A Young Female with Lymphangioleiomyomatosis

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Received: June 24, 2017; Published: July 20, 2017

Abstract

Lymphangioleiomyomatosis (LAM) is rare and progressive pulmonary disorder that mainly affects females of childbearing age. It is divisible into sporadic and tuberous sclerosis associated forms. It is characterized by presence of multiple lung cysts. Progressive dyspnea, pneumothorax, chylous effusion are presenting features of LAM. It is complicated by pulmonary hypertension and respiratory failure. Here we describe a young female with sporadic LAM who was diagnosed quiet late in the course of disease and was treated multiple times for tuberculosis based on X-ray findings without microbiological evaluation. She had poor outcome.

Keywords: Lymphangioleiomyomatosis; Dyspnea; Cystic lung; Tuberculosis

Abbreviations

LAM: Lymphangioleiomyomatosis; ATT: Anti-Tuberculous Therapy; TB: Tuberculosis; HRCT: High Resolution Computed Tomographic; TSC: Tuberous Sclerosis; DLCO: Diffusion Capacity

Introduction

Multiple cystic diseases are rare but distinct pulmonary diseases. Lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis and folliculin gene-associated syndrome (Birt-Hogg-Dubé) constitute majority of these disorders [1]. History, clinical examination, and radiological evaluation specifically HRCT are important in making diagnosis of cystic lung disease. Here we describe a young female with probable diagnosis of LAM who had poor outcome.

Case Report

Twenty-seven years old female taking anti-tuberculous therapy (ATT) for pulmonary tuberculosis (TB) was admitted with worsening breathlessness and swelling of feet for three months. She had breathlessness on exertion from last ten years. Breathlessness was noted after an episode of chest infection that was characterized by cough, sputum and fever. It lasted for a week and improved with treatment from a general physician. Afterwards, she did not become fit as it used to be before. Breathlessness was initially on moderate to severe exertion, as the time passed, it progressed and limitation of activities started developing. For last three months, breathlessness had increased to such extent that she became breathless even on mild exertion. This had led to bed bound status. There was no diurnal/seasonal variation of breathlessness. She did not complain of hemoptysis, chest pain, palpitations, paroxysmal nocturnal dyspnea, and fever. No definite aggravating or relieving factors for breathlessness was there as far as environmental changes, allergens, bronchodilators and steroids are concerned. Breathlessness was accompanied by cough. It was mostly dry but occasionally associated with minimal amount of mucoid sputum. Swelling of feet was noted about three months back, it was increasing progressively.

It was third time that she was being treated with diagnosis of pulmonary TB in last 10. Review of record showed that, fever was never her main complaint and each time she was started on ATT based on radiological (chest X-ray) findings, when she was investigated for respiratory complaints. Microbiological evaluation of sputum for TB was always negative. She had been taking bronchodilators (oral, inhaled), steroids (oral, and inhaled), and antibiotics for the symptoms however relief was never obtained.

She was a house wife, married for five years. She was mother of 4-year-old daughter after whose birth she had three miscarriages. During hospitalization, she was noted to be pregnant. This time duration of pregnancy was 2 months. She never owned a pet animal or bird. One of her brother suffered from TB two years back but was alright after completion of ATT course. Except for this, family history was unremarkable.

Citation: Muhammad Khurram., et al. “A Young Female with Lymphangioleiomyomatosis”. EC Pulmonology and Respiratory Medicine 4.2 (2017): 41-45.
On examination she was emaciated, distressed, tachycardic (pulse rate 104/minute), tachypnic (respiratory rate 23/minute), and had pedal edema up to the lower half of legs. She was afebrile and her blood pressure was 100/70 mm Hg. Her jugular venous pulse was raised 6 cm above the manubero-sternal joint. Chest expansion was reduced bilaterally. Right ventricular heave was there. Percussion note was impaired throughout. Scattered inspiratory crackles were noted. Pulmonary component of 2nd heart sound was loud on auscultation. Her liver was 2cm palpable below right costal margin. Rest of clinical examination was unremarkable.

