Lymphangioleiomyomatosis: The One

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Authors: D. Penha¹, P. Paixao², P. Joao¹, E. Rosado², P. Cabral¹, E. Guedes Pinto¹, A. M. D. Costa²; ¹Lisboa/PT, ²Amadora/PT
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Learning objectives

The learning objectives of this Educational exhibit are:

- The understanding of the etiopathology of lymphangioleiomyomatose (LAM)
- The recognition of the clinical findings associated with LAM
- The description of pulmonary findings on plain chest film and computed tomography (CT)
- The description and illustration of extrapulmonary findings of LAM
- The identification of other possible differential diagnosis
**Background**

Lymphangioleiomyomatosis (LAM) is a rare, progressive, cystic lung disease that occurs almost exclusively in females, during their reproductive years. (1-5)

This disease is a multisystem disorder characterized by progressive proliferation of immature smooth muscle and spindle cells along the axial lymphatics. The trademarks of LAM are diffuse infiltration of the pulmonary parenchyma, airflow obstruction, pneumothorax, chylothorax, and progressive respiratory failure. (1-5)

Recent researches believe that LAM is a slowly progressive neoplasm that targets the lung, causing cystic destruction and respiratory failure over one to two decades. (1-5)

A recent study considers that LAM arises from an unknown source and that the smooth muscle cell metastasizes, infiltrates, and destroys the lung with little evidence of proliferation and an innocent histological appearance. (5)

**Etiology and Epidemiology**

LAM may occur sporadically or in association with the genetic disease tuberous sclerosis complex (TSC). (6)

TSC is an autosomal dominant disorder characterized by seizures, cognitive impairment, skin lesions, and benign "hamartomatous" tumors of the brain, heart, and kidney. This disease is caused by mutation of two genes, TSC1 or TSC2. (5-7) Findings of lung and kidney biopsies in both LAM and TSC demonstrate proliferation of LAM cells in the lymphatics and in renal angiomyolipoma (AML). (5-6)

Up to a third of women with TSC may exhibit lung cysts, the hallmark feature of LAM therefore these patients have been categorized as having TSC/LAM (7).

Sporadic LAM affects more a less 1 in 400,000 adult females and in TSC, LAM occurs in 30-40% of adult females. (8)

**Pathogenesis**

Henske et al studies suggest that LAM cells behave as low-grade sarcoma cells, based on their smooth muscle features (spindled morphology, and smooth muscle actin and desmin staining) and their neoplastic, metastatic, and destructive potential. (5,9)
Several researchers support that LAM smooth muscle cells originate from an unknown primary source that might be within the lymphatic system or in renal angiomyolipomas or even from uterine lesions. These cells proliferate and drive a lymphangiogenic program, because of the expression of VEGF-C and VEGF-D, that results in demarcation of tissue by chaotic lymphatic channels and the formation of LAM cell islands surrounded by lymphatic endothelium, which then bud into the lumen of the lymphatic system. These LAM cell clusters ascend the lymphatic tree by serial cycles of implantation and shedding and are transported by lymphatic flow to the venous circulation and ultimately impact in the pulmonary microvasculature., causing airspace enlargement.(5,10-13)

Clinical Presentation

The clinical presentation may occur before any abnormality is detectable on imaging evaluation or functions tests, and usually is often a delay between the onset of symptoms and correct diagnosis.

The most common presentations of LAM include progressive dyspnea on exertion, chylothorax, and pneumothorax in young and middle-aged women.(6,15)

Pneumothorax and chylothorax are often the sentinel events that trigger the ordering of computed tomography (CT) of the chest, resulting in the diagnosis of LAM. (6,16,17)

Other, less common presentations of include chronic cough, atypical chest pain, chyloptysis, and hemoptysis(16).

It also should be considered in patients with LAM, extrapulmonary clinical findings.

