

Pulmonary lymphangiomyomatosis

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ABSTRACT

A 38-year-old Iraqi female, presented with one-year history of exertional dyspnea and exercise intolerance, without systemic or constitutional symptoms. Clinical examination revealed bilateral basal crackles with signs suggestive of left side pleural effusion, chest x-ray showed left sided pleural effusion, and diffuse bilateral basal pulmonary shadowing. Her biochemical analysis, hematological tests, electrocardiogram and echocardiography were normal, aspiration of the fluid revealed a chylothorax, the radiological shadowing was proved by computed tomography scan of the chest to be diffuse cystic lesions involving mostly the lower lobes. Open lung biopsy showed dilated lymphatic vessels with surrounding inflammatory cells and smooth muscle fibers consistently with the diagnosis of pulmonary lymphangiomyomatosis (LAM).

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chylothorax and chylous ascites,^{1,2} and runs variable courses culminating usually in respiratory failure.¹ It usually occurs spontaneously, however, it may be a part of the tuberous sclerosis complex.

Lymphangiomyomatosis is a rare disease, and the reported prevalence is approximately one per million in the United Kingdom,³ France, and in the United States of America.⁴ Cases have been reported in Asia, however, the data on its prevalence are not present.² On reviewing the literature, no cases have been reported in Iraq up-to-date. It presents in many ways, however, bilateral spontaneous pneumothorax or chylothorax in females in their reproductive years is the classical one. We present a case of a rare disease, which reported first in Iraq.

Case Report. A 38-year-old Iraqi female, presents with one-year history of exertional dyspnea and exercise intolerance. Her story dated from June 2004 when she started to have progressive exercise intolerance, exertional dyspnea, and paroxysmal nocturnal dyspnea. No fever, constitutional symptoms, or cough were reported. Clinical examination then was unremarkable. Her biochemical analysis, hematological tests including erythrocyte sedimentation rate, electrocardiogram (ECG), and echocardiography were normal. Her chest x-ray (CXR) showed bilateral mottling infiltrate of both lower lobes. Her follow up was lost for 6 months, when she used to consult multiple primary care physicians and many courses of antibiotic failed to produce response. Six months later, she presented with increasing exertional dyspnea and exercise intolerance. She reported no significant weight loss, fever, cough, or pleuritic chest pain. There were no significant skin, mucous membrane, gastrointestinal, urinary, neurological, or musculo-skeletal abnormalities. She had normal menstrual and gynecological history. She is married, with 2 children (15 and 7 years of age), aborted one fetus at second month of pregnancy 5 years prior to her recent complaints. She has no history of hypertension, diabetes mellitus, previous chest infection, or history of seizure. She reported no exposure to drugs including oral contraceptive pills or other chemical substances; she is a housewife, had no history of contact with animals or tuberculous patients, also she had never smoked before. There was no chest problem in her family. On clinical examination, she was tachypneic with bilateral basal crackles and signs consistent with the left sided pleural effusion. The chest roentgenogram showed left sided pleural effusion with

Lymphangiomyomatosis (LAM) is a disease of unknown etiology that occurs in females of reproductive age, and occasionally in postmenopausal women.^{1,2} The LAM presents with recurrent spontaneous pneumothorax, slowly progressive dyspnea, hemoptysis,

diffuse non-homogenous infiltrate in the right lower zone. Hematological and biochemical tests were within normal limits. Aspiration of the pleural fluid disclosed whitish fluid, which was soon diagnosed as being chylothorax by laboratory investigation analysis (Table 1). Pleural fluid was negative for acid fast bacilli (AFB) and malignant cells. Computed tomography (CT) scan of the chest, shows left side pleural effusion with bilateral cystic changes (Figure 1). The ECG, echocardiography, abdominal ultra-sound, Doppler ultrasound study of both lower limbs and spirometric tests were normal. The rheumatoid factor was strongly positive, however, anti nuclear antibodies were negative. Rigid bronchoscopy was carried out under antibiotic cover, which showed congested and swollen right and left main bronchi, the bronchial wash was negative for AFB and cytology showed acute and chronic inflammatory cell with benign and reactive bronchial cells only. Due to her refusal to do open lung biopsy, isoniazid, Rifampicin, Pyrazinamide, and streptomycin with prednisolone 20 mg/day was given a trial, but failed to show any clinical nor radiological response (adenosine deaminase or polymerase chain reaction were not available in Iraq). After her approval, open lung biopsy was performed and histopathological examination with full form of hematoxylin and eosin, Actin, and HMB45 stains (Figures 2a & 2b) showed features confirming pulmonary LAM. She was started on Tamoxifen 200 mg daily for 2 months without significant improvement. The addition of medroxy progesterone acetate 400 mg monthly, showed subjective improvement in her exercise capacity. After 4 months of therapy, her CXR and CT scan of

