CASE REPORT

A Rare Case of Recurrent Pneumothorax Associated with Tuberous Sclerosis

Raghu Srikanti[1], Kalaivani Shanmuganandavadivel[2], Sudheer Diyya[3], Uthara Natarajan[4], Thanujasri Vushakoyala[5], Balamani Ratnam Dollu[6], Dimple Nikhita Avanigadda[7], Siddavali Chagalamarri[8]

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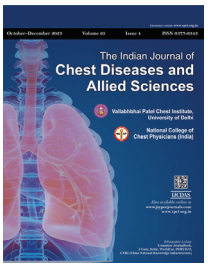

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Abstract

Lymphangioleiomyomatosis (LAM) is a multisystem disorder predominantly affecting women, characterized by cystic lung lesions, abdominal angiomyolipomas (AMLs), and lymphatic abnormalities. It may be sporadic or may also occur in tuberous sclerosis (TSC), an AD disorder resulting from germline mutations in TSC1 and TSC2 gene.

Lymphangioleiomyomatosis occurs in 30% of cases with the condition of TSC. Patients with TSC-LAM have the features of TSC in the form of hamartomas, developmental delay, and cutaneous manifestations, such as ash-leaf macules, facial angiofibromas, Shagreen patches, and seizures. Breathlessness being the most common symptom followed by spontaneous pneumothorax. Pneumothorax occurs in 60–70% of the LAM patients with the recurrence rate of 70%, which is the highest among all chronic lung diseases.

A 22-year-old female presented with sudden onset of dyspnea and pleuritic chest pain. O/E red papules on face involving nose, nasolabial folds, cheek, hypopigmented macules on legs are seen. The past H/O recurrent pneumothorax with repeated tube thoracostomy revealed the presence for 6 times in the past 2 years. H/O seizures revealed the occurrence of seizures from the childhood. Absent breath sounds on left side was observed on auscultation. Further investigations were done. Her complete blood count was normal. Chest radiograph showed multiple cystic lucencies present in the right upper and middle lobes. Left-sided pneumothorax was present.

Computed tomography of the chest showed multiple large cysts in the bilateral upper lobes and small cystic lesions in bilateral lower lobes. Pneumothorax was present on left side. Multiple sub-pleural exophytic cysts were seen at the apex. Computed tomography of abdomen showed multiple variable-sized hepatic lipomatous tumors likely AML. Both kidneys are enlarged showing variable-sized cysts and small AMLs. The MRI of brain had multiple bilateral T2 hypodense signal intensity in the bilateral periventricular region. Bilateral patchy lesions in the subcortical regions were present. Then she was managed with ICD tube thoracostomy, pleurodesis, tab. sirolimus.

Conclusion: Definite LAM may be diagnosed in the presence of characteristic lung high-resolution computed tomography (HRCT) and any of the following: angiomyolipoma (kidney)/thoracic or abdominal chylous effusion/lymphangioleiomyoma or lymphadenopathy/TSC.

Lymphangioleiomyomatosis is a disease of women that usually occurs at the reproductive age. Lymphangioleiomyomatosis should be in differential diagnosis of cystic lung disease and recurrent pneumothorax.

Keywords: Case report, Lymphangioleiomyomatosis, Pneumothorax, Tuberous sclerosis.

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Abbreviations used in this Article

AMLs = Angiomyolipomas; FEV1 = Forced expiratory volume; FVC = Forced vital capacity; GHCCD = Government Hospital for Chest and Communicable Diseases; HRCT = High-resolution computed tomography; LAM = Lymphangioleiomyomatosis; RV = Residual volume; TSC = Tuberous sclerosis; TSC1 = Mutations in tuberous sclerosis complex 1; TSC2 = Tuberous sclerosis complex 2; VATS = Video-assisted thoracoscopic surgery.

Introduction

Lymphangioleiomyomatosis (LAM) is a disorder involving multiple systems which primarily affects women, and is characterized by cystic lesions in the lung, angiomyolipomas (AMLs), and abnormalities in lymphatics. Lymphangioleiomyomatosis is defined clinically by symptoms, such as progressive dyspnea, exhaustion, persistent cough, and chest pain. Pulmonary function tests show either an obstructive or mixed pattern. It may be sporadic or may also occur in tuberous sclerosis (TSC), an autosomal dominant disorder resulting from germline mutations in tuberous sclerosis complex 1 (TSC1) and tuberous sclerosis complex 2 (TSC2) gene.

[1–8]Department of Pulmonary Medicine, Guntur Medical College, Guntur, Andhra Pradesh, India

Corresponding Author: Raghu Srikanti, Department of Pulmonary Medicine, Guntur Medical College, Guntur, Andhra Pradesh, India, Phone: +91 9440181510, e-mail: drraghus@yahoo.com

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Case Description

A 22-year-old female came to our Pulmonary Medicine Department, Government Hospital for Chest and Communicable Diseases (GHCCD) with complaints of sudden onset dyspnea and chest pain which was pleuritic in nature on the left side of the chest.

