A unique presentation of Pulmonary Langerhans Cell Histiocytosis☆

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ABSTRACT

Pulmonary Langerhans Cell Histiocytosis (PLCH) is a diffuse lung disease that primarily affects young adults, with cigarette smoking playing a significant role in developing the disease. Patients with PLCH present with characteristic CT chest findings of small irregular nodules and upper zone cysts. Previously, larger nodules greater than 10 mm and cavitation have only been reported a few times in the literature. We describe the case of a 69-year-old male who presented with dyspnea, non-productive cough and weight loss, who was found to have multiple cavitary nodules on CT imaging of the chest. Histopathologic sampling of the lung revealed Langerhans cells which stained positive for S100 and CD1a, consistent with a diagnosis of PLCH. The patient was counselled to quit smoking as the mainstay of treatment. In 3-month follow-up his symptoms had largely resolved, with evidence of decreased nodule size on repeat CT imaging.

1. Introduction

Pulmonary Langerhans Cell Histiocytosis (PLCH) is a rare interstitial lung disease that primarily affects young adults between the ages of 20–40 [1,2]. The cell type responsible for PLCH are Langerhans-like cells, which are found in large numbers and express CD1a, CD207 and S100 proteins characteristic of the disease [3]. Most patients with PLCH have high-resolution CT chest findings of small nodules (2–10 mm) and upper zone predominant cysts [4–6]. Here, we present the unique case of an elderly patient presenting with multiple non-cystic cavitary nodules up to 17.2 mm in size.

2. Case report

A 69-year-old male presented to the emergency department with a one-year history of dyspnea on exertion, chronic non-productive cough and weight loss of 30 lbs, referred by his primary care physician for further evaluation. He had a significant smoking history of 75-pack-years, and a rare copper deficiency for which he was treated with copper supplementation. He reported no other medications, allergies, recreational drug use or prior tuberculosis exposure.

The patient had normal vital signs but appeared cachectic. He had quiet breath sounds bilaterally, but no adventitious sounds. C-reactive protein was elevated at 13.7, but otherwise his blood work was unremarkable.

CT chest demonstrated multiple bilateral pulmonary nodules and centrilobular emphysema (Fig. 1). There were cysts in the upper lobes, some larger than 1 cm in size. In the lung bases there were a few small nodules but no specific cysts. The pulmonary nodules were
more prominent in the upper lobes with cavitation (Fig. 2). The largest irregular nodule was in the left upper lobe and measured 17.2 mm. The largest nodule in the right upper lobe measured 12 mm. Given the concern for malignancy, the patient underwent a bone scan which was unremarkable, and a CT abdomen and pelvis, which showed mild asymmetric rectal thickening. As a result, the patient had a gastroscopy and colonoscopy, which were normal. Subsequently, a CT-guided core needle biopsy of the largest lung nodule was performed and the patient was discharged due to his stable clinical status.

The patient was seen in follow-up pulmonology clinic and underwent bronchoscopy and pulmonary function testing (PFT). Initial
Fig. 3. Lung with granulomas, dense lymphohistiocytic infiltrate and eosinophils (original magnification ×100).

Fig. 4. Clusters of atypical cellular infiltrate with abundant pale eosinophilic cytoplasm, irregular and elongated nuclei with prominent nuclear grooves and folds (original magnification ×600).

Fig. 5. The atypical cells are positive for CD1a (original magnification ×200).
pathology results revealed non-necrotizing granulomas (Fig. 3 & Fig. 4). Therefore, a bronchoalveolar lavage (BAL) was performed, which ruled out infection, did not reveal any malignant cells and contained sparse histiocytes which were negative for CD1a. PFT revealed FEV1 2.66 L/79%, FVC 4.13 L/93%, FEV1/FVC 0.64, TLC 7.48 L/99%, RV 3.21 L/123% and a diffusion capacity of 58%. The histology was sent for a second opinion to a lung pathologist, demonstrating histiocyte-type cells consistent with Langerhans cells which stained positive for S100 and CD1a (Fig. 5). A PET-CT scan was also completed and demonstrated intensely FDG avid pulmonary nodules but no findings of extrapulmonary Langerhans cell histiocytosis.

