CASE REPORT

Recurrent pneumothoraces in a patient with pulmonary Langerhans cell histiocytosis accompanied with unexpected histological changes

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ABSTRACT

Pulmonary Langerhans cell histiocytosis (PLCH) in adults is an uncommon disorder that occurs almost exclusively in smokers. PLCH has no known gender predilection, and the current consensus of its true aetiology is unknown. Lungs may the sole organ involved, however other organs in the body may be involved as well. With the introduction of 2 possible diagnostic categories, it makes PLCH easier and possibly quicker to diagnose. In this report, we present a 34-year-old adult male PLCH case that was negative for the typical immunohistochemistry findings necessary for a "definite" diagnosis but was instead diagnosed based on his florid imaging findings – who also had an unexpected histological finding of a non-specific interstitial pneumonia.

KEYWORDS: pulmonary Langerhans cell histiocytosis; non-specific interstitial pneumonia; pneumothoraces; recurrent; smoking

INTRODUCTION

Pulmonary Langerhans cell histiocytosis (PLCH) in adults is an uncommon disorder that occurs almost exclusively in smokers and has no gender predilection however its true aetiology is unknown. Lungs may the sole organ involved, or it may involve bones, lymph nodes, hypothalamus, or the organs of haematological system. The current estimated prevalence is between 1-2 cases per million persons [1]. PLCH has had familial occurrences reported in the past, however no clear genetic factor towards PLCH have been found [1,2].

PLCH is characterized by the lung infiltration of bone marrow derived Langerhans cells (LCs) forming focal granulomas, causing a strong inflammatory response and resultant destruction of bronchioles. LCs are normally present in the lungs, skin, and various other mucosa, functioning as sentinels of these regions. The initial activation of LCs is done through damaged cells, dying cells or pathogen sensing cells [2]. These cells then hold the key immunological role of assisting the activation of antigen presenting dendritic cells for the downstream activation of naïve lymphocytes. Exposure to cigarette smoke leads to the release of inflammatory mediators, some of which are potent mitotic factors for LCs – causing its' pathological accumulation [3]. In addition, chemotactic factors are also expressed causing dendritic cells, macrophages, and monocytes to accumulate. These pathological LCs express extensive levels of cytokines, promoting the development of giant cells and granulomas [1]. The cystic destruction of lung parenchyma has been postulated to be caused by degrading enzymes released from these inflammatory cells [1,2]. Hence, the onset of PLCH has notable and significant presence of inflammatory cells, inflammatory mediators and dysfunctional LCs with clonal proliferation happening in the background reinforcing its onset.

On a molecular level, these abnormal LCs may carry any one or more of these somatic mutations of BRAF, ARAF, NRAS, KRAS, MAP2K1, PIK3CA genes [1,2]. Various studies done have shown varying percentages of these mutations in known patients with PLCH. The downstream event of these mutations leads to the activation of the extracellular signal-regulated kinase (ERK) pathway, that is a part of the mitogen-activated protein kinase (MAPK) family. A cascade crucial for the survival, development and spread of cancers through regulation of cell proliferation, differentiation, and stress responses [2]. Understanding more on these genetic mutations involved in this pathway may help guide and tailor targeted treatment to patients with PLCH. Overall, the interindividual differences in single or subsets of these mutations of LCs may relate to the clinical presentation of the disease. Here we report a unique case of a patient with "probable" PLCH with non-smoking related histopathological changes.

CASE PRESENTATION

A 34-year-old male first presented to a respiratory clinic with 1 year of paroxysmal cough with episodic expectoration.