Abdominal manifestations may occur in patients who have TSC-LAM or S-LAM. Manifestation of lymphatic involvement in LAM can range from mild lymph node enlargement to massive, lymph-filled cysts, cystic soft tissue masses (lymphangiomas) that displace abdominal viscera, obstruct ureters, and increase abdominal girth. It is also found chylous ascites, renal angiomyolipomas and uterine fibroids (leiomyomas). (20)

The most common manifestations of TSC are a remote or current history of seizures, cortical tubers, subependymal nodules, or cognitive impairment in childhood. Facial angiofibromas, hypomelanotic macules (including the ash leaf lesion), subungual fibromas, and Shagreen patches of the skin are extremely common in TSC. (Fig. 1) Less common findings include cardiac rhabdomyomas, which can be diagnosed by echocardiography, bone cysts, and gastrointestinal polyps.

Laboratory Evaluation
LAM most commonly presents with chronic airway obstruction, mainly due to airway narrowing, which is characterized by smooth muscle cell infiltration.

Nevertheless some patients also have a restrictive component. In this disease diffusing capacity for carbon monoxide is typically reduced, most likely through a combination of destruction of the pulmonary capillary bed and limitation of diffusion through expansion of the interstitium. Together with an elevated residual volume, reduced diffusing capacity of the lung for carbon monoxide (DLCO) is one of the earliest manifestations of LAM. (6,32)

Usually there are no serum studies that may help on LAM's diagnosis, nonetheless the literature refers that the lymphangiogenesis marker, VEGF-D is elevated in LAM and my be useful as a diagnostic tool. (6)

**Diagnostic Approach**

The European Respiratory Society in 2010 produced evidence based, consensus guidelines for the diagnosis, assessment and treatment of patients with LAM.

These guidelines support that the diagnosis is made by tissue biopsy (generally from the lung but occasionally from lymph nodes or lymphangioleiomyomas) and/or a combination of history and high-resolution computed tomography scanning (HRCT). (20)

The diagnostic work-up is presented on table 1

<table>
<thead>
<tr>
<th>Definite LAM</th>
<th>Probable LAM</th>
<th>Possible LAM</th>
</tr>
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<tbody>
<tr>
<td>Characteristic(^a) or compatible lung HRCT, and lung biopsy fitting the pathological criteria for LAM(^a); or</td>
<td>Characteristic(^a) HRCT and compatible clinical history;</td>
<td>Characteristic(^a) or compatible HRCT.</td>
</tr>
<tr>
<td>Characteristic(^a) lung HRCT and any of the following: angiomyolipoma (kidney)(^b); thoracic or abdominal chylous effusions; lymphangioleiomyomas or lymph-node involved by</td>
<td></td>
<td>Compatible HRCT and any of the following:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>angiomyolipoma (kidney)(^b); and thoracic or abdominal chylous effusions.</td>
</tr>
</tbody>
</table>

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\(^a\) Commonly applicable; \(^b\) Rarer conditions
LAM\(^d\); and definite or probable TSC\(^e\)

\(^a\) As defined below; \(^b\) 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.

The guidelines also define some remarks:

1) LAM is considered associated with TSC (TSC-LAM) when TSC is present. Otherwise LAM is considered sporadic.

2) The diagnosis of LAM defined above is only for females. LAM is very exceptional in males without TSC and exceptional in males with TSC where diagnosis requires both characteristic or compatible HRCT and typical pathological features on lung biopsy.

3) The diagnosis of LAM requires exclusion of the alternative causes of cystic lung disease. A complete diagnostic work-up for these alternative causes of cystic lung disease is necessary in patients with probable and especially possible LAM.

