RARE LUNG DISEASE: LYMPHANGIOLEIOMYOMATOSIS

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ABSTRACT

Lymphangioleiomyomatosis (LAM) is an exceptionally rare disease involving pausal women. The etiology is unknown. Many organ systems are involved but generally patient present with pulmonary manifestations varying from simple cough to heamoptysis, recurrent pneumothoraces and even complicated pleural effusion. It may be associated with tuberous sclerosis. The wide range of symptoms and signs make the differential diagnosis vary extensive and the physician must be familiar with the disorder to arrive to the correct diagnosis. Treatment include estrogen ablatine therapies. Most patients eventually require lung transplant.

Here we report a case of a 28 year old lady whose initial symptoms were cough and dyspnea. Later developed pneumothorax bilaterally. She had a course of antitubercolous treatment before being diagnosed as case of Lymphangioleiomyomatosis. The relevant literature review regarding the case is also provided.

Key Words: Lung disease; Lymphangioleiomyomatosis; Peshawar; Pakistan

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INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a type of interstitial lung disease (ILD) characterized by hamartomatous proliferation of atypical smooth muscle along lymphatics in the lung, thorax, abdomen, and pelvis.[1] Proliferating smooth muscle cells may obstruct pulmonary venules (causing focal edema and pulmonary hemorrhage) or lymphatics (leading to chylothorax), or bronchioles causing airflow obstruction.[1] Destruction of alveolar parenchyma forms cysts, which are surrounded by immature smooth muscle. The walls of the cysts are typically < 2 mm thick.

LAM is exceptionally rare, with an estimated prevalence of 1 to 3 per million persons.[2] It affects exclusively women with the mean age of onset between 30 and 45 years. More than 90% of cases have been in premenopausal women. Several cases have been reported in postmenopausal women who are on hormone replacement therapy. Caucasians are afflicted much more commonly than are other racial groups.

Treatment including estrogen-ablative therapies e.g. oophorectomy, administration of antiestrogen regimens [e.g. progesterone, tamoxifen, androgens, lynestrenol]; luteinizing hormone–releasing hormone antagonists [e.g. goserelin]; gonadotropin releasing hormone agonists [e.g. leuprolide acetate]; and somatostatin. However, these therapies are of unproven benefit. Some case reports cited responses to interferon a2b and somatostatin, but the value of these modalities is unproven. Sirolimus, a macrolide with immunosuppressive properties, inhibits the activity of the mammalian target of rapamycin (mTOR), suppresses smooth muscle proliferation, and suppresses DNA synthesis of LAM cells in vitro is also used with some benifit.

CASE HISTORY

A 28 yrs old female from Afghanistan presented with gradual-onset of dyspnea, cough and fever for the last 7 months where she was treated as chest infection but with no benefit. Then she was started on anti-tuberculous therapy on the basis of chest x-ray findings. She presented to us after 10 days of ATT with additional symptoms of anorexia, nausea, vomiting. Past family and drug histories were not significant except that she had two spontaneous abortions & five alive, healthy kids. On Physical examination she had notable weight loss, jaundice, temperature of 101 ° F & slightly decreased breath sounds on lung bases

bilaterally. Radiologically she had small left side pneumothorax. Her blood smear showed Neutrophilic leukocytosis with raised bilirubin and ALT while other blood chemistry was normal. Sputum smears were negative for acid-fast bacilli and Montoux test was also negative. Ultrasound abdomen and pelvis was normal. Provisional diagnosis of ATT-induced hepatitis and ATT was discontinued temporarily. The patient was sent home on modified anti-tuberculous regimen and advised a follow up visit after 2 weeks but she defaulted After 3 months she presented with large bilateral spontaneous pneumothorax & was intubated bilaterally. She had broncho-pleural fistulae on both sides and lungs were slow to expand. High resolution chest CT scan was done to evaluate the underlying cause of bilateral persistent pneumothoraces. It showed ground glass densities, multiple thin-walled cystic spaces in both lungs and pneumothoraces on both sides. The differential diagnosis included lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis and cystic fibrosis. In the meanwhile we sent BAL fluid for HMB-45 stain which was positive.