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The onset of the cough was sudden and continued repeatedly, worst in the mornings. The patient does not report shortness of breath, chest pain, fever, or fatigue. He has a history of post-nasal drip, gastroesophageal reflux disease and a hiatus hernia. He does not take regular medications or recreational drugs. For the last 15 years, the patient has consumed approximately 50g of tobacco weekly but has reduced his intake to 50g every 2-3 weeks for the past year. He lives and works on a rural farm approximately 80 kilometres from the nearest hospital with his partner and three children. He is a farmer by occupation and he is independent of all his activities of daily living. In addition to his farm work, the patient has worked as a welder and painter in the past. His occupational exposures were mainly dust, chemicals, and cane. There is a family history of asthma in two direct family members. He has never been diagnosed with asthma but reports using inhalers as a child. He examined well on the visit, there was no features of respiratory distress, or suggestive features of autoimmune diseases or mixed connective tissue diseases (MCTD). Auscultation yielded normal but mildly decreased air entry bilaterally.

Basic laboratory investigations were conducted which included full blood count, kidney functions, electrolytes and liver functions were unremarkable. There was an elevated IgE of 149 kU/L with normal ESR. An autoimmune screen was positive for antinuclear antibodies in a low 1:160 titre and showed a speckled pattern. Angiotensin converting enzyme, vasculitis screen, connective tissue disease screen, rheumatoid factor, anti-citrullinated protein antibody (anti-CCP) were all negative, alpha-1-antitrypsin levels were normal, serum vascular endothelial growth factor D (VEGF-D) levels were within range. Serum precipitins were positive for *Micropolyspora faeni* in a 1:4 concentration but negative for Aspergillus and *Thermoactinomyces vulgaris*. Lung function tests were conducted with results showing a forced expiratory volume in 1 second (FEV1) of 2.65 litres (L) (56.2% predicted), a forced vital capacity (FVC) of 4.34L (74.5% predicted) with a FEV1/FVC ratio of 61.14, diffusing capacity of lungs for carbon monoxide (DLCO) was 19.71 (57.22% predicted) and Krogh's corrected diffusion capacity (KCO) of 3.66 (76.7% predicted). An initial echocardiogram performed showed normal right and left ventricular function with a normal right ventricular systolic pressure (RVSP). There were no accompanying valvular pathologies found on his echocardiogram.

The first high-resolution CT (HRCT) scan conducted, demonstrated extensive bilateral bizarre shaped bilateral pulmonary cysts in mid to upper zones with some cavitations. A few mildly enlarged perivascular and right upper paratracheal lymph nodes were noted. These findings were highly suggestive of Langerhans cell histiocytosis.

A bronchoscopy was conducted six weeks later, with biopsies taken from the lateral segment of the right middle lobe lung nodule and bronchoalveolar lavages (BAL) collected subsequently. The bronchoscopy was again repeated 5 weeks later to obtain another repeat biopsy sample of the nodule. The histopathology report identified changes consistent with interstitial lung disease (ILD) with non-specific interstitial pneumonia (NSIP) reaction type fibrotic pattern (Figure 1). BAL collected was unremarkable. Immunohistochemistry for CD1a, Langerin and S-100 were negative. BRAF mutation was not detected in the sample.

The patient was reviewed again in clinic six months after the initial presentation. He was noted to have ceased smoking however there was no change to his symptoms. Another HRCT done (Figure 2) confirmed multiple bilateral irregularly shaped cysts in the middle to upper zones with basal and peripheral sparing. The overall appearance of these cysts was stable when compared to the previous CT scan. Ground glass nodularity was present but not a dominant component. Stable bilateral hilar and central mediastinal lymphadenopathy was present. These radiological findings were in keeping with his initial suspicion of PLCH. This case was later discussed in a state-wide meeting with other respiratory physicians, transplant clinicians, and pulmonology academics. The consensus of the discussion was that PLCH is an appropriate diagnosis. The patient was later referred to the state's lung transplantation services.

A week after this review, the patient was admitted to hospital for three days with a right sided spontaneous pneumothorax confirmed on chest x-ray (CXR), measuring approximately 1.5cm, which was likely caused by a ruptured cyst after experiencing an acute onset pleuritic chest pain. This resolved with the insertion of an intercostal catheter, which stayed in-situ for all three days.