**Pathology**

Macroscopic evaluation reveals enlarged and diffusely cystic lungs. The distribution of the cysts in the lung is homogeneous without lobar differences. (6)

Microscopic examination of the lung reveals foci of smooth muscle cell infiltration of lung parenchyma, airways, lymphatics, and blood vessels associated with areas of thin-walled cystic changes. (6)

The proliferating immature smooth cells have a benign appearance, and immunohistochemistry shows smooth muscle actin and melanoma-associated (HMB-45) antigens. (Fig. 2) The HMB-45 antigens are useful for diagnosis of LAM because LAM is the unique smooth muscle cell proliferation in the lung that expresses such antigen. (6,16,17)

The air-enlarged cavities appear as large spaces because of dilatation rather than destruction. (Fig. 3) They are randomly localized in the secondary lobule. (16)

Hemosiderin deposition in the interstitium and within the alveolar macrophages is also typical finding. The degree of this deposition is associated with the degree of myomatosis. (16,17)
Imaging findings OR Procedure details

I - PULMONARY FINDINGS

Chest X-ray

The appearance of the chest radiograph may be initially normal. Nevertheless reticular opacities usually reported as reported as reticular, reticulonodular, miliary opacities together with cystic changes, tend to develop with progressive clinical deterioration and correspond to increasing pulmonary involvement by cysts (17) (Fig. 4, 5).

It is thought that the reticular and reticulonodular opacities may result from the visualization of numerous superimposed cyst walls (17).

Pneumothorax and pleural effusion are also common radiographic features (17).

Computed Tomography

CT is both sensitive and specific for the diagnosis of LAM. The main pulmonary manifestation of this disease is the numerous of thin-walled cysts surrounded by normal lung parenchyma and distributed diffusely and bilaterally (16,17).

By the time of diagnosis CT is almost always abnormal and usually demonstrates parenchymal cysts, even when the chest radiographs appear normal or reveal only pleural effusion or pneumothorax (16,17).

The CT findings in patients with LAM are reported as indistinguishable from those in patients with TSC-LAM (6,7,16,17).

1. Pulmonary cysts

Cysts are well-defined and circumscribed air or fluid containing lesions with 1 cm or more. They are the hallmark of LAM, and have been seen in all patients with LAM reported on the literature. (Fig. 6)

They typically range from 2 to 5 mm in diameter but have been reported to be as large as 25 mm (22). (Fig. 7)

They appear in a variety of shapes, including polygonal, ovoid and the most commonly reported the round ones. Cyst wall thickness ranges from barely perceptible to 2 mm. (16,17,22)
The cysts are generally symmetrically and uniformly distributed throughout the lungs. Lung parenchyma interposed between the cysts of LAM is typically normal, although thickened interlobular septa have been described. (16,17,22)

With LAM progression, the cysts became numerous and enlarged, with the tendency to replace the normal lung parenchyma. (Fig. 8,9)

**Increased Attenuation / Ground Glass Opacities**

Patchy areas of ground-glass attenuation have been described in patients with LAM and are thought to represent foci of pulmonary hemorrhage or edema, as both are known complications of LAM. (16,17,22) (Fig. 10)

Pulmonary hemorrhage results from the involvement of the venules and may give rise to total occlusion of the vessels, causing pulmonary venous hypertension and hemoptysis (16,17)

**Chylous Pleural Effusion**

Unilateral or bilateral chylothorax is typically large and recurrent and usually appears during the course of the disease. The CT attenuation of chylous pleural effusion is usually low-attenuation (17-HU) and may relate to the presence of fat. (17) More often, however, the high protein content of chylous effusions contributes to higher attenuation values, and the collections are indistinguishable from pleural effusions arising from other causes. (16) (Fig. 11)

**Pneumothorax**

Pneumothorax is a common imaging manifestation of LAM and is characteristically associated with CT demonstration of parenchymal cysts.(16,17) (Fig. 12)

**Small nodules**

Small nodules have also been reported on the literature but are not considered a characteristic imaging feature of the disease (23).

**Thoracic Duct and Mediastinal Ganglia**

Hilar / mediastinal lymphadenopathy and dilatation of the thoracic duct are also known thoracic manifestations of LAM. (16,17) (Fig 13)

**II - EXTRAPULMONARY FINDINGS**
Patients with LAM should also be evaluated looking for abdominopelvic findings, knowing that 70 % of the patients with LAM have abdominal abnormalities.

