Tuberous Sclerosis Alliance

# LUNG INVOLVEMENT IN TSC

Lung involvement in tuberous sclerosis complex (TSC) has been recognized for many years. In 2000-2001, three studies reported that between 26% and 39% of women with a definite diagnosis of TSC have evidence of lymphangioleiomyomatosis (LAM) (see below) (Costello et al., 2000; Franz et al., 2001; Moss et al., 2001). Several subsequent studies suggested that the frequency of lung involvement in adult women with TSC may be even higher than previously suspected, ranging from 42% to 49% (Muzykewicz et al, 2009; Adriaensen et al, 2011; Cudzilo et al., 2013). Importantly, in many of these women, the disease does not cause significant respiratory symptoms. Because of the frequency of lung involvement in TSC, the recent TSC Consensus Conference report recommended that all women age 18 years and older with TSC should have a computerized tomography (CT) scan of the chest and pulmonary function testing. (Krueger et al., 2013)

## What are the lung features of TSC?

Two forms of lung involvement in TSC have been described:

1. lymphangioleiomyomatosis (LAM)/pulmonary cysts; and
2. multifocal micronodular pneumocyte hyperplasia (MMPH).

These manifestations of TSC are described below.

## Lymphangioleiomyomatosis (LAM)

Lymphangioleiomyomatosis (LAM) is a lung disease that affects women more often than men, usually between the onset of puberty and menopause. LAM has also been reported in older women with TSC, but it is not clear when the disease developed in these individuals. The precise number of individuals who have LAM is not known. Scientists estimate that there may be up to 300,000 women with the disease worldwide if you include both individuals who have TSC and LAM and those with sporadic LAM (60% of these individuals have kidney tumors, but no other manifestations of TSC). Smolarek and colleagues (1998) identified mutations in the TSC2 gene in individuals with sporadic LAM, indicating that LAM is caused by mutations in the same gene(s) as TSC.

LAM is characterized by an unusual type of muscle cell that invades the lungs, airways, and blood and lymph vessels. The source of the cells that invade the lung is not clear, although the uterus and angiomyolipomas are possible candidates. Over time, these muscle cells destroy the lungs and make it difficult for oxygen to get across the wall of the airway and into the blood cells. This prevents the lungs from providing oxygen to the rest of the body.

The word lymphangioleiomyomatosis can be broken down into its parts to help explain what the disease is. Lymph- and angio- refer to the lymphatic and blood vessels in the body,

respectively. The lymph nodes and lymphatic vessels are involved in the lung. Leiomyomatosis refers to the formation of the unusual muscle cells in the lung.

Pulmonary LAM has a distinctive appearance on the CT scan of the chest and on pathological examination of lung specimens that are removed at the time of transplant. The lungs of an individual with TSC who has LAM contain a multitude of air-filled cysts, varying in size from a few millimeters to several centimeters, that take the place of the normal fine lacy pattern of the normal lung. The walls of the airways are infiltrated with abnormal muscle cells and cysts, and become thickened and distorted.

**Pulmonary cysts** are the hallmark of LAM. Cysts may remain clinically silent or they may rupture, resulting in pneumothorax (a collection of air or gas in the space surrounding the lungs). The pneumothorax may produce sudden shortness of breath and chest pain. If this occurs, the patient should go to the nearest emergency room, to have the lung re-expanded. It is recommended that a procedure called pleurodesis be performed to lessen the chance that pneumothorax will occur again.

If an individual has many cystic lesions, as is the case with severe LAM, they may develop respiratory insufficiency and/or pulmonary hypertension (high blood pressure in the arteries that supply the lungs).

There have been only a few case reports of men with TSC who have biopsy documented LAM. However, recent studies have shown significant rates of lung cysts in men with TSC (Adriaensen et al., 2011; Ryu et al., 2012). Importantly, most of these men have not had lung symptoms and it is not known whether men with TSC who have lung cysts truly have LAM.

Another problem that can develop is the collection of a milky fluid called ‘chyle’ in the chest. The fluid accumulates because LAM cells clog the lymphatic drainage system in the chest, and block the flow of fluids, fats and nutrients from the abdomen on their way to the veins in the neck. Sometimes this fluid needs to be drained, and sometimes pleurodesis needs to be performed to prevent recurrence.

## Multifocal Micronodular Pneumocyte Hyperplasia (MMPH)

Multifocal micronodular pneumocyte hyperplasia (MMPH) consists of overgrowth (hyperplasia) of the pneumocytes (a specific type of cell found in the lining of the air sacs in the lung) into small nodules. An individual with TSC who has MMPH may have a few or many nodules in their lungs. This condition occurs with equal frequency in men and women with TSC and does not usually produce clinical symptoms. It is important to be aware of this entity, however, since doctors may otherwise wonder whether these small nodules are due to a variety of other possible causes.

## How are the lung manifestations of TSC diagnosed?

The diagnosis of the lung features of TSC can be difficult because many of the early symptoms can be similar to those of other lung diseases such as asthma, emphysema, or pulmonary bronchitis. Symptoms including lung collapse (called pneumothorax), fluid in the lungs, shortness of breath, or chest pain may be signs of LAM in individuals with TSC. Often, many individuals with TSC who are diagnosed with LAM will be completely free of any symptoms.

Chest CT scan of the chest is the main way that the lung manifestations of TSC are diagnosed. Chest CT and other tests that may help diagnose lung manifestations of TSC are listed below:

1. **Chest X-ray:** This is a simple procedure that produces a picture of the lungs and other tissues in the chest. The chest x-ray is used to diagnose a pneumothorax or the presence of fluid in the chest cavity. The cysts that are suggestive of LAM can be difficult to see on a chest x-ray, and therefore a chest x-ray is usually not sufficient for diagnosis.

