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Pulmonary Histiocytosis with Use of Chewing Tobacco (*Misri*) Causing Pulmonary Hypertension in Western India: A Rare Case

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Abstract: A 55 year old Female non-smoker presented with progressive shortness of breath for last 8 months. There was no significant past medical history. On physical examination, she was ectomorphic, febrile and dyspnoeic with respiratory rate of 34/min; not cyanosed but pedal edema was present. Respiratory Examination reveals use of accessory muscles of respiration & widespread crepitations and wheezes over both lungs. CVS Examination show right ventricular lift, loud second heart sound with accentuated pulmonic component and tricuspid regurgitation murmur on auscultation. All blood tests were normal. Chest X-ray showed non-specific interstitial infiltrates bilaterally. High resolution CT scan was consistent with reticulo-nodular and cystic changes in upper and middle lobes and ground glass appearance in posterior basal lobes of lungs. There was mix obstructive and restrictive pattern on pulmonary function tests. Surgical Lung biopsy was taken which confirmed Pulmonary Langerhans cell histiocytosis. Patient was advised to stop smoking and started on medical management. Unfortunately patient lost follow up and presented again with worsening symptoms and clinical signs of right sided heart failure. Echocardiography showed severe pulmonary hypertension. Patient was started on treatment for pulmonary hypertension which made little symptomatic improvement but her symptoms got worsen over time and is now being considered for lung transplantation. Learning points/conclusion: Pulmonary function tests may be of normal, obstructive, restrictive or mixed pattern as is the case with our patient. Pulmonary hypertension is a common and under recognized complication due to direct vasculopathy (arterioles but predominantly venules) and can occur at any time during course of disease as it may or may not co-relate with lung function abnormalities and severity of parenchymal involvement. Investigations for pulmonary hypertension should be done early to prevent unnecessary delay in management.

Keywords: Pulmonary langerhans cell histiocytosis; Pulmonary hypertension; Langerhans cell histiocytosis; Obstructive and restrictive lung disease; Rare cause of dyspnea; Reticulonodular; Cystic lung disease.

INTRODUCTION

Pulmonary Langerhans cell histiocytosis (PLCH), also called eosinophilic granuloma of the lung, pulmonary Langerhans cell granulomatosis, and pulmonary histiocytosis X, is an uncommon interstitial lung disease that primarily affects young adults[1,2]. The true incidence and prevalence are unknown. However, the diagnosis is made in less than 5 percent of lung biopsies and has been seen in less than 2 percent of the patients in Interstitial Lung Disease. No occupational or geographic predisposition has been reported, but nearly all affected individuals have a history of current or prior cigarette smoking. Thus, tobacco smoke is thought to be an etiologic factor [3].

Chewing tobacco (*Misri*) is very common addiction in western India especially among women because it can be done without anyone noticing it, unlike in smoking and paan chewing. Pulmonary Langerhans Cell Histiocytosis (PLCH) is a comparatively rare disease and its diagnosis is frequently missed due to other common conditions causing similar clinical presentation[4].

The main objective of writing this case report is to highlight its differential diagnosis in a chewing tobacco (*misri*) user presented with breathlessness and

we report a case of PLCH in a misri user which has not been reported earlier.

A lot of studies have been done on PLCH but any relationship between severity of pulmonary hypertension and impairment of pulmonary function tests is difficult to formulate in contrast to other chronic pulmonary diseases[5].

CASE REPORT

A 55-year old female patient presented with gradual onset of breathlessness for last 8 months. There was no significant occupational, past, medical or family history other than *misri* use. The preliminary X-ray of chest showed reticulonodular opacification in all lung fields bilaterally (Figure 1). She was advised to quit *misri* and put on Metered Dose Inhalers (MDI) by her General Practitioner who then referred her to chest physician for further investigations and management.

