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Case Report

A 24-year-Old woman with recurrent pneumothoraces

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ABSTRACT

Lymphangioleiomyomatosis (LAM) is an abnormal proliferation of smooth muscle-like cells and may occur sporadically or in association with tuberous sclerosis complex. Patients are typically female, nonsmoking and may have cystic lung disease with pneumothorax. Diagnosis can be made by compatible imaging findings with a history of tuberous sclerosis complex, or in conjunction with vascular endothelial growth factor-D 800 pg/ml or greater, a highly specific finding. Sirolimus is first line treatment for LAM.

Abbreviations

TSC	Tuberous sclerosis complex
PTX	pneumothorax
CT	computed tomography
LAM	lympangioleiomyomatosis
S-LAM	sporadic-LAM
TSC-LAM	tuberous sclerosis-associated LAM
mTOR	mechanistic target of rapamycin
VEGF-D	Vascular Endothelial Growth Factor

1. Introduction

Lymphangioleiomyomatosis (LAM) is a rare progressive disease characterized by abnormal proliferation of smooth muscle cells in the lungs, causing cystic lung lesions. This is a disease typically of nonsmoking females, and is most often related to tuberous sclerosis complex (TSC) [1]. Here we report a female patient with LAM who initially presented for pneumothorax.

2. Case presentation

24-year-old female, non-smoker presented with a history of recurrent right-sided pneumothoraces. She was in her usual state of health until she developed a right-sided pneumothorax (PTX), which was initially managed conservatively with complete resolution. Over a period of six weeks, she experienced four recurrences of PTX, and was subsequently discharged on a Heimlich valve. After discharge from the hospital, she developed worsening hypoxic respiratory failure with chest pain and was admitted to our institution.

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3. Physical examination findings

Physical examination revealed a healthy-appearing young woman with absent breath sounds over her right lung base, with moderate respiratory distress but was able to complete sentences in full. Vital signs on presentation were notable for respiratory rate of 24/minute, SpO2 of 91% while on 4 L via standard nasal cannula, blood pressure of 118/74 mmHg, and heart rate of 104/minute. There were no abnormal cutaneous lesions or findings, joint edema, or tenderness noted. No cervical lymphadenopathy was observed.

4. Diagnostic studies

Chest radiograph showed a large right-sided PTX with small to moderate right-sided effusion (Fig. 1). Computed Tomography (CT) of the chest was performed that confirmed large right-sided PTX and ipsilateral pleural effusion (Fig. 2, Fig. 3). CT abdomen/pelvis showed numerous liver masses composed predominantly of macroscopic fat density, consistent with hepatic angiomyolipomas with surrounding hemorrhage and innumerable left renal angiomyolipomas. Thoracentesis was performed on the right and pleural fluid analysis was notable for WBC of 4900/mm^3 (79% lymphocytes), protein count 4.7 g/L, lactate dehydrogenase of 237 U/mL, and triglyceride count of 89 mg/dL. VEGF-D was found to be elevated to 4032 pg/ml.

She was ultimately diagnosed with LAM. She underwent right-sided tube thoracostomy for the PTX followed by definitive therapy for her secondary spontaneous PTX with povidone-iodine pleurodesis (Fig. 4). Her chest tube was removed successfully at discharge. She was referred to a LAM center for further management.

5. Discussion

LAM occurs predominantly in females of childbearing age at a prevalence of 3.4–7.8 per million women, without racial or geographical predilection. LAM may be in association with TSC in both men and women, or sporadic (S-LAM) in women from somatic

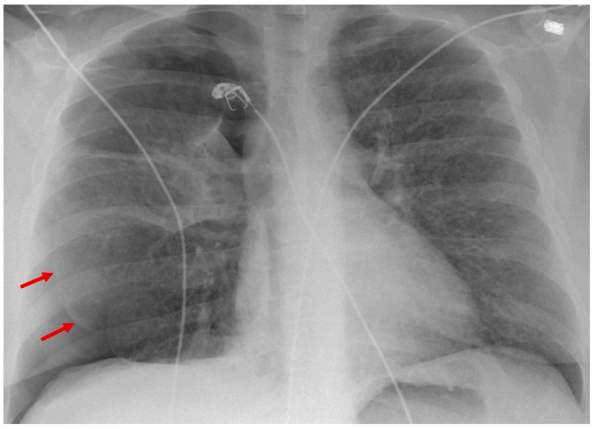

Fig. 1. Chest radiograph on presentation showing moderate right-sided pneumothorax (red arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