The lung transplantation services reviewed the patient 1 month after this episode of pneumothorax. Due to his good functional capacity, they determined that he was too well for a lung transplant at this current stage. Due to the stability of the patient's symptoms, he was placed on a 6 monthly review and HRCT scans over the next year. Both HRCT scans done over this period showed stable appearances of his cysts. Other scans done to rule out systemic involvement of other organs were all negative. His yearly echocardiogram was unremarkable.

A year after his last review, the patient presented to the emergency department with ten days of worsening left sided pleuritic chest pain. He continued to experience the usual paroxysmal cough but denied any infective symptoms. CXR identified a left apical pneumothorax measuring less than 1cm. He was tachypnoeic and saturated at 84% on room air, but examined well apart from the pneumothorax which caused reduced breath sounds on the left apex. He was admitted under a general medical team and placed on four litres of low flow nasal prongs oxygen overnight at saturations of 94%. An echocardiogram done showed normal left and right ventricular size, normal left ventricular function and an elevated RVSP of 61mmHg – markedly raised from the previous. The patient was later discharged with home oxygen and for repeat follow up at the respiratory clinic.

Throughout the entire period from the time of first contact up till the latest hospital admission, the only formal management done was smoking cessation and the commencement of home oxygen. The patient remains on the lung transplantation services list to await further review if he remains a suitable candidate. No other extra-specific empiric medication treatment was given at any time.

DISCUSSION

PLCH remains to be an uncommon cystic-interstitial lung disease. CXR is not useful in patients with PLCH without a suspected presentation of pneumothorax. If reticulonodular patterns, cystic lesions or lymphadenopathy are present on CXR, it is often suggestive of advanced PLCH [1,2]. Instead, a HRCT plays a significant role in diagnosing PLCH. A summary of the common possible HRCT findings in