Her hemoglobin was 11.9g% and MCV 71.6 fl. Rest of complete blood count, liver/kidney function tests, and serum electrolytes were unremarkable. Her ESR was 45 mm. C reactive protein was in normal limit. CXR was suggestive of interstitial lung disease (Figure 1). High resolution computed tomographic scan (HRCT) chest (Figures 2) showed multiple thin walled, round, well circumscribed, 2 - 30 mm in size, and diffusely distributed cysts throughout the lungs with normal intervening lung. Some cysts had coalesced into larger bodies with near-complete replacement of the lung parenchyma which appeared patchy but normal outside these cysts. Ground-glass opacities, presumably from recurrent haemorrhage and relatively diffuse proliferation of immature smooth muscle cells were also noted. Areas of air trapping were found on expiratory films. Nodular lesions were rare. Spirometry showed restrictive pattern.

**Figure 1:** Chest X ray showing right pleural effusion and bilateral interstitial infiltrates.

**Figure 2:** Multiple thin wall, well circumscribed cysts on HRCT.
EG and echocardiography were suggestive of pulmonary hypertension. Dilated right atrium and ventricle and normal left side of heart were noted on echocardiography. Pulmonary artery pressure was 45 mmHg. Arterial blood gases were suggestive of type I respiratory failure. Work up for autoimmune/rheumatological diseases (AKNA, RA factor, anti dsDNA, anti-cardiolipin antibodies, antiphospholipid antibodies etc.) were negative. Serum lactic dehydrogenase and D dimers were normal.

Diagnosis of cystic lung disease, probable LAM complicated by pulmonary hypertension and respiratory failure was made. Patient was treated with steroids, and broad-spectrum antibiotics. She was administered oxygen and prophylactic heparin. Counseling for termination of pregnancy was done; long term oxygen therapy was planned. Patient was discharged on request when dyspnea partially improved after 5 days of hospitalization. Patient did not follow up and presented two months later with hypoxic respiratory failure and septic shock in emergency. She expired after short stay despite aggressive management in intensive care unit.

Discussion

LAM is progressive multisystem disease. It is of two types: 1) sporadic, and 2) associated with autosomally dominant genetic disease tuberous sclerosis (TSC-LAM). Proliferation of smooth muscle like cells in LAM lead to cystic destruction of lung interstitium [2]. Cysts are evenly distributed and filled with air or fluid that is either chylous or serosanguineous. LAM cells are noted in cyst wall which are spindle shaped or epithelioid along with bronchial and alveolar epithelium.

In LAM abnormalities of TSC1 and TSC2 genes are noted. TSC1 gene encodes hemartin and TSC2 encodes tuberin protein. Hemartin and tuberin control cell proliferation in response to growth factor stimulation. Hemartin and tuberin combine to form hamartin tuberin complex that inhibits mammalian target of rapamycin (mTOR). In LAM hamartin tuberin complex is not formed and mTOR pathway remains active. This lead to smooth muscle proliferation in lungs along with hamartoma formation in skin, kidney, and brain [3,4]. Sporadic LAM is caused by mutation of TSC 2 gene. TSC-LAM is caused by inactivating mutation of either TSC1 or TSC2 gene.

Females in reproductive age group are commonly affected by LAM [1]. Compared to in TSC-LAM which is commoner than sporadic LAM, males are also involved [1]. Slowly progressive breathlessness and non-productive cough are common presenting of LAM [5]. Other common pulmonary manifestations are spontaneous pneumothorax, pleural effusion and chylothorax. 3-5 years generally lapse between onset of symptoms and LAM diagnosis [1]. Patients are usually misdiagnosed as asthma or emphysema and this can lead to diagnostic delay. Pulmonary hypertension may develop in portion of patients after about mean nine years. It is caused by hypoxia and decreased pulmonary vascular capacitance [6]. Pedal edema in LAM patients develop as a complication of pulmonary hypertension. Rarely it may develop due to venous and lymphatic obstruction due to paracaval lymphangioleiomyomas [7]. Respiratory failure and cor-pulmonale may complicate LAM. 5-year survival varies from 50 - 97%. FITs, cognitive dysfunction and other hamartoma related features may predominate in TSC-LAM [1] Sporadic LAM patients can have renal hemartomatous lesion as well [3].

