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Case Report
Pulmonary Langerhans

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Pulmonary Langerhans Cell Histiocytosis in a young non-smoker – a rare case report.

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Pulmonary Langerhans cell histiocytosis (PLCH) is a diffuse cystic lung disease strongly associated with exposure to cigarette smoke. In recent times, activating pathogenic mutations in the MAPK (mitogen-activated protein kinase) pathway have been described in the dendritic cells in patients with PLCH. The outcome and disease course of PLCH are highly variable. Smoking cessation is the mainstay of treatment and can lead to disease regression or stabilization in a large percentage of patients. Further, the study of molecular pathogenesis of PLCH has anteceded the development of disease-specific biomarkers and targeted treatment options.

We present an interesting case report of a young non-smoker, asthmatic male with a definitive diagnosis of PLCH, clinically and radiologically. However, the classic features of Langerhans cell histiocytosis (LCH) were not seen in histopathology. We wish to highlight that advanced cases of LCH may not always have a textbook histological picture. In the appropriate clinical and radiological setting, the pathologist must consider the possibility of LCH even if classic Langerhans cells are not seen. In this paper, we would like to present the features of LCH, in the advanced stage without classic presentation.

Keywords: Imaging, MAPK, Nodules, Pulmonary Langerhans' cell histiocytosis, Smoking

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Introduction

Pulmonary Langerhans cell histiocytosis (PLCH), an isolated form of Langerhans cell histiocytosis, is an uncommon cystic interstitial granulomatous lung disease.[1] It is invariably associated with cigarette smoking and this includes current and ex-smokers [2] and is rare in non-smokers.[1] It can spontaneously resolve or lead to the development of pulmonary hypertension and progression to terminal respiratory failure. Recently activating pathogenic mutations in the MAPK (mitogen-activated protein kinase) pathway have been described in the dendritic cells in patients with PLCH. Though smoking cessation is the mainstay of treatment, the study of the molecular pathogenesis of PLCH has anteceded the development of disease-specific biomarkers and targeted treatment options.

Case :

An 18-year-old male presented to the hospital in March 2024 with complaints of left-sided chest pain for 2 months, and dry cough for many years with a history of recurrent pneumothorax and ICD insertion. Physical examination showed only weakened breathing sounds and wheezing during lung auscultation. He has a known case of Bronchial Asthma, on bronchodilators for 13 years, and also has a known case of coeliac disease and is on a gluten-free diet.

There was no history of pulmonary TB/ATT and COVID.

Spirometry showed very severe impairment of lung function and very severely reduced vital capacity. (FEV1+ 26%).

Radiological findings:

Chest Radiograph showed bilateral COPD changes and fine reticulonodular infiltrates.

CT showed multiple cystic lesions in both lung fields, diffuse areas of mosaic attenuation with few areas of interlobular septal thickening. It also showed multiple variable-sized centrilobular nodules with irregular margins. Few of them show central margins.

Imaging manifestations of nodules, cavitating nodules, and thick-walled or thin-walled cysts prompted suspicion of PLCH.

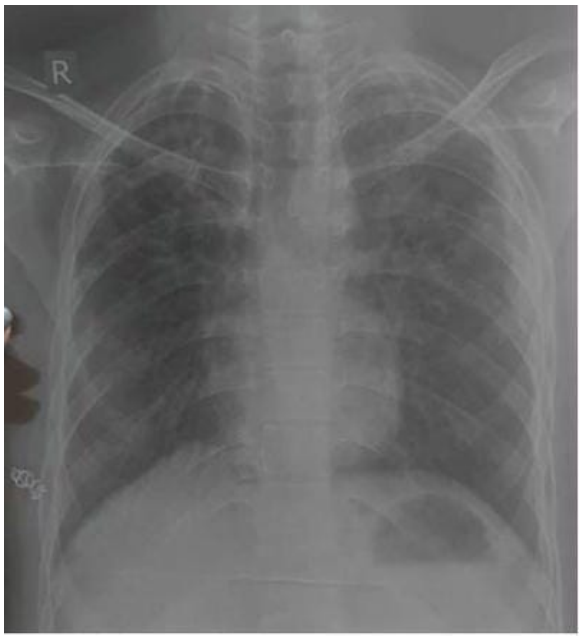

Fig 1: Chest Radiograph showed bilateral COPD changes and fine reticulonodular infiltrates.

