Pulmonary Lymphangioleiomyomatosis - A Silent Killer?

Nandini Chakrabarti*, Manish Saha**, Bhaskar Basu#

Abstract

Pulmonary lymphangioleiomyomatosis (LAM) is a rare disorder presenting with remarkable features like recurrent pneumothorax or chylothorax, usually in young women. We report a case of sporadic LAM who presented with nothing but recent onset exertional dyspnoea and it was this unobtrusive presentation that led to delay in diagnosis.

Introduction

Pulmonary Lymphangioleiomyomatosis has a prevalence of 1-2 in a million. It belongs to the rarer group of interstitial lung diseases who have a more or less normal lung volume. The coexistence of obstructive features often tends to cloud the clinicians’ vision. Therefore, it was furthest from our minds when we first encountered our patient, who presented with progressive shortness of breath in the recent months.

Case Report

A 28 year old lady came to the OPD complaining of gradually progressive breathlessness for last eight months. Initially it was exertional in nature, but with time it had increased in intensity to hamper daily living. There was no history of cough, seasonal variation of symptoms, fever or haemoptysis. History of paroxysmal nocturnal dyspnoea, chest pain, palpitation, syncope, rheumatic fever or joint swellings were absent. Patient was non-diabetic and non-hypertensive.

On physical examination patient had average build and normal nutrition, mild pallor and normal vitals. No cyanosis or clubbing was present. Apart from a few basal crepitations and scattered rhonchi bilaterally, respiratory system examination was unremarkable. Cardiovascular system examination did not reveal any abnormality. Other systems were essentially normal. Routine blood examination showed Haemoglobin 9mg/dl, Blood Cell Count 12000/cc and Erythrocyte Sedimentation Rate of 64mm in 1st hour. Other blood parameters were found to be normal. Chest X ray was normal except a few basal infiltrates. The patient was put on antibiotics and bronchodilators but there was poor response even after seven days. We re-evaluated the patient and thought in terms of an ILD or a concealed cardiac anomaly. Echocardiography was normal. ANA and VCTC were negative. Pulmonary Function Test showed a mixed obstructive and restrictive pattern. High resolution CT scan of thorax (Figure 1) showed multiple thin walled cysts in apicoposterior and middle lobes of right lung and lingular lobe of left lung. We spared the patient further investigations by directly going for Video assisted Thoracoscopic surgery (VATS) and lung biopsy. Histopathology of that biopsy specimen (Figure 2) revealed alveolar spaces and interstitium with extensive haemorrhage. Cystic spaces were seen in interstitial tissue. There were also many blood vessels which had thickened smooth muscle wall. The interstitium showed proliferation of spindle cells and infiltration by few polymorphs, lymphocytes and pigment laden macrophages. The final diagnosis was pulmonary lymphangiomyomatosis. We sent the specimen for HMB45, oestrogen and progesterone receptor, they were found to be negative.

The patient and her party were informed about the prognosis of the disease and she was advised for single lung...
transplantation. As they did not agree, we discharged the patient on regular follow up.

**Discussion**

On encountering the patient at first, we were looking for either a congenital or valvular heart disease or at best an interstitial lung disease in the background of connective tissue disorders. However, preliminary clinical examination and initial investigations failed to give us any direction. The mixed obstructive and restrictive pattern on PFT prompted us to go for the CT Thorax which led to the diagnosis.

Pulmonary Lymphangioleiomyomatosis may occur sporadically (sLAM) or in association with tuberous sclerosis (TSC-LAM). sLAM is exclusively found in females of childbearing age. The mean age onset is 36 years. The first case was described by Cornog and Enterline in 1966.3

The tumor suppressor genes TSC1 and TSC2 have been implicated in the etiology of LAM, as mutations and loss of heterozygosity (LOH) in TSC2 have been detected in LAM cells. TSC1 encodes hamartin, with a postulated role in actin cytoskeleton reorganization. TSC2 encodes tuberin, a protein with roles in cell growth and proliferation, transcriptional activation, and endocytosis.4 Loss of TSC gene function leads to activation of mammalian target of rapamycin (mTOR), and thereby, effects on cell size and number.5

The disease is characterised by nodular and diffuse proliferation of the smooth muscle cells in the lungs, lymph nodes and thoracic duct. Oestrogen plays an important role in the development of disease and its progression. Pathologically it is characterized by replacement of normal lung parenchyma by multiple small cysts, ranging from 0.1 cm to several cm in diameter. The interstitium is thickened with evidence of smooth muscle proliferation around and within the pulmonary lymphatic, venule and airways.

Clinical manifestations of LAM may be commonplace, like dyspnea, cough, chest pain, haemoptysis (leading to diagnostic dilemmas) or dramatic, like chylothorax, recurrent spontaneous pneumothorax, chylous ascites, lymphangioleiomyoma masses, chyluria, uterine fibroids, and lower-extremity lymphedema. Common extrapulmonary features are retroperitoneal adenopathy and renal angiomyolipomas in around 40% of patients.6

Diagnosis of lymphangioleiomyomatosis is done by open lung or thoracoscopic lung biopsy based on characteristic histological findings. Immunostaining with HMB-45, specific for smooth muscle components namely actin and desmin are being employed to improve sensitivity and specificity. High resolution CT thorax can often confirm diagnosis and tissue confirmation may not always be necessary. High-resolution CT finding suggestive of LAM are, small thin-walled, air-containing cysts ranging from 2-50 mm in a diffuse symmetric pattern. The cyst walls range from 2 mm to an almost imperceptible thickness. A recent Korean survey showed that LAM patients had increased sharply after 2004 and they cited increasing use of HRCT Thorax as primary factor. Screening for LAM by HRCT in nonsmoking women age 25-54 that present with SPTX (spontaneous pneumothorax) is being advocated as it seems to be cost-effective.7

The natural history of lymphangioleiomyomatosis is thought to be progressive with median survival of 8 to 10 years from the date of diagnosis. Therapy of LAM is still a matter of ongoing research but oophorectomy, progesterone (10mg/day) and more recently tamoxifen (20 mg/day) and LHRH analogues have been employed with some anecdotal support.8 Work has also been done with doxycycline with inconsistent results. Sirolimus and rapamycin are two options for ‘targeted therapy’ against mTOR.5 Lung transplantation offers the only hope for cure despite reports of recurrent disease in the transplanted lung.

Our patient has shown marked symptomatic improvement with progesterone therapy, doxycycline and bronchodilator. There has been no radiological deterioration as well. It is not known how long these simple, inexpensive drugs would hold good for our patient, it is this peculiar characteristic of this inexorably destructive disease that underscores the importance of diagnosing it early.

**References**