the chest (Figure 3) showed not only halting the disease progression but also measurable improvement of pleural fluid accumulation and widespread lung infiltration. The clinical improvement and persistently normal spirometric tests are maintained after 10 months of close follow-up.

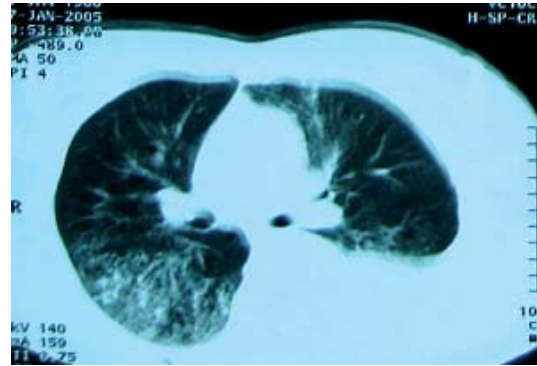


Figure 1 - Chest CT scan on presentation, showing bilateral pleural effusion with diffuse reticulonodular infiltrate and cystic changes.

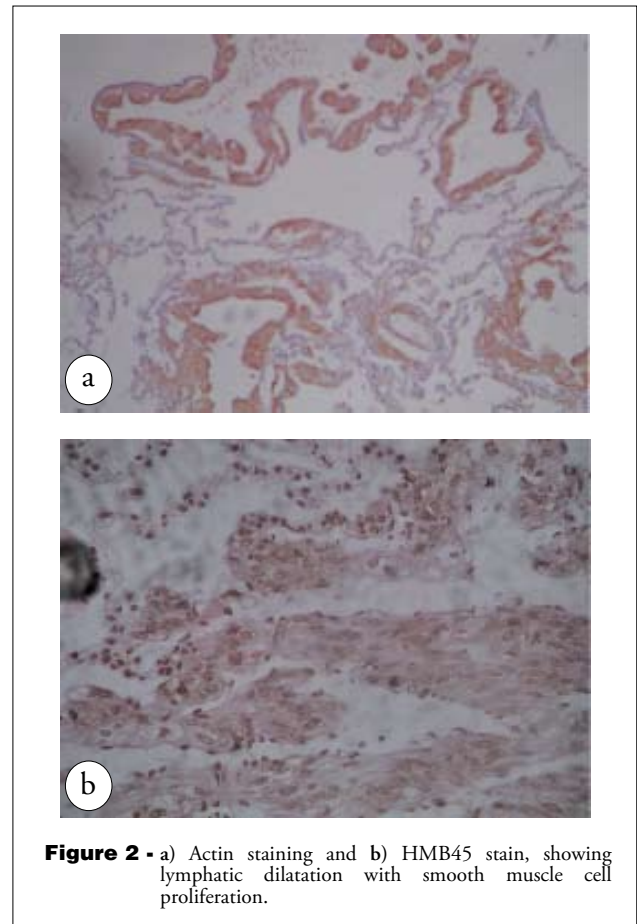


Figure 2 - a) Actin staining and b) HMB45 stain, showing lymphatic dilatation with smooth muscle cell proliferation.

Table 1 - Pleural fluid aspirate.

Laboratory	Pleural fluid (%)	Blood	Normal range
Sugar	144 mg/dl	81 mg/dl	75-115 mg/dl
Protein	3.4 gm/dl	6.4 gm/dl	5.5-8 gm/dl
Albumin	2.3 gm/dl	4.5 gm/dl	3.5-4.5 gm/dl
Triglyceride	592 mg/dl	200 mg/dl	<160 mg/dl
Cholesterol	143 mg/dl	194 mg/dl	<200 mg/dl
pH	9		
Gram stain	No microorganism detected		
Acid fast bacilli stain	Negative		
White blood cell	2100		
<i>Neutrophil granulocyte</i>	(2)		
<i>Lymphocyte</i>	(96)		
<i>Monocyte</i>	(1)		
<i>Eosinophil granulocyte</i>	(1)		
<i>Basophil granulocyte</i>	(0)		
Cytology	Mature lymphocyte with reactive mesothelial cells		



Figure 3 - Chest spiral CT scan, 6 months after starting therapy. The pleural effusion and the cystic changes are less.