The patient was counselled to quit smoking as the mainstay of treatment, and no pharmacological therapy was required. On 3-month follow-up, with smoking cessation, the patient had experienced near resolution of his symptoms. Repeat CT chest also demonstrated significant decrease in his pulmonary nodules, with the largest nodule measuring 10 mm in size (Fig. 6).

| Table 1 | Characteristic high-resolution CT scan imaging findings of PLCH [6,9]. |
|---|---|---|
| Early Findings | Late Findings | Smoking-related imaging findings |
| • Upper lobe predominance of findings with sparing of lung bases | • Upper lobe predominance of findings with sparing of lung bases | • Centrilobular emphysema and emphysematous bullae |
| • Bronchiolocentric stellate micronodules (usually 1–10 mm) in size | • Irregularly shaped, branched or bizarre thin-walled cysts with cysts predominating over nodules | • Thickening of bronchial walls |
| • Thick-walled cysts | • Can also include imaging abnormalities listed in early findings | • Ground glass opacities |
| • Nodules which are initially more numerous than cysts | | |

Fig. 6. Follow-up CT scan of the chest in axial and coronal views 3 months after smoking cessation demonstrating a significant decrease in the size of the nodules, with the largest nodule in the left upper lobe now measuring 10 mm in size.
3. Discussion

PLCH often presents with non-productive cough and dyspnea, and constitutional symptoms such as fever, fatigue and weight loss [7]. PFT often demonstrates normal lung volumes and limited obstruction [8]. The diagnosis of PLCH can be made on characteristic high-resolution CT chest findings or on histology from lung biopsy. Early imaging findings of PLCH can consist of bronchiolocentric micronodules (2–10 mm), often stellate, along with thick-walled cysts in the upper lung zones [6]. As the disease progresses, thick-walled cysts can progress to thin-walled, are often bizarrely shaped, and can be of increased size (>1 cm). They are also primarily in the upper lobes (Table 1) [6]. Other imaging findings in PLCH are those that are likely related to smoking exposure such as centrilobular emphysema, emphysematous bullae and thickening of bronchial walls [6]. Lung biopsy results will show a characteristic cluster of Langerhans-like cells on histology, which stain for the CD1a, CD207 and S100 proteins [2]. BAL can support the diagnosis when it demonstrates greater than 5% Langerhans-like cells which are positive for CD1a and CD207 [2].

Our patient presented with a case of PLCH that did not fit common diagnostic and clinical parameters, leading us to strongly consider malignancy as a potential diagnosis. Our patient had large cavitary nodules, up to the size of 17.2 mm. Larger non-cystic nodules greater than 10 mm with cavitation is common in malignancy but is extremely rare in PLCH, with only a few cases reported of the same [10–13]. The evolution of nodules on CT imaging appears to be that of smaller nodules progressing over time to cysts, but our patient had large non-cystic nodules on presentation [14]. Additionally, our patient was 69 years of age, which is uncommon, as most cases of PLCH occur between the ages of 20–40 [1].

The pathology of PLCH consists of the presence of an excess number of Langerhans-like cells producing the pathognomonic CD1a, CD207 and S100 immunohistochemical markers [9]. Recent sequencing studies demonstrate that the pathophysiology of PLCH may involve somatic mutations of the mitogen-activated protein kinase (MAPK) pathway, specifically BRAF and NRAS mutations, which have been implicated in the development of certain cancers [9]. Cigarette smoking may be involved in the pathogenesis by promoting the recruitment and proliferation of CD1a cells with oncogenic mutations [3,15]. It is also possible that cigarette smoking may directly contribute to the development of such oncogenic mutations, but that has yet to be firmly elucidated [9,15]. Treatment of the disease thus far has therefore focused primarily on smoking cessation [16]. In a case series of 40 patients, smoking cessation was the only treatment needed in 25 patients for resolution or stabilization of the disease [16]. For patients with progressive disease despite smoking cessation, systemic glucocorticoids can be trialed, but appear to have variable results [17,18]. Cladribine, a synthetic cytotoxic purine analogue may be effective in inducing remission in some patients, but needs further study through clinical trials [9]. For refractory cases, identification of these somatic mutations recently has led to the consideration of targeted therapy of the MAPK pathway [9]. These medications, such as Vemurafenib, an inhibitor of mutated BRAF, are now being used for Langerhans’ cell histiocytosis treatment [3,19]. Further study of these inhibitors with regard to PLCH in particular will need to be conducted to demonstrate its efficacy. Of note, extrapulmonary LCH is reported in 5–15% of cases of PLCH, commonly with bone lesions, diabetes insipidus or skin lesions [20]. Our patient did not demonstrate any symptoms, signs or imaging findings consistent with extrapulmonary LCH and on 3-month follow-up he had complete resolution of his symptoms with smoking cessation.

Although malignancy was initially the leading differential diagnosis, interestingly, our case did offer subtle clues that suggested an alternative diagnosis on initial presentation. The patient’s large cavitary nodules were in the upper lobes, whereas metastatic cancer would be most likely to present in the lower lobes due to greater perfusion to the lung bases. Additionally, although the patient reported significant weight loss and other constitutional symptoms, this is also a common finding in interstitial lung diseases such as PLCH [7]. Our case report therefore highlights a unique presentation of this disease and serves to encourage physicians to consider PLCH in their differential diagnosis when faced with an atypical presentation.

Declaration of competing interest

No conflicts of interest exist for either author.
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Appendix A. Supplementary data

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