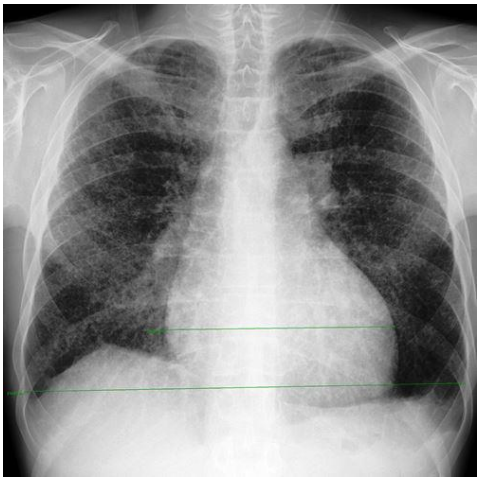


Fig-1: Diffuse reticular and cystic changes typically sparing costophrenic angles

On examination, she was ectomorphic in built, febrile with Temperature of 101ºF and dyspnoeic with Respiratory rate of 34/min, not cyanosed with SaO2 is 92% on room air but pedal edema was present.

Respiratory Examination - She had signs of respiratory distress with use of accessory muscles of respiration & widespread crepitations and wheezes over both lungs.

CVS Examination - She had right ventricular lift, loud second heart sound with accentuated pulmonic component and tricuspid regurgitation murmur on auscultation.

She was admitted for further workup and given inhaled Short acting (salbutamol) initially then Long acting β2 agonist bronchodilators (formoterol), anticholinergic agents, antibiotics and corticosteroids (inhaled as well as parenteral) as provisional diagnosis of Acute Exacerbation of ILD was considered.

But above treatment failed to show any improvement in her condition

Her High-resolution CT scan chest showed multiple nodules and thick wall cysts of differ in size and shapes (Honeycomb Pattern) bilaterally in upper and middle lobes without involvement of basal region on posterior aspect. Centri-lobular ground glass attenuation is showed in basal regions (Figure 2).

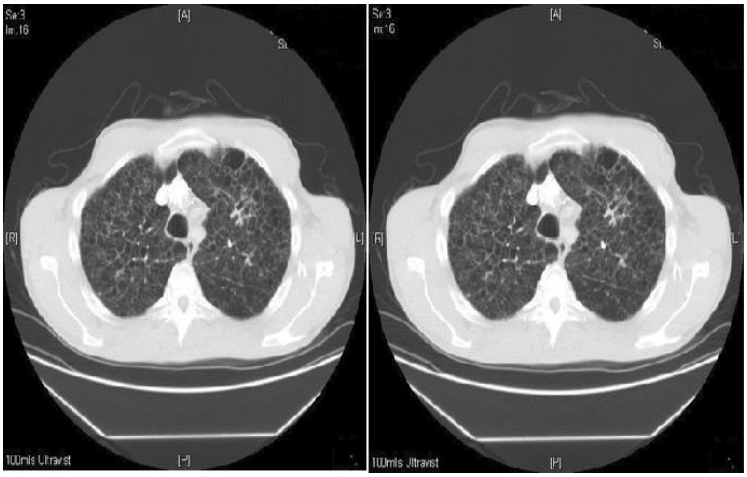


Fig-2: hrct chest showing bilateral cystic changes and scattered nodularity with an upper lung predominance and sparing of the costophrenic angles

As a part of further workup Pulmonary Function Test (Spirometry) was performed that showed:

FVC = 2.72 litre (120% predicted)
FEV1 = 1.92 litre (62% predicted)
FEV1/FVC = 70.59 (52% predicted)
FEF 25-75% = 232 L/min (27% predicted)
PEFR = 730 L/min (18% predicted)

Based on history, radiological findings and PFT, differential diagnosis of Pulmonary Langerhans cell Histiocytosis, Centrilobular Emphysema, Lymphangiomyomatosis (LAM) and Nonspecific Interstitila Pneumonia (NSIP) was considered.

Results from routine laboratory testing and HRCT are nonspecific and as above investigations doesn't reveal any definitive diagnosis, invasive test like surgical lung biopsy was advised which will be confirmed on immunohistochemistry.

