IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

Human Journals
**Case Report**
August 2018 Vol.:10, Issue:2


# Tuberous Sclerosis Variant of Lymphangioleiomyomatosis Presenting as Primary Spontaneous Pneumothorax

IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

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**Submission:** 20 July 2018
**Accepted:** 29 July 2018
**Published:** 30 August 2018



**Keywords:** Lymphangioleiomyomatosis, pneumothorax, tuberous sclerosis, chylothorax

**ABSTRACT**

Introduction: Lymphangioleiomyomatosis (LAM) is a rare progressive pulmonary condition, but important to identify early and consider in the differential diagnosis of primary spontaneous pneumothorax. Case presentation: A 40 year old female presented with a complete spontaneous left-sided pneumothorax. High-resolution computerised tomography (HRCT) scan revealed diffuse thin-walled pulmonary cysts, consistent with LAM. The diagnosis of LAM was confirmed following a video-assisted thoracoscopic surgery (VATS) biopsy. A renal angiomyolipoma was also found on computerised tomography kidney ureter and bladder (CTKUB), leading to the diagnosis of LAM with tuberous sclerosis complex (TSC-LAM). The patient was initially treated with a chest drain and supportively. She then had a left sided pleurodesis for recurrent left pneumothoraces and was started on Sirolimus. Discussion: LAM mainly affects pre-menopausal women and often presents with dyspnoea, spontaneous pneumothorax and chylothorax. Diagnosis is supported by HRCT and treatment is primarily supportive. Conclusion: LAM is often a difficult diagnosis due to its clinical and radiological mimickers. Sirolimus shows promise for effective treatment, especially if introduced early.

## INTRODUCTION

Lymphangioleiomyomatosis with tuberous sclerosis (TSC-LAM), a cystic lung disease, is a rare diagnosis with mainly supportive treatment and varying prognosis. However, recent advances of using Sirolimus in the treatment of LAM shows promise.[1]

A 40 year old lady, with a history of smoking but no known underlying pulmonary disease, presented with dyspnoea on exertion and pleuritic pain on deep inspiration. She was treated for complete spontaneous left-sided pneumothorax and diagnosed with primary spontaneous pneumothorax. On further investigation, she had normal alpha-1 antitrypsin enzyme levels. She was found to have diffuse thin-walled pulmonary cysts, distributed bilaterally, and a raised vascular endothelial growth factor D (VEGF-D) serum level of more than 800pg/ml, which suggests LAM over other cystic pulmonary conditions. A VATS lung biopsy was performed that confirmed the diagnosis of LAM. A renal angiomyolipoma was also found that led to the diagnosis of TSC-LAM. Differential diagnoses of LAM include the more common diagnoses, such as emphysema and primary spontaneous pneumothorax.

This case study highlights the importance of considering this rare condition, which often presents with non-specific symptoms, as a differential in patients presenting with primary spontaneous pneumothorax.

## CASE PRESENTATION

A forty year old female with a background history of smoking presented with a 6 day history of dyspnoea on exertion and pleuritic pain on deep inspiration. The patient had no known underlying lung disease and was normally fit and well. She was haemodynamically stable and on examination, she had increased resonance and reduced breath sounds throughout the left hemithorax. Chest radiograph (CXR) on admission showed a complete left-sided pneumothorax which was later confirmed as a primary spontaneous pneumothorax. See Figure 1.

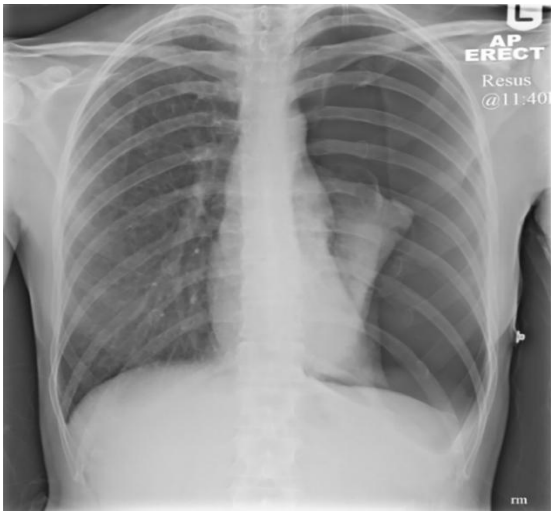


**Figure 1: Chest radiograph showing a complete left-sided pneumothorax.**

## INVESTIGATIONS

Subsequent investigations of the primary spontaneous pneumothorax revealed alpha-1 antitrypsin enzyme levels were normal at 1.75g/L. A high-resolution computerised tomography (HRCT) scan revealed diffuse small thin-walled cysts of varying sizes distributed throughout all lobes bilaterally. See Figure 2. Given the patient demographic and the raised VEGF-D serum level, the likely diagnosis was pulmonary lymphangioleiomyomatosis (LAM). Her case was discussed at the Lung MDT at a University Hospital, a VATS lung biopsy was performed and a diagnosis of LAM was confirmed.