On examination, red colored papules were seen over nose, cheeks, and nasolabial folds (Fig. 1). Hypopigmented macules were seen over legs. She had a past history of recurrent pneumothorax for which tube thoracostomy was done for 6 times in the last 2 years. A history of seizures from the childhood was present. Absent breath sounds were noted in the left side on auscultation.

Her complete blood count was normal. Her chest X-ray showed multiple cystic lucencies present in the right upper and middle lobes and pneumothorax on the left side. In her computed tomography (CT) of the chest, both upper lobes showed large cystic lesions and both lower lobes showed small cysts. On the left side, pneumothorax was seen (Fig. 2). Sub-pleural multiple exophytic cysts were seen at the apex. She was further evaluated for cystic lung diseases.

Her CT abdomen showed multiple variable-sized hepatic lipomatous tumors likely AML (Fig. 3). Both kidneys were enlarged showing variable-sized cysts and small AMLs.

MRI brain showed multiple bilateral T2 hypotense signal intensity in periventricular region (Fig. 4). Bilateral patchy lesions were present in the subcortical regions. She was finally diagnosed as pulmonary LAM associated with TSC. Pneumothorax was managed by tube thoracostomy (Fig. 5). Pleurodesis was done due to high chance of recurring pneumothorax and she was started on sirolimus. Gradually, she was recovered and finally discharged.

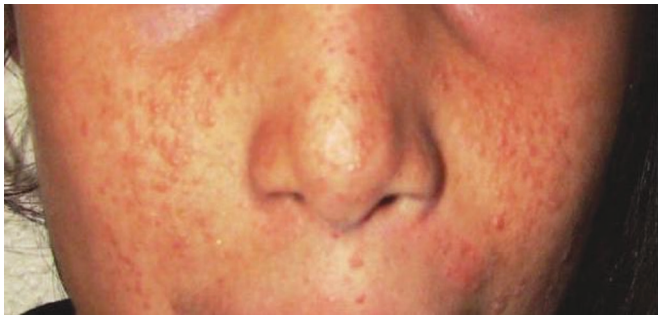

Fig. 1: Facial angiofibromas involving nose, nasolabial folds, and cheek

Discussion

Lymphangioleiomyomatosis is a rare cystic interstitial lung disease that most commonly affects women of child-bearing age and is associated with proliferation of smooth muscle cells in lung and cystic destruction of lungs and the accumulation of LAM cells within the lungs and axial lymphatics.[1] Lymphangioleiomyomatosis exists in two primary forms: sporadic LAM and LAM associated with TSC. Sporadic LAM is rare and occurs 1 in 1,000,000 people[2,3] of whole population. Lymphangioleiomyomatosis associated with the genetic disease like TSC is usually identified in 40% of adult females.[4–6] In LAM patients, 15% is constituted by TSC-LAM, but in TSC patients, LAM can occur in 30% of the patients.[1]

Clinical Features

Pneumothorax, progressing dyspnea, and chylothorax are the most prevalent pulmonary symptoms, which typically predominate the clinical course.[7–11] Persistent cough, hemoptysis are the other pulmonary symptoms. Breathlessness occurring in LAM is due to airflow obstruction and lung parenchymal destruction by cysts.

Spirometry may be varied from no abnormalities to obstructive or mixed pattern. Initially, due to proliferation of smooth muscle in the bronchi obstructive pattern will be seen but alveolar air trapping and cysts and bullae formation leads to restriction pattern later. Cellular proliferation of smooth muscle in the bronchial walls and vascular walls results in the reduction in diffusion capacity and also leads to cor-pulmonale and respiratory failure.[12]

Lymphadenopathy, massive lymphatic cystic masses (called lymphangioleiomyomas), and chylous abdominal collections are examples of extrapulmonary symptoms of LAM,[13,14] and in 50% of the cases angiomyolipoma of kidneys.[14–16] Commonly found in the abdomen, pelvis and retroperitoneum. Lymphangioleiomyomas can also occasionally be found in the neck and mediastinum. They can cause symptoms, such as nausea, abdominal distension, vomiting, bloating, pedal edema, and urinary problems.[17]