Plain chest X ray show hyperinflation, reticulonodular pattern, cystic appearance, or complications of LAM like pneumothorax and pleuon [1]. High resolution CT scan chest shows well circumscribed thin wall cyst which in advanced stages can involve the whole lung parenchyma. Cystic lung disease can be graded based on HRCT findings. Less than 10 cysts is considered minimal disease (Grade 0), involvement of less than one third of the lung is mild disease (Grade 1), involvement of one to two third of lungs is moderate disease (Grade 2), involvement of more than two third of lungs is severe disease (Grade 3). Most of the TSC-LAM patients have minimal or mild lung involvement as compare to sporadic LAM [8]. Mixed (obstructive and restrictive) pattern is generally noted on spirometry in LAM patients. Diffusion capacity (DLCO) is usually reduced. Diagnostic criteria for LAM are given in Table 1.

![Table 1: Lymphangioleiomyomatosis (LAM) diagnostic criteria [9].](image-url)

- a) HRCT features characteristic of LAM are multiple (>10) thin-walled round well-defined air-filled cysts with preserved or increased lung volume with no other significant pulmonary involvement specifically no interstitial lung disease with the exception of possible features of multifocal micronodular pneumocyte hyperplasia in patients with tuberous sclerosis. HRCT features are compatible with pulmonary LAM when only few (>2 and ≤10) cysts are present
- b) Diagnosed by characteristic CT features and/or on pathological examination
- c) Based on visual and/or biochemical characteristics of the effusion
- d) Based on pathological examination.
- e) Compatible clinical features include pneumothorax (especially multiple and/or bilateral) and/or altered lung function tests as in LAM

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Pulmonary rehabilitation, influenza and pneumococcal vaccination is advised to all LAM patients [9]. About 20% of LAM patients show positive response to bronchodilators on spirometry [10]. Patients with LAM are usually young population and they qualify for pulmonary rehabilitation. Long term oxygen therapy is prescribed to those patients who fulfill its standard criteria [3]. Oral contraceptive use and pregnancy lead to worsening in LAM. Oral contraceptive should thus be avoided [10]. Role of anti-estrogens, progesterone and oophorectomy is controversial. Patients with pneumothorax are treated conservatively. For recurrent pneumothorax pleurodesis is done [11]. Thoracentesis, low fat diet, and pleurodesis are used for chylothorax treatment [12].

For patients with respiratory failure and poor quality of life, lung transplantation should be considered. As LAM affects the younger population, they are excellent candidates for transplant. Promising results of lung transplantation have been noted in LAM patients although there are chances of recurrence [3]. Sirolimus is an mTOR inhibitor and experimental studies are done in vitro which showed decreased progression of LAM cells. Matrix metalloproteinase inhibitor, doxycycline is also being considered for LAM treatment [3,10].

Criteria for probable not definite sporadic variety of LAM were fulfilled in our patient. Characteristics noted in her case are; 1) female gender, 2) child bearing age, 3) progressive shortness of breath, 4) development of pulmonary hypertension, cor pulmonale and respiratory failure, 5) delayed diagnosis, 6) pregnancy, 7) recurrent treatment for presumed tuberculosis (TB), and 8) non-fulfillment of definite LAM criteria. We may have further worked her up, however follow up was lost. Although in resource de deficient scenario like our lung transplantation is a remote possibility but earlier diagnosis may have helped her a lot. Although TB is common in our scenario treating it without microbiological evidence is inappropriate and leads to missing diagnosis as was there in our case.

Conclusions

Lymphangioleiomyomatosis is important cause of cystic lung disease that should not be missed. Earlier diagnosis may have altered the outcome in our patient. Diagnosis of tuberculosis should be based on microbiological and or histopathological evaluation.

Acknowledgements

Nil.

Conflict of Interest

Nil.

Bibliography


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*Volume 4 Issue 2 July 2017*

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