2. **Pulmonary function tests:** To perform pulmonary function tests (PFT), the individual breathes through a mouthpiece into a spirometer (a machine that measures the volume of air in the lungs, the movement of air into and out of the lungs, and the movement of oxygen from the lungs into the blood. Because other lung problems can also affect lung function, PFTs do not provide a diagnosis of LAM. However, this test can be used for screening for lung disease and to determine the severity of effects that lung involvement in TSC have on lung performance over time.

3. **Blood tests:** A blood sample may be obtained to measure the serum VEGF-D level, which may be elevated in women with TSC who have LAM.

4. **Computed tomography:** High resolution computed tomography (CT) is the most useful imaging test for diagnosing LAM or MMPH in individuals with TSC. The presence of thin-walled cysts and/or nodules can be observed using a CT scan of the lungs. CT scans of the abdomen that images the kidneys will also provide information about the presence of kidney tumors (angiomyolipomas) in both individuals with TSC and those with sporadic LAM.

5. **Lung biopsy:** A lung biopsy should be performed only as a last resort to diagnose LAM. In this procedure, a few small pieces of lung tissue are removed through an incision made in the chest wall between the ribs. This procedure must be done in the hospital under general anesthesia. In general, lung biopsy is not required to diagnose LAM in women with TSC who have characteristic lung cysts on CT scan. When lung biopsy is performed, it may be done via thoracoscopy or transbronchial biopsy.

## Monitoring

1. **Pulmonary Function Tests:** PFTs are performed at regular intervals, at least yearly in individuals with TSC who have lung cysts. PFTs may be done more often in individuals with lung symptoms.

2. **Blood tests:** In individuals with more advanced LAM, a blood sample called an arterial blood gas may be performed to determine whether the lungs are providing an adequate supply of oxygen to the blood.

3. **HRCT:** Chest CT may be repeated to re-assess extent of lung cysts. The Consensus guideline suggests repeating a chest CT in 5-10 years for women who have a normal initial chest CT and who remain asymptomatic. For those with significant numbers of lung cysts on their first scan and who have lung symtpoms, chest CT is sometimes repeated after 2-3 years.

## Treatment

In patients with moderate to severe lung disease, rapamune (sirolimus) has been shown to result in overall stabilization of lung function (McCormack et al., 2011). In the Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) trial, the effect only lasted while individuals were taking the medication, and decline in lung function resumed when the medication was stopped. It is not known whether rapamune can prevent decline in lung function in women with mild LAM disease, and whether sirolimus is safe to take over multiple years. Most patients in MILES had sporadic LAM, and therefore it is unclear whether the results of the trial can be directly applied to patients with TSC LAM.

Everolimus is frequently used to treat kidney tumors and brain tumors in patients with TSC. Everolimus is very similar to sirolimus, and most physicians believe they can be used interchangeably for TSC and LAM. However, that question has not yet been answered. A small trial of everolimus in LAM has been completed and will soon be published.

Everolimus and sirolimus are also very effective for the chylous problems that can develop in LAM.

Because LAM affects women of childbearing age, physicians have thought that the hormone estrogen might be involved in the abnormal muscle cell growth that characterizes the disease. Although there is no direct evidence that there is a relationship between estrogen and LAM, it is recommended that estrogen-containing medications be avoided in women with TSC. It is also important to avoid tobacco smoke.

Inhalers may be helpful for some LAM patients who have asthma like symptoms of wheezing and intermittent shortness of breath. Oxygen therapy may become necessary if the disease continues to worsen and lung function is impaired. Some individuals will require surgery following a pneumothorax to help prevent future occurrences. Lung transplantation is considered as a last resort to treat LAM.

## TSC and LAM Research Protocols

Several clinical trials are underway at TSC and LAM clinic sites. Some women and men with TSC and LAM may be eligible to participate in clinical studies at the Clinical Center at the National Institutes of Health in Bethesda, MD. The LAM Foundation (www.thelamfoundation.org) can be contacted for up-to-date information about LAM research studies and trials.

Table. Lung Health Considerations for Adult Women with TSC

| Considerations for All Adult Women with TSC: |
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| • Receive educational counseling on pulmonary manifestations of TSC and possible signs and symptoms |
| • Avoid all estrogen containing medications |
| • Avoid smoking or exposure to second-hand tobacco smoke |
| • Undergo screening high-resolution chest CT at age 18-21 years |
| • Perform pulmonary function testing annually after age 18 years, if able |
| • Consider serum VEGF-D screening after age 18 years |
| • Receive annual influenza vaccination |
| **Considerations if LAM Diagnosed:** |
| • Receive additional counseling on symptoms and management of pneumothorax and chylothorax |
| • Receive counseling regarding pregnancy and air travel |
| • Perform pulmonary function testing approximately every 6-12 months depending on disease severity and progression |
| • Undergo screening for hypoxemia at rest, or with sleep or exercise; consider supplemental oxygen therapy if indicated |
| • Consider serum VEGF-D testing |
| • Consider rapamune therapy |
| • Consider referral for lung transplant evaluation for FEV1 <30% or disabling dyspnea or hypoxemia |
| • Receive Pneumovax |

## References


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## Resources

American Lung Association
Phone: 1-800-LUNGUSA (1-800-586-4872)
To speak to a lung health professional, contact the American Lung Association Lung HelpLine at 1-800-548-8252
www.lungusa.org

American Thoracic Association
61 Broadway, 4th Floor
New York, NY 10006
Phone: 212-315-8600
www.thoracic.org

The LAM Foundation
10105 Beacon Hills Drive
Cincinnati, OH 45241
Phone: 513-777-6889
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