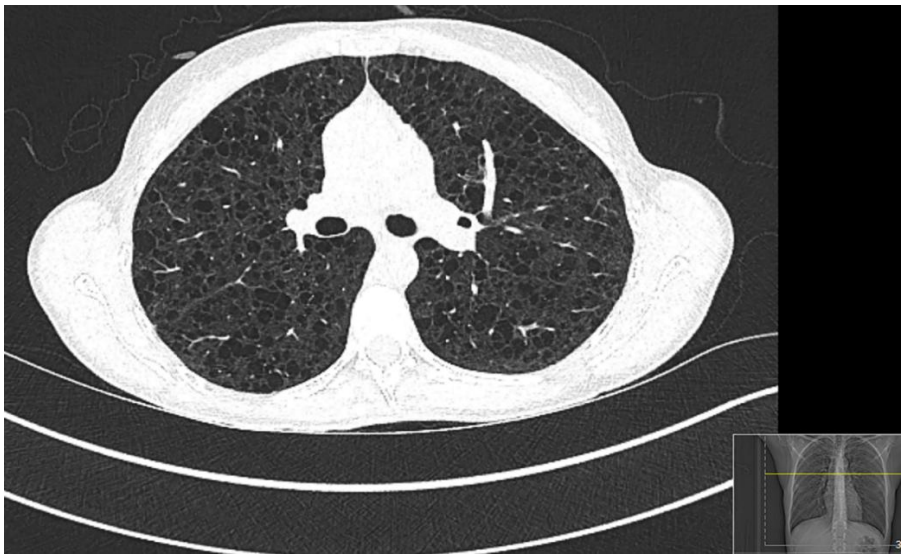

**Figure 2: HRCT showing small thin-walled cysts of varying sizes distributed throughout all lobes bilaterally.**

Following recommendation of the Lung MDT, the patient underwent both a computerised tomography kidney ureter and bladder (CTKUB) and a magnetic resonance imaging (MRI) brain to look for evidence of tuberous sclerosis. The MRI brain was unremarkable but the CTKUB showed a small 4mm hypodensity (-30HU) in the mid pole of the right renal parenchyma, consistent with an angiomyolipoma. See Figure 3. Consequently, the diagnosis of tuberous sclerosis was made.