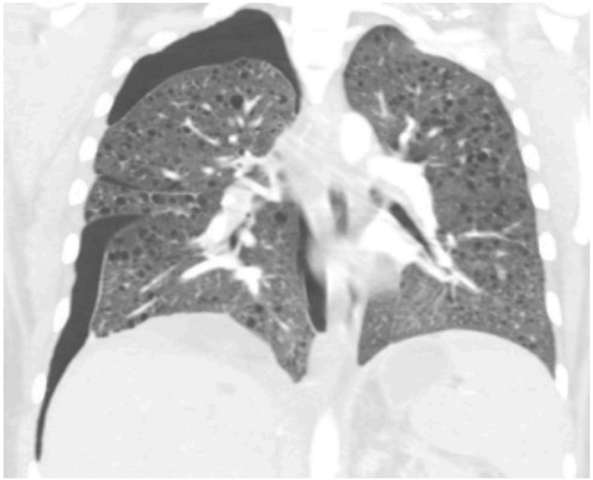

Fig. 2. Coronal section of non-contrast chest CT showing right-sided PTX with diffuse cysts bilaterally and small right-sided pleural effusion.

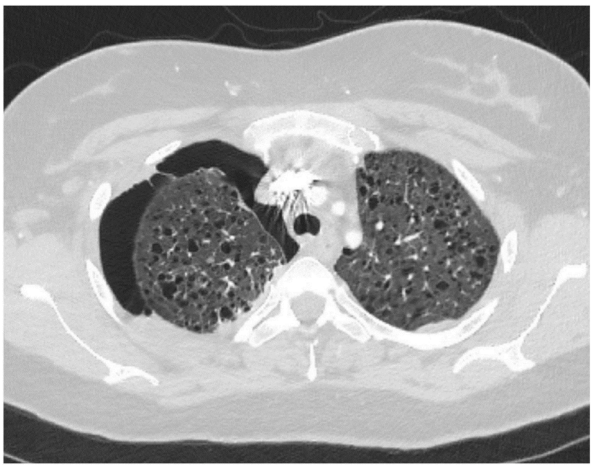

Fig. 3. Axial section of non-contrast chest CT showing right-sided PTX with diffuse cysts bilaterally and small right-sided pleural effusion.

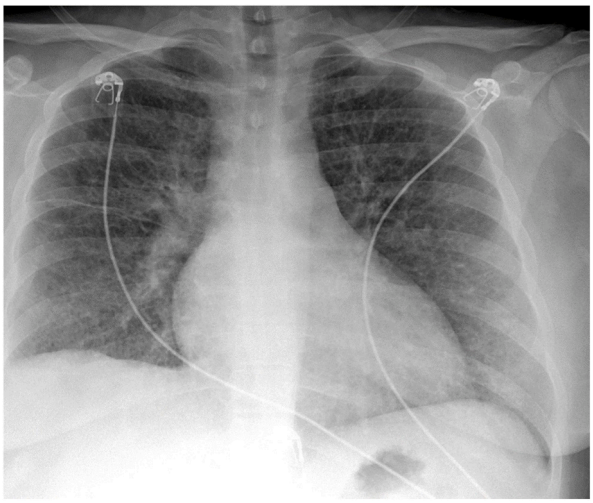

Fig. 4. Chest radiograph four days post-pleurodesis and removal of chest tube, showing resolution of right sided PTX.

mutations in the TSC2 gene. 30–60% of adult females with tuberous sclerosis have tuberous sclerosis-associated LAM (TSC-LAM) on imaging. 10–38% of males with tuberous sclerosis complex (TSC) may develop radiological evidence of LAM but they are rarely symptomatic.

LAM cells are of smooth muscle origin expressing actin, desmin, and vimentin, but also have granules containing melanoma-related protein like glycoprotein 100 and tyrosinase. LAM cells form nodules lining the airways and cysts which progressively destroy normal lung tissue as smooth muscle proliferates and releases proteolytic enzymes such as metalloproteinases. LAM cells also proliferate in lymphatics, eventually causing lymphatic obstruction and cystic dilatation resulting in the development of chylothroax. Further, these cells have estrogen and progesterone receptors, which may explain its female predilection. LAM cells have mutations in the TSC genes which results in constitutive activation of the downstream mechanistic target of rapamycin (mTOR) pathway, ultimately leading to cell survival and proliferation. Another downstream effect of this pathway is increased expression of vascular endothelial growth factor D (VEGF-D), a lymphangiogenic and angiogenic biomarker now used to aid in diagnosis [1,2].

Clinically, patients most commonly present initially with dyspnea. 65% of patients have PTX, which is typically recurrent, and 28% develop chylous pleural effusions over the course of their illness from infiltration of lymphatic channels as mentioned above. Less commonly, hemoptysis and chyloptysis may occur. Extra-pulmonary manifestations include lymphadenopathy, abdominal lymphangioleiomyomas, and angiomyolipomas. Angiomyoplipomas are most often in the kidney, but can occur in other organs such as the liver, lung, bowel, and bladder wall. Angiomyolipomas occur in 90% of patients with TSC-LAM, and in 30–40% of patients with S-LAM. These extrapulmonary features are sometimes the first signs of LAM [1,2].