When the lung failed to expand and there was persistent air leak even after 3 weeks, case was discussed with thoracic surgeon for possible surgical intervention, but as patient was not fit for GA having extensively diseased lung, a rather conservative approach was followed. Fortunately the lungs expanded after 2 weeks of incentive spormetery and negative suction. Pleurodesis was done on both sides and tubes were removed successfully.

Keeping in mind a female of child-bearing age with gradual onset dyspnea, cough and persistent pneumothoraces & the CT chest findings of ground glass densities, multiple thin-walled cystic spaces & pneumothoraces with positive HMB-45 staining, the most probable diagnosis of Lymphangioleiomyomatosis (LAM) was made. She was put on progesterone and showed good response and on follow up visit she had gained weight. However there was no clinical and radiological evidence of recurrence of pneumothorax.

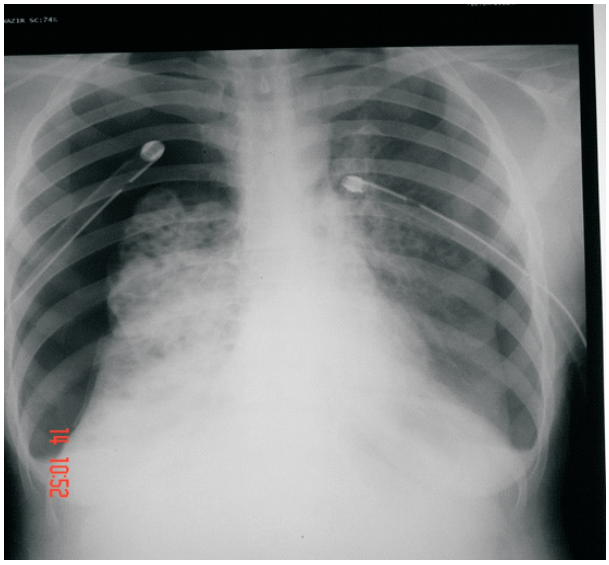
DISCUSSION

The exact etiology of LAM is unknown because it only affects women, estrogens likely play a key role in the pathogenesis. Exogenous or endogenous estrogens accelerate the course of the disease. Development or worsening in pregnancy is reported. Recent evidence suggests that LAM is a cancer resulting from biallelic mutations at a single genetic locus, resulting in unregulated growth of lymphatic's, vessels and tissue destruction. Unlike other forms of ILD, there is very little fibrosis in LAM.

The main symptoms are:

Dyspnea (73%), wheezing (47%), cough (31%), hemoptysis (34%), phlegm production (27%), and chyloptysis (7%), chest pain. The physical examination can be unrevealing or may disclose end-expiratory rales (22%), hyperinflation, decreased or absent breath sounds, and intra-abdominal or adnexal masses. Chylous effusions have been noted in 7 to 39% of women with LAM. Clinical features of spontaneous pneumothorax occurs in 50 to 80% of patients. The rate of recurrence is >70%, the highest among all chronic lung diseases. Recurrent pneumothoraces in women of childbearing age may be a clue to the diagnosis. Chyloperitoneum (chylous ascites) occurs in approximately 10% of patients. More rarely, chyluria (due to abnormal connections between dilated retroperitoneal lymphatics and the renal collecting system) and chylopericardium may also occur.[3-6] Clubbing is uncommon (<5%).Lower extremity lymphedema may also occur. Extrapulmonary Involvements are angiomyolipomas (AML) or cysts involving abdominal or retroperitoneal lymph nodes, spleen, kidney, periadrenal blood vessels, liver, uterus, and ovaries. An increased risk of renal cell carcinoma has been noted in patients with tuberus sclerosis complex (TSC) and angiomyolipomas.[7] The prevalence of meningiomas appears to be increased in patients with LAM and tuberus sclerosis complex, both are caused by mutations in the tuberous sclerosis genes, TSC1 and TSC2. Further, compared with sporadic LAM, patients with TSC-LAM have a lower incidence of abdominal lymphangioleiomyomas (9% vs 12%), thoracic duct dilation (0% vs 4%), pleural effusion (6% vs 12%), and ascites (6% vs 10%). Additionally, patients with TSC-LAM have a greater frequency of hepatic (33% vs 2%) and renal (93% vs 32%) AMLs, previous nephrectomy (25% vs 7%), and noncalcified pulmonary nodules (12% vs 1%). LAM & other features of TSC (that are not present in sporadic LAM) include seizures, facial angiofibromas, digital fibromas, periungual or ungual fibromas, sebaceous adenomas, depigmented skin lesions, sclerotic bone lesions, and cranial calcifications.[7-9] Plain chest radiographic changes in LAM are nonspecific and variable, ranging from normal early in the course of the disease to severe emphysematous like changes in advanced disease. Pneumothorax has been noted in 39 to 53% of patients at the time of presentation and occurs in approximately 80% of patients during the course of the disease. Reticulonodular infiltrates are evident in 47% to >85% of patients. Cysts or bullae are detected in 41 to 58% of patients. Radiological changes of hyperinflation develops as the degree of airways obstruction worsens, and may be seen in up to two thirds of patients late in the course of the disease.

Figure 1:

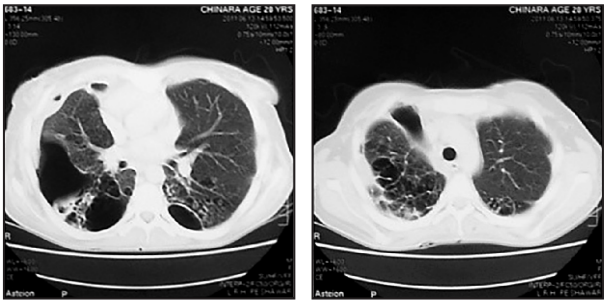


Pleural effusions occur in 7 to 39% of patients. Mediastinal and hilar lymphadenopathy are not features of LAM. Kerley B septal lines occur due to lymphatic obstruction. Both effusions & pneumothoraces can occur in the face of otherwise normal chest radiograph. HRCT Scans in LAM reveal numerous thin-walled cysts, ranging in size from a few millimeters to 6 cm throughout both lungs; intervening lung parenchyma is normal. In LAM, the cysts are distributed diffusely without predilection for specific regions or lobes. Cavitation is not a feature of pulmonary LAM. Nodules, interstitial fibrosis, or irregular lung-pleural interfaces features commonly observed in other chronic ILDs are absent or a minor feature in LAM. In HRCT scans ground glass opacities were noted in 12% (8 of 66) and 59% (22 of 37) of patients in two more recent series. Ground glass opacities may reflect foci of alveolar hemorrhage, pulmonary hemosiderosis, or diffuse proliferation of smooth-muscle cells. Abdominal CT may reveal (1). cysts or angiomyolipomas (AMLs) in the kidney, spleen, or pelvic organs or (2). retrocrural or para-aortic lymphadenopathy. Cysts, cavitation and sparing of the costophrenic angles may be observed in PLCH but are rare in LAM.

Pulmonary Function Tests early in the course of LAM may be normal. But the DLco is reduced in >65% of patients. An obstructive or restrictive ventilatory defect, often with air trapping, has been cited in 29 to 78% of patients.[10-11] Pulmonary arterial hypertension at rest in LAM is uncommon (<10% of cases) but may be elicited by exercise.