**Renal Angiomyolipomas**

Angiomyolipoma, also known as renal hamartoma, is most common abdominal finding. Angiomyolipomas contain fat, smooth muscle, and blood vessels. They are often small (1 cm), multiple, bilateral, and asymptomatic and occur in 20%-54% of patients with LAM. (16,19)

The demonstration of intratumoral fat with negative attenuation values at CT is virtually pathognomonic of angiomyolipoma. Thin-section unenhanced CT is essential to visualize the fat content of angiomyolipomas.(16,17)

The clinical manifestations and management of these tumors depend on their size. (16,17,19)

Although they are benign masses, renal angiomyolipomas can grow large, can distort renal architecture, and may compromise renal function. (16,17,19). Renal angiomyolipomas may hemorrhage, resulting in severe abdominal pain and ureteral obstruction. This complication is very important because hemorrhagic angiomyolipomas may be mistaken for malignancy. (Fig 14)

**Lymphangioleiomyoma**

Lymphangioleiomyomas begin with the proliferation of smooth muscle cells in the lymph vessels resulting in cystic masses, resulting from dilatations of the abdominal lymph vessels due to lymphatic obstruction. (16)

At CT, the dilated retroperitoneal lymph vessels may have either thin or thick walls and may contain material low in attenuation (3-25 HU). (19)

Lymphangioleiomyomas may lie between and displace vascular structures in the retroperitoneum and, along with abdominal adenopathy, may be misdiagnosed as a neoplastic process such as lymphoma.(19)

**Lymphadenopathy**

Enlarged lymph nodes are described in up to 40% of cases in the reviewed literature. Lymph nodes can measure up to 4 cm in diameter. Some lymph nodes contain low attenuation areas, which several authors believe that indicates the presence of chylous lymph collections, or hamartomatous hyper-attenuating areas that enhance after contrast material administration (16,17,19).

**Chylous Ascites**
Chylous ascites is an uncommon overdistention of lymphatic cysts that may result from intraperitoneal rupture. (19)

Differential Diagnosis

LAM as different differential diagnosis, therefore the most suitable approach would be using a multidisciplinary method considering the patient's clinical history, physical examination, and the radiologic appearance.

Important chest imaging factors that should be taken into consideration include:

- Lung volume
- Cyst Size
- Cyst Wall thickness
- Cyst Shape
- Distribution of the pulmonary cysts
- Associated findings: such as pulmonary nodules, septal thickening, pleural effusions, lymphadenopathy, and extrathoracic abnormalities.