Physical exam may be normal, unless complications of the disease are present such as pleural effusion and PTX when decreased or absent breath sounds are present. One should assess for features of tuberous sclerosis such as fibromas, angiomas, and hypomelanomic macules. Chest radiograph is often normal, but may show interstitial markings or pleural effusion early in the disease course. Pulmonary function testing most commonly shows reversible airflow obstruction, but may have a restrictive or mixed process, with

reduced diffusion capacity. CT of the chest shows characteristic diffuse thin-walled cysts, typically with normal lung parenchyma between the cysts but may have focal ground glass opacities [1,2]. S-LAM and TSC-LAM may have subtle differences in CT features. One retrospective study comparing the CT features of the two showed that S-LAM had more extensive lung involvement and lymphangioleiomyomas, while TSC-LAM had more pulmonary nodules, and renal/hepatic angiomyolipomas [3].

Importantly, LAM cysts in LAM must be distinguished from cysts in Langerhans' cell histiocytosis, Birt-Hogg-Dube, and emphysema among others entities. In Langerhans' cell histiocytosis, nodules are present, and cysts are thicker, stellate shaped, and predominantly in upper lobes with sparing of costophrenic angles and is predominant in smokers. Birt-Hogg-Dube cysts are thin, round, and mostly in the lower zone and associated with pleura and blood vessels [4].

Alpha-1 antitrypsin deficiency, connective tissue disease, and lymphoproliferative disease should be ruled out. Vascular Endothelial Growth Factor (VEGF-D) levels should be obtained in women, as levels over 800 pg/mL are highly specific for LAM. Abdomen and pelvis CT may show angiomyolipomas and lymphangioleiomyomas. Clinical diagnosis can be made with a compatible high resolution chest CT (diffuse, thin-walled and round cysts), with TSC, renal angiomyolipoma, VEGF-D≥ 800 pg/mL, chylous pleural effusion or chylous ascites, or cystic lymphagioleiomyoma. For definitive diagnosis of LAM in those with atypical history and imaging where diagnosis cannot be made clinically, lung biopsy can be obtained. Pathologically, LAM cells stain for actin, and for pre-melanocytic lineage which are identified by human melanoma black (HMB-45) antibody [1,2].

Treatment of LAM involves management of pulmonary complications and mTORC1 inhibitors to slow lung function decline. Secondary spontaneous PTX should be treated definitively with pleurodesis after the first episode given the high rate of PTX recurrence [2,5]. Although it has been suggested that preoperative talc pleurodesis results in higher complication rates at time of lung transplant, a small retrospective study suggested this was not the case in lung transplant for LAM [6]. As per American Thoracic Society (ATS) Guidelines, prior pleurodesis is not a contraindication to lung transplant in LAM patients [2]. Chylous pleural effusions can be drained for symptomatic relief, but the mTOR inhibitor, sirolimus, has been shown to reduce fluid accumulation. A 2011 MILES trial, a randomized control trial with 89 patients, demonstrated a slower decline of FEV1, improved forced vital capacity, and improved functional capacity in those who were treated with MTor inhibitor (Sirolimus) [7]. Subsequent subgroup analysis stratifying menopausal status, baseline pulmonary function testing, and bronchodilator responsiveness also demonstrated benefit [8]. Sirolimus is recommended in patients with FEV≤70% predicted and/or symptomatic chylous fluid accumulation (pleural or ascites). Sirolimus can be also considered in patients with FEV1 decline of ≥90 mL per year or manifestations suggesting high disease burden (requiring supplemental oxygen, air trapping, abnormal diffusion capacity, elevated residual volume on pulmonary function testing). Pregnant patients should be counseled that they are at increased risk of disease progression and complications. Lung transplant is performed in those with end-stage disease, with 73% 5-year survival, at 55% 10-year survival [1].

LAM is a progressively debilitating disease if left untreated. Patients usually develop worsening dyspnea and decline in FEV1 at a mean of 89 mL per year. Transplant-free survival probability is 94% at 5 years, 85% at 10 years, 75% at 15 years, and 64% at 20 years. Markers of worse prognosis are premenopausal status, dyspnea as initial presentation, abnormal baseline pulmonary function testing, or the need for supplemental oxygen [9].

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CRediT authorship contribution statement

Daniel J. Greenberg: Writing – original draft, Writing – review & editing. **Anuraag Sah:** Writing – original draft. **Amit Chopra:** Supervision, Writing – original draft. **Nagendra Madisi:** Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

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