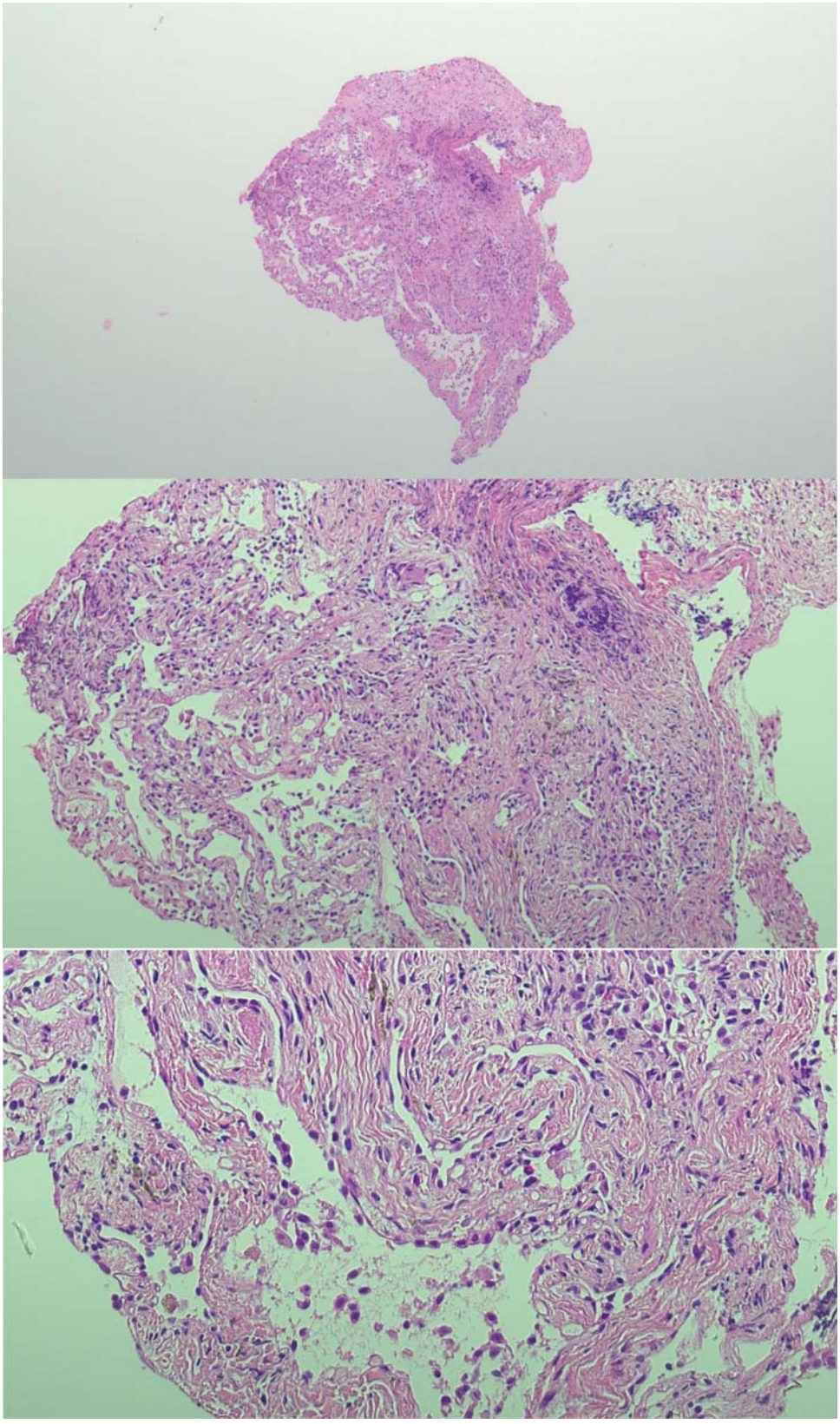

Fig. 1. Histopathology findings showing non-specific interstitial pneumonia in low and high power (HE, x50, x100, x200). Alveolar wall thickening due to fibrosis, rimmed with type II pneumocytes, with no normal alveolar wall.

PLCH is present in Table 1. Positron emission tomography (PET) has its limitations in identifying isolated PLCH due to observed low relative uptake of the radionuclide used. However, it is highly sensitive for identifying other system involvement, particularly, bone involvement [1,3].

The histological findings of PLCH may vary based on disease stage. But focal bronchiolocentric lesion, with accompanying granulomatous formation near the terminal airways, with wall destruction and possible extension into the interstitium, are all commonly found [3]. A confluence of