Discussion. Lymphangiomyomatosis is exclusively confined to premenopausal women, the mean age of onset being 34-38 years.^{2,5} The presentation after menopause is very unusual. In a large series of 186, 8 patients were postmenopausal, 6 of them (76%) were using estrogen containing hormonal replacement therapy.¹ Our case is a female in her reproductive age. Evidences suggest that, estrogen administration and pregnancy⁶ may accentuate disease progression whereas oophorectomy and progesterone¹ reduce it.

The cardinal pathological findings are proliferation of immature appearing smooth muscle cells (LAM cells) in the lungs and axial lymphatics in the thorax and abdomen, forming variable sizes (few millimeters to few centimeters) cysts. Proliferation of the LAM cells leads to obstruction of air way, air trapping, and alveolar disruption causing cystic changes, which on rupture leads to pneumothorax.⁵ Obstruction to venules causes hemoptysis and hemosiderosis, while obstruction to lymphatic vessels causes dilatation of these vessels with chylothorax and chylous ascites. The LAM is a multisystem disease often involved the other organs such as kidneys, retroperitoneal lymph node, liver, uterus, and pancreas.⁷ Angiolipoma of the kidneys is reported to be one of the common associated pathology (15-57%).⁷ The LAM cells are histochemically distinctive type of smooth muscle cells as it stains with the monoclonal antibodies HMB 45,⁸ and by this, we can distinguish it from other conditions that mimic the LAM such as, metastatic endometrial sarcoma. Patient with LAM could be presents with dyspnea (59%), pneumothorax (49%), cough (39%), chest pain (22%), chylous pleural effusion (13-20%), and hemoptysis (18%) while wheezes are less common.^{1,2,4,5} Extrapulmonary features include renal angiolipoma recorded in up to 60% of patients

with pulmonary LAM. It is usually asymptomatic, however, may present with hematuria sometimes massive bleeding and shock.^{5,9} Retroperitoneal lymph node masses, cystic soft tissue lesion, chylous ascites (33%), and uterine fibroid¹⁰ are other extrapulmonary manifestations. None of these are seen in our case, so, it is isolated to pulmonary system.

The natural history of LAM is of progressive airflow obstruction leading to respiratory failure and cor pulmonale.⁵ The rate of progression is highly variable between the patients ranging from a rapid decline over few years to a more indolent disease over 2-3 decades.⁵ Most recent series reported a 10 year survival of 70%.⁴ Pulmonary function tests in LAM, shows variety of abnormalities from airflow obstruction to restrictive pattern with gas transfer abnormalities or combinations of both, occasionally, pulmonary function tests are normal at presentation.² Our case had normal spirometry after 10 months, with no signs of respiratory failure. The LAM is usually missed or there is a delay in the diagnosis as its presenting symptoms that are shared with other more common pulmonary pathologies, the mean interval between onset of symptoms and diagnosis is over 4 (0-25) years.¹ The radiological features are that of cystic changes of variable sizes with preservation of lung volumes, these can be seen more precisely by High Resolution Computerized Tomography, Ventilation/perfusion lung scan usually show nonspecific, diffuse changes.³ Due to the CT findings in LAM are so distinctive, many physicians do unnecessary resort to open lung biopsy to make the diagnosis. This strategy is probably reasonable, if the CT appearance is classical and the history is fully consistent with LAM. The treatment consists of supportive therapy by trial of Beta 2 agonist, if an element of airflow obstruction is identified. Pneumothorax and chylothorax can be treated by surgical intervention, if supportive measures failed to control them.¹ Anti-estrogen therapy is widely used in form of progesterone or tamoxifen, and oophorectomy. Rarity of the disease makes the evaluation of any therapy more difficult, but 3 large retrospective studies proved that the effect of progesterone in improving or stabilizing the disease is better than other therapies. Lung transplantation has been successfully carried out in patient with the end stage LAM.^{1,3,2}

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REFERENCES

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