Case Report

Lymphangiomyomatosis : Rare Cases of Cystic Lung Disease

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Lymphangioleiomyomatosis (LAM) is a rare multiple cystic lung disease of unknown etiology that traditionally affects young women of child bearing or premenopausal age. It is characterized by proliferation of atypical smooth muscle cells, preferentially along bronchovascular structures that causes progressive respiratory failure. Due to its unusual and nonspecific presenting symptoms, patients often receive missed or delayed diagnosis. Diagnosis is made by a combination of clinical features and computed tomography scanning specially High resolution CT of Thorax (HRCT) or, in cases of doubt, lung biopsy. In patients with rapidly progressive disease, hormone treatment (predominantly progesterone) is tried. The only treatment for severe LAM is currently lung transplantation.

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Key words **: Lymphangioleiomyomatosis (LAM), HRCT, Progesterone.**

Pulmonary Lymphangioleiomyomatosis (LAM) is a rare hamartomatous proliferation of smooth muscle induced in blood vessels and lymphatics in the lung[1,2]. It extends into the pulmonary interstitium leading to diffuse thin walled cystic lesions and pulmonary hemorrhage and lymph node involvement which may result in chylous effusion[3].

LAM is a multisystem disorder that may also result in extrapulmonary manifestations such as angiomyolipomas and lymphatic tumours. It predominantly occurs in premenopausal women but can also present in postmenopausal women.

Clinically, LAM is characterized by progressive dyspnea with exertion, fatigue, chronic cough, wheezing and chest pain, complications of spontaneous pneumothorax and chylothorax; pulmonary function tests (PFTs) usually show an obstructive and/or mixed restrictive/obstructive pattern with air flow limitation and impaired lung diffusion.

Chest radiography show diffuse interstitial infiltrates and high resolution computed tomography (HRCT) usually reveals thin walled cystic lesions, distributed in diffuse manner.

There are various therapeutics modalities for LAM with differing efficacy and lung transplantation remains the only therapeutic option for patients with advanced disease.

Case Report

Case 1 :

A 36 year Hindu female of Tripura presented with history of progressive breathlessness on exertion of last 3 year duration. No history of seasonal variation, cough, wheezing, chest pain, paroxysmal nocturnal dyspnea, hemoptysis or fever. No history of Tuberculosis. She is non-diabetic and non-hypertensive. She was treated as bronchial asthma for the last 3 year.

On examination patient was averagely built and nourished. All the vitals were in normal limits. Patient was hypoxic and cyanosed, but improved with oxygen supplementation. Clubbing was absent. Respiratory system examination was unremarkable except bilateral basal crepitations and diminished vesicular types of breath sounds. Cardiovascular system examination did not reveal any abnormality. Other systems were essentially normal. All the routine blood investigations were not significant. Antinuclear antibody (ANA) and human immunodeficiency virus (HIV) test were negative.

Her chest radiograph was suggestive of bilateral extensive reticulonodular pattern with cystic changes (Fig 1) High resolution computed tomography (CT) thorax (Figs 2&3) showed multiple thin walled cysts scattered bilaterally with areas of interseptal thickening. It also showed mediastinal lymphadenopathy. Spirometry showed obstructive pattern with increased lung volumes and reduced diffusion capacity (DLCO). Arterial blood gas revealed pH 7.35, PaO_2 59 mmHg, $PaCO_2$ 30.3 mmHg, and O_2 saturation 68%. The diagnosis was confirmed on the basis of classical high resolution CT(HRCT) findings. In view of severe hypoxia invasive procedure like bronchoscopy was not done.

The subject was put on oral progesterone with O_2 therapy. She showed good improvement in oxygen saturation and was discharged with oral progesterone and domiciliary oxygen supplementation.

Editor's Comment :

- **Pulmonary lymphangiomyomatosis (LAM) is a rare cystic lung disease of premenopausal women.**
- **HRCT Thorax is a good modalities non-invasive investigation to diagnose LAM.**
- **LAM can be treated with progesterone for improvement of Oxygen saturation though there is no structural changes in the lung.**

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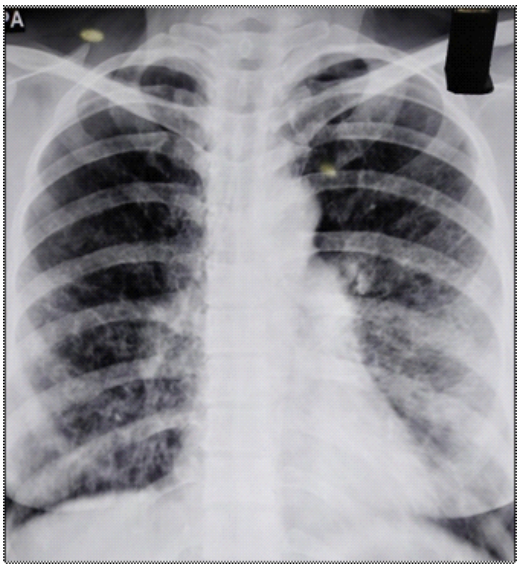