PLCH was finally confirmed on surgical biopsy of lung and supported by positive immunohistochemistry for S100 and CD1a markers

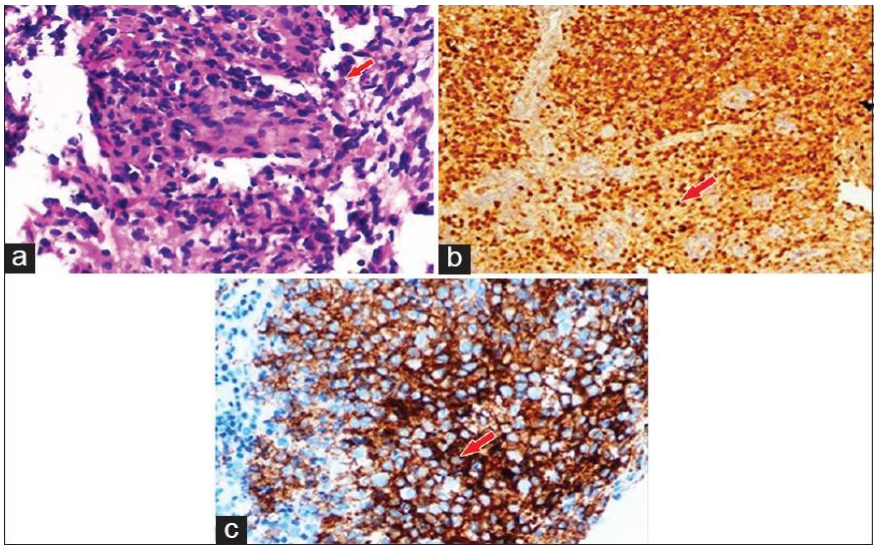
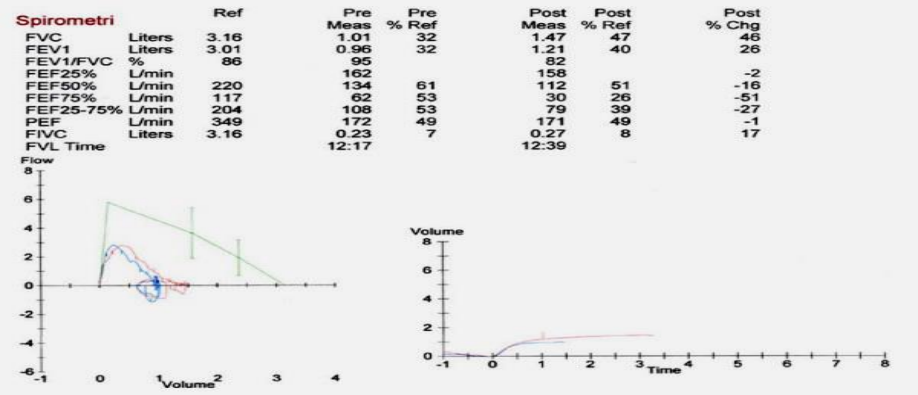


FIG-3: Microphotographs of lung biopsy of the case of plch

a) Large mononuclear pale staining cells with ill-defined cellular margins, Langerhans cells interspersed with inflammatory cells are seen on microscope.
b) Immunohistochemistry showing presence of Langerhans cell S100 protein.
c) Immunohistochemistry showing presence of Langerhans cell CD1a antigen

Patient was then started on treatment with long acting inhaled β2 agonist bronchodilators (formoterol) and inhaled as well as oral steroids with anticholinergic agents and advised to quit using *misri* to slow the progression of disease. But she was not compliant on treatment and again presented with worsening of symptoms. Physical examination at time of presentation now showed clubbing; Loud wide split P2 and raised jugular venous pressure.

Repeated Spirometry was worse than previous ones which show Restrictive Patten of Lung disease
FVC = 1.01 (32% predicted)
FEV1 = 0.96 (32% predicted)
FEV1/FVC = 95%
FEF 25-75% = 108 L/min (53% predicted)
PEFR = 172 L/min (49% predicted)



2 D Echocardiography showed dilated right ventricle and D-shaped LV cavity due to bulging of septum into LV cavity with grade 2 diastolic dysfunction and mild systolic dysfunction.

Pulmonary Artery Systolic Pressure: 74 mmHg (Normal: 12 – 16 mmHg)

Mean Pulmonary Artery Pressure: 46 mmHg (Normal: 10 – 20 mmHg)

Treatment for pulmonary hypertension with endothelin receptor antagonist, Bosentan and phosphodiesterase-5 inhibitor, Sildenafil was started which lead to some improvement in patient's symptoms.