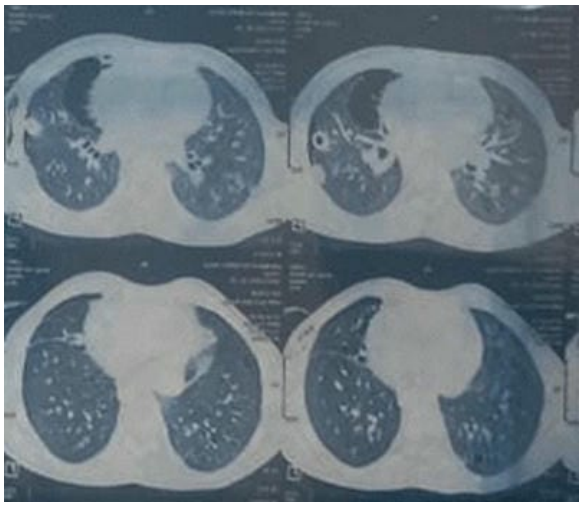

Fig 2: Chest computed tomography (CT) showed multiple cystic lesions in both lung fields, diffuse areas of mosaic attenuation with few areas of interlobular septal thickening. It also showed multiple variable-sized centrilobular nodules with irregular margins. Few of them show central margins.

A right lung upper lobe wedge biopsy was done.

Histopathological findings:

Gross: Single globular grey-brown wedge biopsy measuring 4.3 x 0.8 x 0.7 cm. One end showed a thin-walled cystic area. The external surface is smooth, grey-brown with an attached cystic area, cut surface is irregular grey-brown.

Microscopy: Sections showed a cyst wall with fibro-collagenous tissue, chronic inflammation, and blood clots. Other sections showed lung parenchyma with intra-alveolar histiocytes and septal breakdown, interstitial widening along with inflammation and fibrosis. Classic Langerhans cells with their vesicular chromatin and abundant pale cytoplasm were not identified, however, few areas show aggregates of histiocytes with few admixed eosinophils.

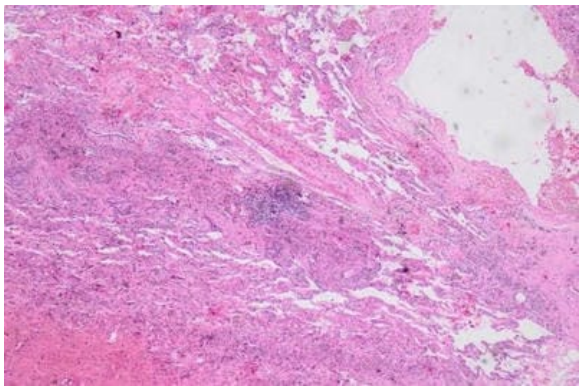

Fig 3: Fibrocollagenous tissue, chronic inflammation, and lung parenchyma.

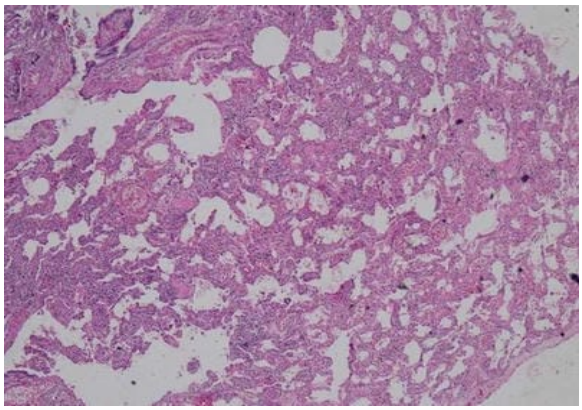

Fig 4: Septal breakdown, interstitial widening along with inflammation and fibrosis.