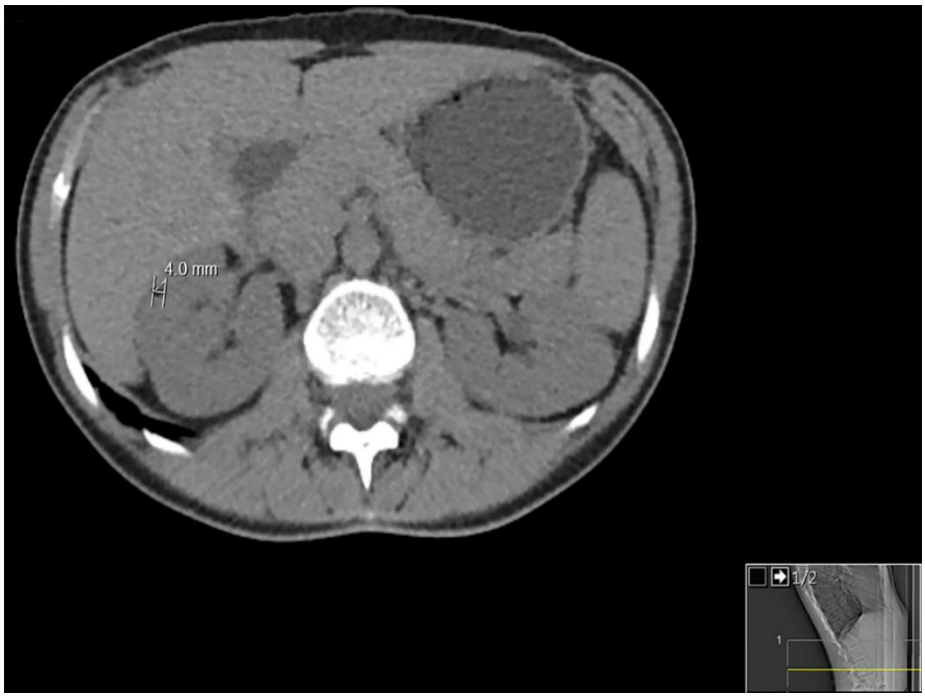


**Figure 3: CT KUB showing** small 4mm hypodensity (-30HU) in the mid pole of the right renal parenchyma**.**

A full lung function test with transfer factor was done showing a mild obstructive pattern with an FEV1 of 1.92L, 71% predicted versus a FEV1 of 2.1L 3 months previously. FEV1/FVC ratio was 71%, FVC was 2.7L, 86% predicted. Transfer factor for carbon monoxide (TLCO) was moderately reduced at 50% with moderately reduced constant transfer factor (KCO) at 58%.

**Differential diagnosis**

Differential diagnoses of LAM have included asthma, emphysema, primary spontaneous pneumothorax, Langerhans cell histiocytosis (LCH), Birt-Hogg-Dubé syndrome,[2] $\alpha_1$-antitrypsin deficiency, chronic extrinsic allergic alveolitis, and cystic sarcoidosis.[3]

## TREATMENT

The patient was initially managed with US guided insertion of a 12 F Seldinger chest drain, under aseptic technique according to BTS pneumothorax Guidelines.[4] Low pressure (10Kpa) suction was applied for a total of 24 hours in addition to high flow oxygen and regular analgesia. Repeat chest radiograph showed complete resolution of the left sided pneumothorax, the chest drain was removed and a bio-occlusive dressing was applied.

### Outcome and follow-up

The patient was given smoking cessation advice and referred to pulmonary rehabilitation. She was commenced on a long acting antimuscarinic inhaler and short acting bronchodilator as needed and was referred to a LAM centre of excellence for trial medication such as Sirolimus for TSC-LAM.

On discharge, the patient was given recommendation not to fly or dive for 4 weeks post chest drain removal according to the BTS guidelines for pneumothorax. Advice on birth control was also given.

As well as being started on Sirolimus, the patient had a left sided pleurodesis for recurrent left sided pneumothoraces.

## DISCUSSION

Lymphangioleiomyomatosis (LAM) is a rare progressive lung disease that mainly occurs in pre-menopausal women, mostly between 20 and 40 years of age. LAM can also present in males with TSC, although very rarely.[5-7] It is more commonly seen in Caucasians compared to other racial groups. The disease is characterised by abnormal growth of smooth muscle-like cells (LAM cells) in the lungs and axial lymphatic system, and the development of cystic dilatation of the terminal airspaces.[3]

There are two forms of LAM, sporadic LAM (S-LAM) and Tuberous Sclerosis LAM (TSC-LAM). S-LAM has a prevalence of 1-2 per million and the cause of the disease is unknown. TSC-LAM affects approximately 40% of patients with the autosomal dominant genetic disease tuberous sclerosis complex (TSC). It is associated with germline mutations in TSC2, or less commonly in TSC1 gene, which results in aberrant activation of mammalian target of

rapamycin (mTOR), abnormal cellular growth and migration. Somatic TSC2 mutations play a role in S-LAM.

Patients present clinically with dyspnoea on exertion, spontaneous pneumothorax, recurrent pneumothoraces and chylothorax. Less common presentations include haemoptysis, cough and chyloptysis. A review of published cases found pneumothorax (43%) and dyspnoea (42%) to be the most common presentation of LAM, followed by cough (20%), chest pain (14%), haemoptysis (14%) and chylous effusion (12%).[8] Due to its' non-specific symptoms, diagnosis of LAM is often delayed. Misdiagnosis may also occur, for example, early presentation of patients being mistaken for asthma.[9] Extra-pulmonary manifestations may also occur; for example, approximately 40% of patients with LAM have an angiomyolipoma, a benign renal tumour. This is more common in patients with TSC-LAM. Migration of LAM cells to the abdominal cavity and pelvic lymphatics results in lymphadenopathy and can also cause lymphangioleiomyomas (large cystic masses containing chyle).