DISCUSSION

Pulmonary Langerhans cell histiocytosis (PLCH) is also called Histiocytosis X or Eosinophilic granuloma of lung, is an uncommon interstitial lung disease that is epidemiologically related to tobacco smoking. It chiefly affects young adults, primarily occurring in the third or fourth decades of life[6].

The use of tobacco without burning is referred to as smokeless tobacco (SLT). Smokeless tobacco is taken in several forms e.g. snuff/naswar (finely ground tobacco leaves), chewing tobacco (loose and sweetened tobacco leaves), zarda/kiwan (paste), paan (betel quid) and khaini/mawa (tobacco with lime)[7]. Prevalence of smokeless tobacco use is 26% which is far greater than smoking 14% among adults as reported by Global adult tobacco survey report of India [8].

In our case, the mean value of all the pulmonary function tests (PFT) parameters was decreased. A study showed that impaired PFT in chewers had shown a highly significant ($p<0.001$) reduction in FEF 25-75% & PEFR and a significant ($p<0.05$) reduction in FVC and FEV1[9].

Chest radiographs in our patients with Pulmonary Langerhans cell histiocytosis X (PLCH) characteristically reveal bilateral, symmetric, ill-defined nodules and reticulonodular infiltrates. As the disease progresses, cystic lesions appear. An upper-zone predominance of radiographic findings with sparing of the costophrenic angles is typically observed.

HRCT of the chest may be virtually diagnostic in the appropriate clinical setting. Pathognomonic findings include nodules and cysts, predominantly in the mid and upper lung zones, with sparing of the costophrenic regions. The nodules may be cavitary and variable in size. Likewise, the cysts may be of various diameters and wall thicknesses. A broad differential diagnosis must be considered in the following situations.

When cysts are an isolated finding, Lymphangiomyomatosis (LAM) must be considered as well. Unlike PLCH, cysts of LAM are uniform rather round than irregular as in PLCH while predominance of cysts in upper and middle lobes, sparing of the costophrenic angles again favouring the diagnosis of PLCH.

Centrilobular Emphysema is usually distinguishable, as walls do not surround the cystic spaces found in emphysema. However, extensive emphysema is sometimes difficult to differentiate from PLCH. But the disease generally tends to affect elderly population and lacks nodularity on imaging. Combination of nodules and cysts typically in upper and middle lobes are sufficient to consider about PLCH.

Nonspecific Interstitial Pneumonia (NSIP) most commonly found in women who never smoke. Chest radiography findings are frequently abnormal in patients with fibrotic lung disease and reticular and/or nodular opacities are the hallmark. On HRCT, linear reticular opacities are the most common findings. A ground-glass pattern is less common and honeycombing is rarely present, which also favours towards PLCH.

Pulmonary Hypertension is an important but often missed complication of PLCH, which can develop early in the course of disease. It develops due to direct vasculopathy (arterioles but predominantly venules) and can occur at any time during course of disease as it may or may not co-relate with PFTs and severity of parenchymal involvement. Its diagnosis is often delayed due to poor correlation with disease severity[4].

Below two studies which shows how Pulmonary Hypertension (PH) as a complication of PLCH is associated with increased mortality.

- First study demonstrated the remarkable response of PLCH related PH to vasodilator therapy. Patient then offered combination therapy of endothelin receptor antagonist, Bosentan and phosphodiesterase-5 inhibitor, Sildenafil. After 10 years, significant Echocardiographic and functional class improvement was seen[10].
- In Second study, 29 patients with PLCH with PH having mean Pulmonary Arterial Pressure (mPAP) of 45 ± 14 mmHg. Use of PAH therapy in 12 patients was followed by an improvement in mPAP. PAH therapies improved hemodynamics without oxygen worsening or pulmonary edema[11].

CONCLUSION

With the recent advances in research and updates, we can effectively understand the prevalence of PH associated with PLCH. Early diagnosis of PLCH in misri user who presented with typical features of PH can reduce mortality and can improve quality of life.

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