The following table (table 2) helps to analyse the clinical and radiological characteristics of the most common cystic lung diseases, thus helping the radiologist to formulate a differential diagnosis, and correctly achieve LAM's diagnosis.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical Features</th>
<th>Imaging Characteristics</th>
</tr>
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<tbody>
<tr>
<td>Tuberous Sclerosis</td>
<td>Autosomal dominant disease (TSC1 on chromosome 9q34 and TSC2 on chromosome 16p13)</td>
<td>Pulmonary involvement in tuberous sclerosis is very uncommon, occurring in only 0.1%-1% of cases. Pulmonary LAM can occur as part of the tuberous sclerosis complex.</td>
</tr>
<tr>
<td></td>
<td>Affects men and women equally</td>
<td>The most common abdominal findings are:</td>
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<td></td>
<td>Characterized by the triad of mental retardation, epilepsy, and adenoma sebaceum</td>
<td>Renal or hepatic angiomyolipomas</td>
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<tr>
<td></td>
<td></td>
<td>Lymphangioleiomyoma</td>
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<td>Ascitis</td>
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<tr>
<td>Condition</td>
<td>Cell</td>
<td>Disease</td>
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<tr>
<td>Langerhans Histiocytosis</td>
<td>Smoking-related disease</td>
<td>Male predominance</td>
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<tr>
<td>Pulmonary Fibrosis</td>
<td>Related to:</td>
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<td></td>
<td>Idiopathic pulmonary fibrosis</td>
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<td></td>
<td>Collagen-vascular diseases</td>
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<td></td>
<td>Abestosis</td>
<td></td>
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<tr>
<td>Pneumatocele</td>
<td>Immunodeficiency and AIDS</td>
<td></td>
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<tr>
<td>Pneumocystis pneumonia</td>
<td>Pneumatoceles are reported in up to 30% of patients with Pneumocystis carinii pneumonia</td>
<td></td>
</tr>
<tr>
<td>Emphysema</td>
<td>Smoking-related disease</td>
<td></td>
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<tr>
<td>Disease</td>
<td>Related to</td>
<td>Description</td>
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<td>-------------------------------</td>
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</tr>
<tr>
<td>Lymphocytic Interstitial Pneumonia</td>
<td>Related to: HIV, Collagen-vascular diseases, Castleman disease, Lymphoproliferative disorders</td>
<td>Terminal bronchioles with destruction of their walls. May have areas of low attenuation with or without visible walls. Commonly affects the upper lobes in smokers.</td>
</tr>
<tr>
<td>Birt-Hogg-Dubé Syndrome</td>
<td>Autosomal dominant disease</td>
<td>Few cysts distributed along the peribronchovascular interstitium. Basilar and peripherally predominant lentiform cysts abutting the pulmonary arteries and veins. This disease involves skin, lungs, and kidneys.</td>
</tr>
</tbody>
</table>
Fig. 1: TSC in a female patient with Shagreen patches of the skin

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Fig. 2: Photomicrograph (original magnification, 20x) Immunohistochemistry shows smooth muscle actin in lung parenchyma

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**Fig. 3:** Photomicrograph (original magnification, 10x) Immunohistochemistry cytokeratin shows epithelial covering of the enlarged airway spaces.

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Fig. 4: LAM in a 37-year-old woman with history of dyspnea. Posteroanterior and lateral chest radiograph, demonstrating slightly increased pulmonary volume and diffuse bilateral interstitial reticulonodular opacities

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**Fig. 5:** LAM in the same 37-year-old woman 2 years after the diagnosis. Posteroanterior chest radiograph, shows marked increased of the pulmonary volumes diffuse bilateral interstitial reticulonodular opacities (mainky linear) and right side pneumothorax.

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Fig. 13: CT scan shows mediastinal lymphadenopathy in a female patient with LAM.

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**Fig. 12:** CT scan shows a large right side pneumothorax, with collapse of the right lung. Left lung shows several small cysts.

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Fig. 11: CT scan demonstrate right side pneumothorax. Both lung have uncountables cysts with few normal parenchyma between. Left pleural effusion.

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**Fig. 10:** CT scan exhibits uncountable small cysts and diffuse patchy areas of ground-glass attenuation.

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Fig. 9: CT scan displays the same female patient (fig. 8), six months later. The scan shows a great progression of the disease with almost no lung parenchyma between the cysts.

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Fig. 8: CT scan displays a female patient with one year diagnosed LAM's disease. The scan shows several sized and shaped cysts replacing great majority of lung parenchyma.

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Fig. 7: High-resolution CT scan displays several sized cysts between normal lung parenchyma.

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**Fig. 6:** High-resolution CT scan shows round well-defined thin-walled bilateral lung cysts diffusely distributed throughout the lungs.

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**Fig. 14:** CT film of a female patient with TSC-LAM, with bilateral renal angiomylipomas (multiple cortical lesions with fat attenuation values). Left side kidney is involved by hemorrhage from an angiomylipoma.

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Conclusion

LAM is an uncommon progressive disease leading to respiratory failure and death. Therefore it is important to recognize the clinical signs, which combined with the characteristic radiological findings suggest the diagnosis of LAM, consequently leading to a more fast and easy identification of this rare disease.
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