Fig 1 — CXR suggestive of bilateral extensive reticulonodular pattern with cystic changes

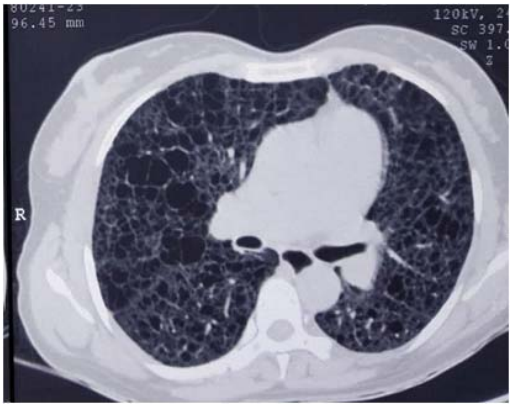

Fig 2 — Sagital section of HRCT Thorax showing multiple thin walled cysts

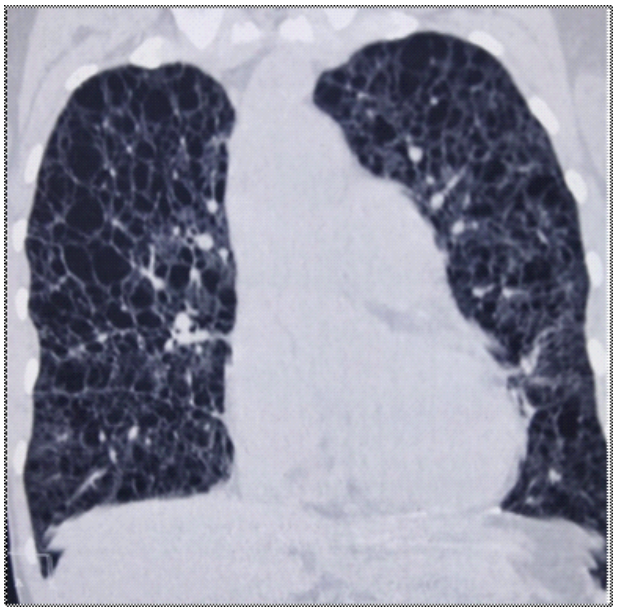

Fig 3 — Coronal Section of HRCT Thorax showing multiple cysts and interseptal thickening

The case was reviewed after 6 months. There was significant improvement in dyspnea, spirometry, and arterial blood gas values. However, radiological features remained stationary with no deterioration.

HRCT can often confirm the diagnosis and tissue diagnosis may not be necessary. HRCT findings suggestive of LAM are small, thin walled, air containing cyst ranging from 2-20 mm or more in diameter scattered throughout the lung fields.

Case 2 :

A 44 year old Hindu, smoker female from South Tripura, presented to the casualty department with 3 days of high grade fever and progressive shortness of breath with dry cough and mild chest pain on deep inspiration. She had no history of seasonal variation, hemoptysis, paroxysmal nocturnal dyspnea, tuberculosis or such contact. No history of diabetes or hypertension. She is treated as chronic obstructive pulmonary disease for past 8 years. She had history of menorrhagia due to leiomyoma which lead to her hysterectomy 1 year back.

General physical examination revealed average Indian built with pallor, bilateral pitting pedal edema, raised jugular venous pressure without clubbing, cyanosis, lymphadenopathy and icterus. Clinically, she had tachycardia, tachypnoea with decreased O_2 saturation which improved moderately after oxygen supplementation.

Her respiratory system examination revealed prominent accessory muscles of respiration, diminished chest expansion with bilateral hyperresonant notes of percussion and bilateral coarse crackles with wheeze. Cardiovascular system examination revealed apex beat at 6th intercostal space 3 cm lateral to mid clavicular line with loud P_2, low pitched ejection systolic murmur in pulmonary area, with otherwise normal findings. On per abdominal examination, liver was just palpable and soft in consistency with tenderness on palpation and on other organomegaly or palpable masses.