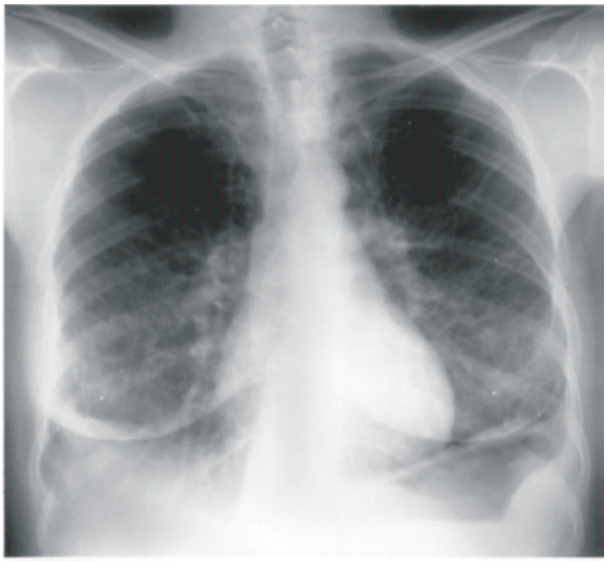
Immunohistochemical staining with Human Melanoma Black-45 (HMB-45), a monoclonal antibody derived from melanoma hybridomas that stains

Figure 2:



LAM cells has improved the usefulness of transbronchial lung biopsy in the diagnosis of LAM, provided that clinical and radiographic features (especially HRCT Lung) are consistent. Renal angiomyolipomas may also be positive for HMB-45 in LAM as well as Open Lung Biopsy, transbronchial lung biopsy, video-assisted thoracoscopic lung biopsy.[12-13] The diagnosis of LAM can be established without lung biopsy provided HRCT features are characteristic, clinical criteria are consistent, and any of the following features are present: typical renal angiomyolipomas, chronic chylous ascites with abdominal lymphadenopathy, or characteristic histopathologic findings on lymph node biopsy. However, serum vascular endothelial growth factor-D (VEGF-D) shows promise as a screen for pulmonary cyst development in women with Tuberus sclerosis complex. VEGF-D is increased more than threefold in the serum of patients with LAM and may prove to be a useful biomarker for LAM. No randomized or controlled studies have been performed that corticosteroids, immunosuppressive agents, cytotoxic drugs, and radiation therapy have role in LAM. Because LAM is exclusively a disease of

Figure 3:



women and appears to be exacerbated by estrogens, physicians should advise against pregnancy or the use of exogenous estrogens. Treatment include estrogen-ablative therapies (e.g. oophorectomy, administration of antiestrogen regimens [e.g. progesterone, tamoxifen, androgens, lynestrenol]; luteinizing hormone–releasing hormone antagonists [e.g. goserelin]; gonadotropin releasing hormone agonists [e.g. leuprolide acetate]; and somatostatin. However, these therapies are of unproven benefit. Anecdotal case reports cited responses to interferon a2b and somatostatin, but the value of these modalities is unproven. Sirolimus, a macrolide with immunosuppressive properties, inhibits the activity of the mammalian target of rapamycin (mTOR), suppresses smooth muscle proliferation, and suppresses DNA synthesis of LAM cells in vitro is under study. Recent studies found that simvastatin inhibits migration of human LAM cell cultures and inhibits LAM cell proliferation; furthermore, combined treatment with simvastatin and sirolimus abrogated cell proliferation to a greater degree than either agent alone. Bronchodilators and supplemental oxygen have adjunctive roles in selected patients with pulmonary LAM. Sildenafil or vasodilators have a theoretical role among patients with pulmonary arterial hypertension complicating LAM, but data are lacking.

Course and Prognosis of LAM: the natural history is one of progressive airflow limitation leading to respiratory failure, cor-pulmonale & death. However, the pace of the disease is extremely variable. In 1990, Taylor et al reported that 25 of 32 patients with LAM (78%) were alive a mean of 8.5 years after onset of the disease. Data from Asia cited survival rates of >70% at 5 years after the onset of LAM but only 38% (10 of 26 patients) at 8.5 years.

CONCLUSION

Pulmonary lymphangioleiomyomatosis is a rare cause of recurrent pneumothorax and should be considered a differential diagnosis, especially in young women with diffuse bilateral bullous emphysema.

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