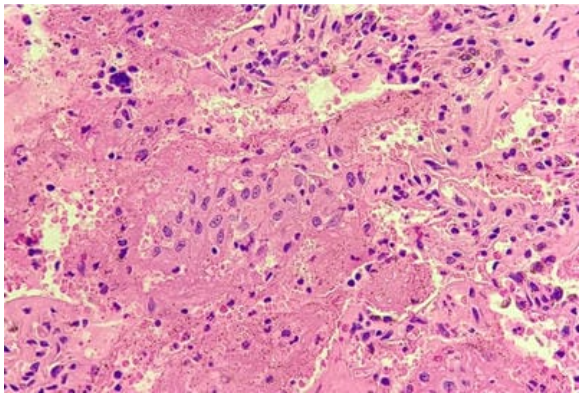

Fig 5: Lung parenchyma with intra-alveolar histiocytes.

Discussion

Pulmonary LCH (PLCH) is included in the group of rare pulmonary diseases. The prevalence of PLCH is unknown but may account for about 3%–5% of all adult diffuse lung diseases.[3]

The exact prevalence of PLCH might be higher than estimated in earlier studies because it can be asymptomatic, remit spontaneously, and might be difficult to identify in advanced forms. Although cigarette (tobacco) smoking and second-hand smoke-related PLCH have been described, their association with non-cigarette smoke (NCS) is extremely rare.[4]

Lung involvement is observed in multisystem LCH irrespective of the smoking status.[5]

The clinical presentation of PLCH can manifest either as chronic symptomatic PLCH with respiratory and constitutional symptoms or as spontaneous pneumothorax. Patients can also be asymptomatic with abnormal radiology in 10-25% of cases.[6,1] It may be bilateral and recurrent.

HRCT of the thorax is mandatory for every suspected case of PLCH and findings depend on the stage of the disease.[1]

In the early florid stage, nodular lesions predominate. The nodules vary in number and diameter (1–10 mm). They are stellate or peripherally irregular. In the advanced stage, fibrotic changes are seen with irregular, bi-lobed, cloverleaf, branched, or bizarre cysts.[7,8]

PFT in PLCH can be either normal, obstructive, restrictive, or a mixed pattern and usually depends on the stage of the disease and the extent of cystic involvement in HRCT.[9]

CD1A, S100, and langerin (CD207) are characteristic immunophenotype expressed.[10]

At present, there is no definite treatment for PLCH. The first therapeutic approach recommended for patients affected by PLCH is smoking cessation. [11,12]

Corticosteroids are the second line of treatment, after smoking cessation. Cytotoxic drugs (*e.g.*, vinblastine, methotrexate, cyclophosphamide, and etoposide) are also used to treat progressive PLCH. Cladribine (2-chlorodeoxyadenosine), a purine nucleoside analogue, has been reported to induce

Remission or improve lung disease in several PLCH cases.[12,13]

Conclusion

PLCH is a rare pulmonary cystic disease. It is diagnosed clinically, radiologically, and with histopathological correlation, but all the classic histopathological findings (including stellate nodules, with interstitial scarring and aggregates of Langerhans cells) are not always present. Older fibrotic lesions have fewer Langerhans cells and eosinophils and more fibrosis. At present, there is no definite treatment for PLCH. Smoking cessation and limiting exposure to all kinds of smoke is advised and usually leads to the resolution of the disease. A trial of corticosteroids may be considered in persistent symptomatic progressive disease before switching to second-line therapy, which includes cladribine and BRAF inhibitors for the treatment of aggressive PLCH.

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