All routine blood investigations were normal other than

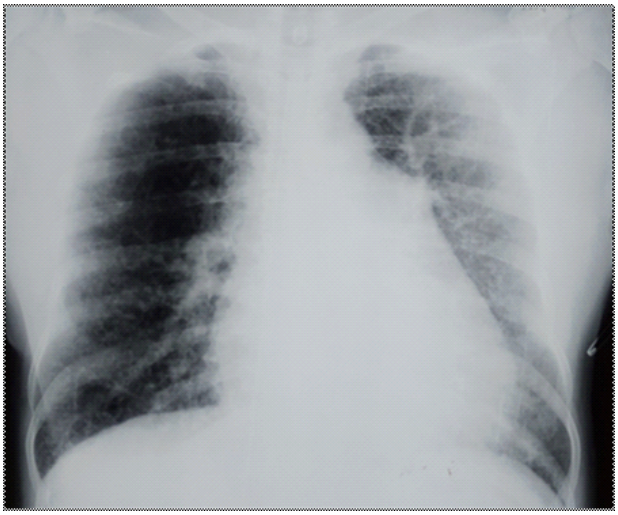

Fig 4 — CXR Bilateral Gound Glass Appearance with Cardiomegaly

iron deficiency anemia. Anti nuclear antibodies test was negative.

Electrocardiogram showed sinus tachycardia; chest X ray showed bilateral diffuse ground glass opacities with honeycombing and cardiomegaly and straightening of left heart border with fullness of pulmonary conus and bilateral hilar lymphadenopathy(Fig 4). 2D echocardiography confirmed pulmonary hypertension without any evidence of regional motion wall abnormalities and ejection fraction of 67%. PFT showed mixed obstructive and restrictive pattern with increased lung volumes and decreased diffusion capacity. Arterial blood gas (ABG) analysis suggested type I respiratory failure.

HRCT of thorax showed multiple thin walled cysts diffusely in both lung fields suggestive of bilateral cystic lung disease and features of fibrosis in right middle lobe along with bilateral hilar lymphadenopathy and bilateral lower lobe consolidation (Figs 5&6). These classical findings confirmed our diagnosis of LAM. Ultrasound of abdomen did not suggest any mass in liver or kidneys. Thoracoscopy could not be performed because of severe hypoxia and toxic condition of the patient.

Patient was initially treated with bronchodilators and intravenous antibiotics and oxygen therapy, resulting in improvement of her oxygenation status also her later ABG reports.

After recovery, oral pirfenidone and progesterone were started. Her daily oxygen requirement decreased drastically and was discharged with home nocturnal oxygen therapy. On 8 months follow up, her PFTs and ABG showed moderate improvements but radiographic findings however, showed no regression.

Discussion

LAM is a rare cystic lung disease that usually affects women of child bearing age and may present with developmental delay and cutaneous manifestations like ash leaf macules, shagreen patch and seizures when associated with tuberous sclerosis(30%). But it mostly occurs sporadically[1].

It may also be seen in postmenopausal women who present with progressive exertional dyspnea, chronic cough and spontaneous pneumothorax (57%) or chylothorax and is frequently associated with renal angiomyolipomas (32%)[3].

Clinical presentation greatly varies; ranging from chronic cough to hemoptysis(32%) to pleural effusion(12%)[3]. One study reported 40-80% of LAM patients can have recurrent pneumothorax[4]. These symptoms usually present in later stages of disease and therefore initially is often mistaken for reactive airway disease. Often these patients are misdiagnosed and treated with bronchodilators[5].

Pathologically, this condition is characterized by proliferation of immature smooth muscle cells derived from associated lymphatics. These smooth muscle cells infiltrate the walls of alveoli and bronchi with resultant air trapping and impaired gas transfer which may mimic emphysema[1,3]. Involvement of pulmonary venous vasculature may lead to hemosiderin deposition in lung parenchyma due to recurrent

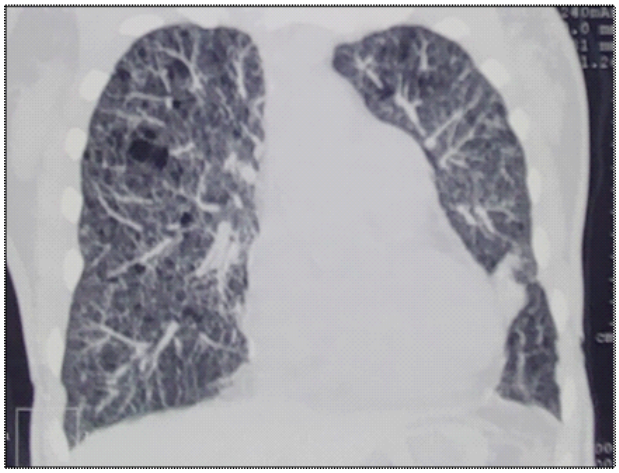

Fig 5 — Coronal Section of HRCT Thorax suggestive of bilateral cystic lung disease and features of fibrosis in right middle lobe along with bilateral hilar lymphadenopathy

