor beta, interleukin 1 beta, and tumor necrosis factor alpha [3, 12]. These cytokines contribute to granuloma formation and the growth of large cells, with activated Langerhans cells expressing higher levels of CD40, CD80, and CD86, and increased osteopontin and Bcl-xL expression [13]. The involvement of the RAS/MAPK signaling pathway, with mutations in genes like BRAF and MAP2K1, is also crucial [14].

In this case, the patient's extensive cannabis use might contribute to similar pathway of inflammation in the lungs however further research is needed in the area to establish the process. The classic imaging findings of PLCH include bilateral, symmetric nodules and cysts primarily in the upper lobes, which can progress to irregularly shaped cysts, emphysematous bullae, and ground-glass opacities [15, 16]. The CT findings and biopsy results in this patient, showing interstitial fibrosis and pigmented alveolar macrophages, align with PLCH's characteristic pattern [17, 18].

Based on the recommendations from the Histiocyte Society in 2019 [19], the case fulfills the criteria as a single-system PLCH. Characteristic clinical and radiologic features (category B recommendation) and typical bronchoscopic biopsy features of the lesional tissue (category A recommendation) helped in establishing the diagnosis of Langernhan's cell histiocytosis. With no symptom reported that may indicate involvement of any other system, imaging of any other organ was not performed during his initial work-up to establish the diagnosis.

A literature review from the Orphanet Journal of Rare Diseases in 2012 elaborately discusses the diagnostic approach to Langerhan's cells histiocytosis [20]. Traction emphysema is commonly observed in patients with PLCH due to fibrotic changes and destruction of bronchiolar walls. In advanced disease, the lung shows hyperinflation and advanced cystic changes, often resembling emphysema. The formation of irregular, bizarre-shaped parenchymal cysts occurs as peribronchial lesions destroy the bronchiolar walls, leading to luminal dilatation and fibrosis [21]. Stellate scars and peribronchial fibrotic rings contribute to traction emphysema, particularly in areas adjacent to these fibrotic changes [20], findings which are like the histopathology in this case.

The microscopic features of lung biopsy specimens in Langerhans cell histiocytosis vary based on the disease stage at the time of biopsy. In the early stages, the lesions appear as loosely organized cellular nodules located near small airways and dispersed throughout the lung parenchyma, forming granuloma-like structures. These nodules consist of a mix of inflammatory cells, including Langerhans cells, along with varying levels of T-lymphocytes, macrophages, plasma cells, monocytes, and eosinophils [22, 23]. And while S-100 and the CD1a antigen are specific for PLCH, the mere presence of these cells would not establish the diagnosis of PLCH [20]. Rather, there should be appropriate light microscopic features including varying combinations of nodular and cystic lesions with sizable aggregates of Langerhans cells [20]. Based on this, special stains are not required to make the diagnosis if you have other supporting evidence as in this report.

PLCH treatment emphasizes smoking cessation, which remains the most crucial intervention by far [24]. Smoking cessation alone improved clinical outcomes in the case presented by Angela et al. [8] among many others. It has also been established by the Histiocyte Society as the first line therapy for single system PLCH [19]. Systemic corticosteroids are commonly prescribed in severe cases but come with significant long-term side effects. Inhaled corticosteroids and bronchodilators may also be beneficial for managing symptoms [25]. For refractory cases, treatments like cladribine, vinblastine, or methotrexate can be considered [26, 27]. Emerging therapies, such as MEK inhibitors like trametinib, have shown promise for patients with specific genetic mutations [28]. Additional supportive treatments include supplemental oxygen for

hypoxia and surgical pleurodesis for pneumothorax [10, 29].

Conclusions

This study underscores the need for further research into the association between heavy cannabis use and PLCH. While cannabis has not been traditionally linked to PLCH, the patient's extensive use in the absence of tobacco use suggests a potential risk factor that warrants investigation. The systematic review conducted in our study further corroborates the association between PCLH and cannabis use. As cannabis use becomes more prevalent with changing legislation, understanding its impact on lung health and potential role in diseases like PLCH is increasingly important. This study highlights an emerging area of concern and emphasizes the need for comprehensive assessment and research into cannabis-related lung disorders.

Abbreviations

PLCH	Pulmonary Langerhans Cell Histiocytosis
MAPK	Mitogen-activated protein kinase
LCH	Langerhans' Cell Histiocytosis
CT	Computed tomography
PFT	Pulmonary function testing
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analyses
MeSH	Medical Subject Headings
AMSTAR	A measurement tool for assessment of multiple systematic reviews
VATS	Video-Assisted Thoracic Surgery

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03513-3.

Supplementary Material 1

Acknowledgements

None.

Author contributions

AS and RT were involved in literature review. IZ, AS, RT and MB were major contributors in article writing. BJH managed and compiled the case and contributed to article writing. All authors reviewed and approved the final manuscript.

Funding

None to report.

Data availability

All data pertaining to this patient are included in this report.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare no competing interests.

Received: 8 September 2024 / Accepted: 21 January 2025
Published online: 27 January 2025

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