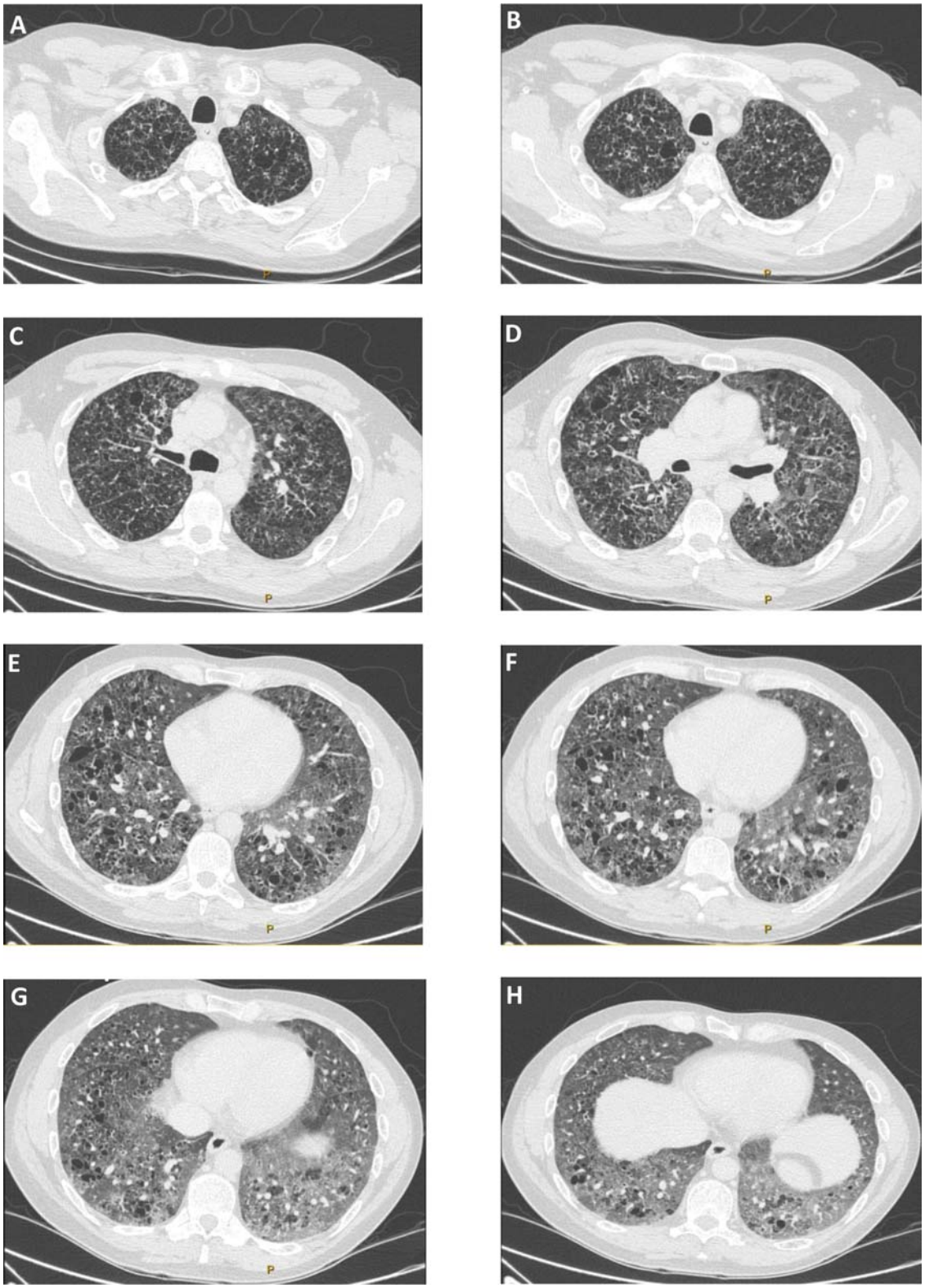

Fig. 2. Continued.

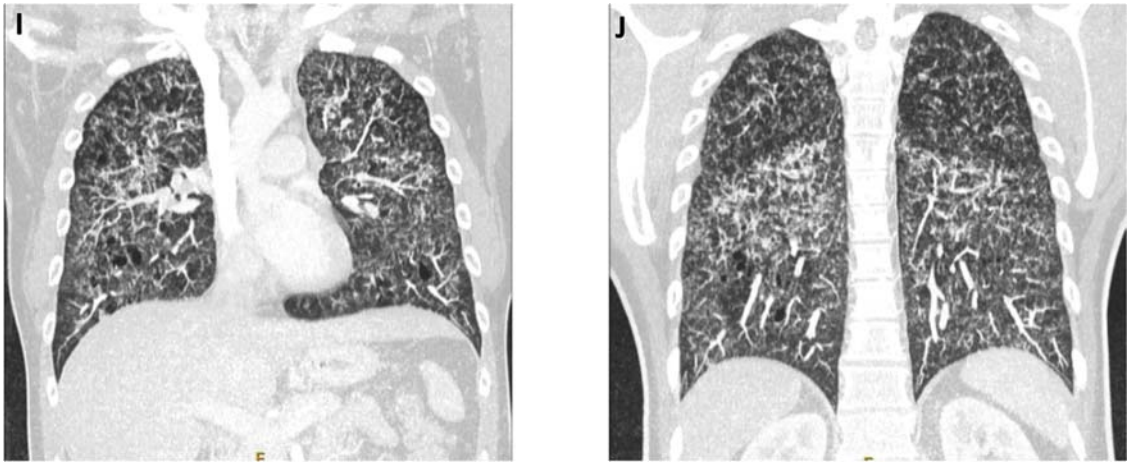

Fig. 2. Findings from HRCT at the time of consensus diagnosis of PLCH. Overall showing multiple bilateral innumerable and irregularly bizarre-shaped cysts with varying wall thickness. Ground glass opacities and reticulonodular patterns. Upper to middle zone involvement is more significant, no involvement of costophrenic angles. Multiple lymph nodes seen along the perivascular, paratracheal and hilar regions. Enlarged lymph nodes predominantly at the hilar and subcarinal region. A-D: Axial scan of upper to middle zone. E-H: Axial scan of middle to lower zone. I-J: Coronal scan.