Diagnosis is confirmed by positive findings on lung biopsy or using high-resolution computed tomography (HRCT) alongside a typical LAM presentation.[10] A raised VEGF-D serum level (>800pg/ml) with typical HRCT findings also suggest LAM over other cystic conditions. However, a negative VEGF-D test does not exclude LAM. HRCT of a patient with LAM typically show thin walled cysts spread throughout the lung fields, surrounded by normal lung parenchyma, as was seen in this patient. The gold standard diagnostic investigation is testing lung biopsy for alpha-smooth muscle actin and HMB45 positive cells; however, this is not necessary if a typical LAM presentation and HRCT findings are present and it does not provide prognostic information. All patients should also be investigated for extra-pulmonary manifestations of LAM and signs of tuberous sclerosis complex (TSC). Some of the major features of TSC include facial angiofibromas, ungula fibromas, hypomelanotic macules, shagreen patches, cortical tuber and renal angiomyolipomas.[2] Therefore, a full dermatological examination, abdominal CT scan and brain MRI should also be performed. Renal and hepatic angiomyolipoma and lung nodules are more common in TSC-LAM than in S-LAM; however, lymphatic involvement including thoracic duct dilatation, chylothorax and ascites are more common in S-LAM.[11]

Lung function tests typically show airflow obstruction with preserved lung volumes and impaired gas transfer in patients with LAM.[2] This pattern was also seen in this patient,

whose findings included mildly reduced FEV1, normal FVC with reduced TLCO and KCO. Complex lung function tests should be conducted every 3 months in the first year from diagnosis and every 6 months afterwards in order to monitor disease progression. Patients with an FEV1< 25% and TLCO<27% predicted should be assessed for pulmonary transplant. LAM accounts for 1.1% of all lung transplants.[12]

Patients with LAM can often be hypoxic and therefore should have ABGs as part of their initial workup and for consideration of the need for LTOT. As part of the assessment for LTOT and in severe LAM, screening for pulmonary hypertension should be performed; however, this is not necessary in non-severe LAM.

Treatment is primarily supportive with supplemental oxygen, bronchodilators and pulmonary rehabilitation. Rehabilitation has been found to improve exercise capacity, dyspnoea, muscle strength and quality of life in a clinical trial including 40 patients with LAM and low physical activity level.[13] Aspiration or chest drain is used to treat symptomatic chylous effusions, and if persistent, pleurectomy may be performed. However, the use of a VATS talc pleurodesis should be decided upon carefully as this can affect the patient's eligibility for a future lung transplant, although this is not an absolute contraindication. Low-fat diets may also be encouraged to help reduce chyle formation. Patients are advised to have prophylactic influenza and pneumococcal vaccinations.[2] Patients with LAM are to be given travel advice not to fly or dive for 4 weeks following pneumothorax; fitness to fly is a relative contraindication in patients with severe LAM or recurrent pneumothoraxes.

Studies have shown that oestrogen can accelerate disease progression therefore patients are advised to avoid oestrogen containing preparations and should be counselled on the potential manifestations that can occur in pregnancy including effusions and pneumothoraces.[1, 14] However, previous case reports have described benefit from the use of hormone therapy in patients with poor or rapidly reclining lung function, such as progesterone, gonadotrophin-releasing hormone agonists and oophorectomy, though, its' efficacy is unclear.[8]

In clinical trials, the mTOR inhibitor Sirolimus (rapamycin) shows promise for effective treatment of LAM. Sirolimus has shown to improve $FEV_1$, FVC and TLCO, reduce the size of angiomyolipoma and reduce chylothorax in selected patients, also improving their quality of life.[1] However, discontinuation of Sirolimus has shown to lead to resumed decline in lung function.[15] A prospective cohort study suggested that early management with low-

dose Sirolimus may be more effective at preserving lung function with fewer side effects. Reduced efficacy of Sirolimus was associated with increased duration of disease and lower lung function prior to starting the therapy.[16]

The prognosis of patients with LAM is uncertain; however, it is thought that the median survival is approximately 8 to 10 years after diagnosis. Some cases with long-term survival of 20 years after diagnosis have been reported.[3] A young age at onset, low initial TLCO and increased progression of LAM at diagnosis may be associated with a poorer prognosis.[2]

## CONCLUSION AND LEARNING POINTS

1) To consider other orphan lung conditions such as LAM early in the differential diagnosis of a primary spontaneous pneumothorax in female, pre-menopausal patients.

2) Following the diagnosis of LAM, patients must be investigated for extra-pulmonary manifestations, which could also lead to a further diagnosis of tuberous sclerosis (TSC-LAM can affect approximately 40% of patients with TSC).

3) Prognosis is uncertain; however, a young age at onset, low initial TLCO and increased progression of LAM at diagnosis may be unfavourable prognostic factors.

4) The mTOR inhibitor Sirolimus shows promise for effective treatment of LAM, especially if introduced early.

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