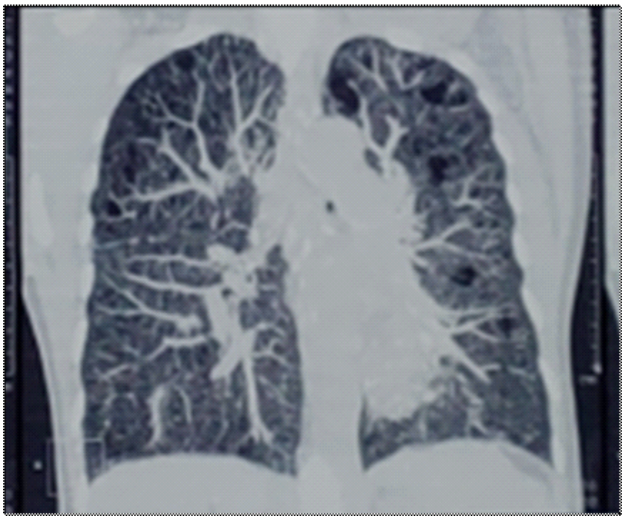

Fig 6 — Coronal Section of HRCT Thorax Suggestive of bilateral cystic lung disease and features of fibrosis

hemorrhage[4]. There are close histological parallels between LAM and pulmonary manifestations of tuberous sclerosis, although the hereditary condition effects both sexes and also has cutaneous and cerebral manifestations[5].

Radiographic findings often vary depending on disease severity and progression. Typically, chest Xrays show hyperinflated lungs due to obstructive nature of disease. Reticular pattern can also be seen in later stages due to coalescence of the cysts. This must be differentiated from Langerhans' cell histiocytosis, which may also present with similar symptoms and reticular pattern on chest X-ray[6]. It may also show ground glass appearance from hemosiderosis[7].

Concomitant with chest X-ray findings, PFTs with LAM is often obstructive or mixed pattern[5,7]. total lung capacity is often increased and residual volume to total lung capacity(RV/TLC) is also increased. Air flow is limited with decreased forced expiratory volume in first second(FEV1)[6].

disease progression can be best monitored with diffusion capacity and FEV1[8].

Cysts and bullae can be anatomically detailed on HRCT[6,17,18]. CT changes can vary from a reticular infiltrate to honeycombing with diffuse cysts depending on disease progression[10]. The diagnosis can be made with HRCT but in many cases tissue biopsy is obtained by various means. Besides taking tissue biopsy, Visually assisted thoracoscopic surgery(VATS) can also be implemented in cases of spontaneous pneumothorax as well. It can also be used for surgical wedge resection of apex of lung, pleural abrasion or chemical pleurodesis[15,16].

Diagnosis is confirmed with characteristic immunochemical stain that are specific for smooth muscle cells e.g. actin, desmin as well as melanocytic markers HMB45, HMSA1 and MELAN A[11]. Amongst them, HMB45 is the gold standard for atypical cells of LAM[11].

The fact that LAM presents predominantly in premenopausal women[1] and is shown to subside after menopause led to numerous studies to determine the role of estrogen in pathogenesis of LAM. However, no association has been established. Hence, there is no definite therapeutic strategies targeting the hormonal receptors[9]. According to latest evidence, even the first episode of pneumothorax in a case of LAM should be treated with pleurodesis since it opens the possibility of recurrent pneumothorax[3]. Bronchodilators are the mainstay of supportive measures initially. Some patients have been started on sirolimus, everolimus, which provides a median transplant free survival of approximately 29 years from the onset of symptoms and 10 years transplant free survival of 86%[12,13]. these therapeutic options are only disease stabilizing and not curative. Lung transplantation remains the last treatment resort for advanced LAM patients for survival[14].

The estimated prevalence of LAM is thought to be around one to 2.6 patients in 1,000,000 in the general female population[10]. Knowledge of LAM as a cause of chronic cough, spontaneous recurrent pneumothorax and especially in young females would be helpful for primary care physician for diagnosis. It is also necessary to understand that early cases are often treated as reactive airway disease or interstitial lung disease mistakenly. HRCT thorax alone can sensitively diagnose the disease, however, tissue biopsy remains the definitive diagnostic test.

The rarity of this cystic disease is a principal cause behind reporting the cases, as well as the efficient diagnosis without biopsy and the salient treatment measures. This case series is aimed to create awareness and better understanding of the disease.

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