Table 1. HRCT Findings associated with PLCH [1,2,4].

Early stages of PLCH	**Late stages of PLCH**
- Upper to middle lobe predominance, sparing of bases	- Upper to middle lobe predominance, sparing of bases
- Bronchiolocentric nodules (Frequently with "tree-in-bud" appearance)	- Thin-walled cysts of bizarre and irregular shapes
- Thick-walled cysts of various shapes (May be isolated or multiple with "cloverleaf" appearance)	- Typically, cysts more numerous than nodules by this stage
- Typically, nodules more numerous than cysts in this stage	
Common findings	
- Smoking related changes (Predominant upper lobe centrilobular emphysema with potential emphysematous bullae)	
- Bronchial wall thickening	
- Ground glass opacities	

nodules forming a serpentine sheath around smaller airways may be present. A mixture of other inflammatory cells would also be present. If further electron microscopic examination is carried out, Birbeck granules may be identified – a characteristic feature of LCs [1]. Late-stage disease involves fibrosis in the form of stellate scars or fibrocystic ring like cavities, LCs are usually absent by this stage. Immunohistochemistry can also be carried out to assess for presence of CD1a, langerin or S-100. It is crucial to note that the expression of S-100 is not specific to PLCH [1,2,5]. It is important to note that due to smoking being a key pathogenetic factor, histological findings such as bronchiolitis, desquamative interstitial pneumonia, respiratory bronchiolitis-interstitial lung disease and emphysema is not an uncommon histological finding [1-3].

The diagnosis of PLCH can be divided into a "definite" category or a "probable" category. The "definite" category requires a clinical picture in line with PLCH and the identification of LCs in biopsies which should be positive for langerin or CD1a. While the "probable" category should once again include a clinical picture but also radiological findings in line with PLCH as requirements [1-3]. Differential diagnosis of PLCH with such cystic changes on HRCTs can include pulmonary lymphangioleiomyomatosis, tuberous sclerosis, lymphoid interstitial pneumonia, Birt-Hogg-Dubé syndrome, and sarcoidosis – all of which were considered in this instance [1,3].

The diagnosis of PLCH in our patient falls under "probable" due to a negative immunohistochemistry while all HRCT findings were in line with PLCH. However, the diagnostic confidence greatly increased post discussion of his case on a state-wide level. The expected findings of smoking related histopathological changes were not seen, instead an unexpected NSIP pattern was observed. Radiological NSIP features were not observed on both prior HRCTs done. Furthermore, the likely differentials associated with an NSIP such as MCTD, drug-induced fibrosis, chronic viral infections and hypersensitivity pneumonitis were all excluded through history, examination, and investigations [1,6].

CONCLUSION

In conclusion, PLCH is an uncommon disease, as a result, the literature available for PLCH is limited. The peculiarity of this case lies in the two possible ways of diagnosing PLCH along with the possibility of a type of overlap pathology. In our knowledge, this is the first reported case of PLCH with histologically confirmed overlapping idiopathic NSIP fibrosis.

Ethics Approval and Consent to Participate

Full and written informed consent was obtained from the next of kin of this patient. This case report was conducted and written in accordance with the Townsville Hospital and Health Service Human Research Ethics Committee EX/2023/QTHS/102000 (Approved and endorsed on the 18th September 2023).

Consent for Publication

The patient has given a full and written consent in line for the publication of this case report which would include the use of clinical details, investigation findings, and various discussions which have occurred.

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Disclosure

The authors declare that they have no conflicts of interest.

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