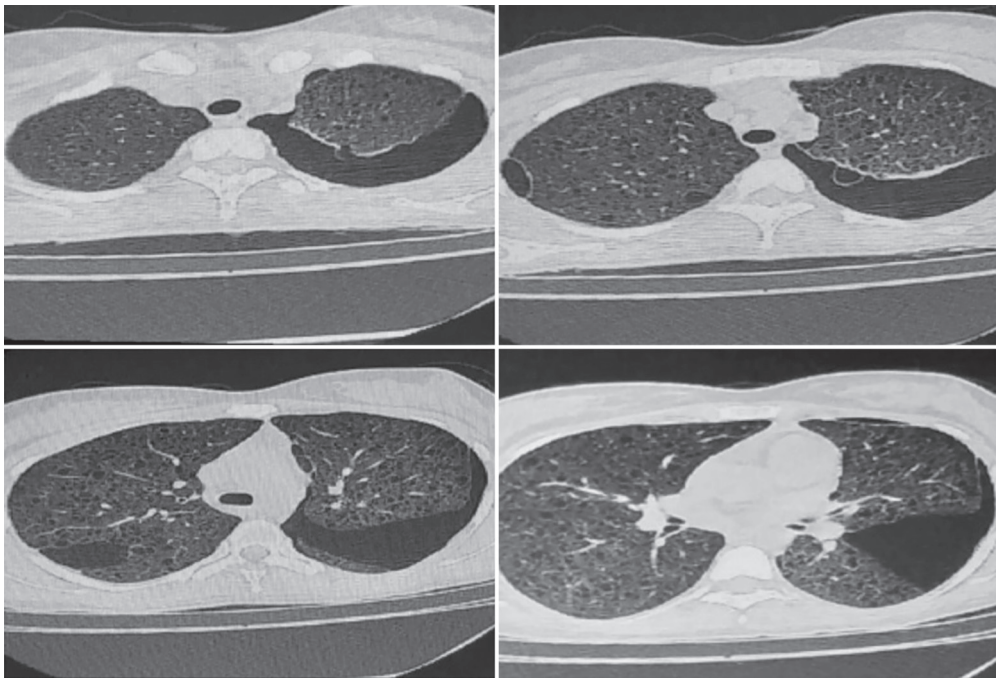

Fig. 2: Computed tomography (CT) chest showing bilateral cystic lesions and left-sided pneumothorax

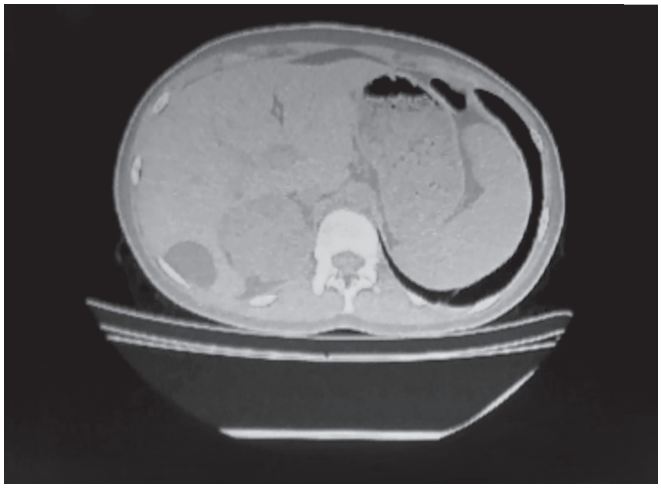

Fig. 3: Computed tomography abdomen showing hepatic angiomyolipoma

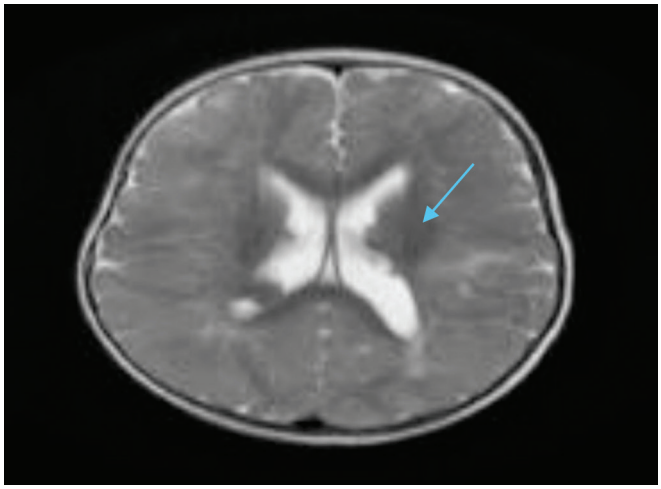

Fig. 4: MRI brain showing bilateral T2 hypotense signal intensity lesion in periventricular region

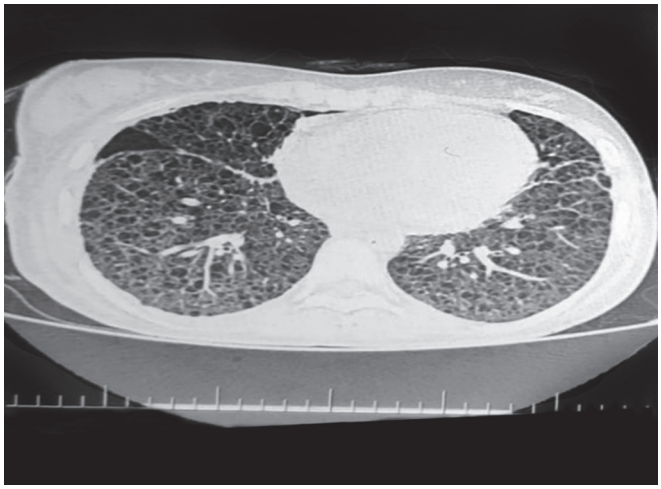

Fig. 5: CT chest of the same patient showing expanded lung after tube thoracostomy

Angiomyolipoma is the most typical abdominal presenting feature of LAM. When patients are screened by CT scan it will present in up to 50% of patients. These tumors are usually asymptomatic.[14–16] Multiple or large tumors may bleed and cause symptoms, such as hematuria, abdominal pain, and bleeding that can be occasionally fatal.[18–20]

Most individuals present with dyspnea and cough as their initial sign of pneumothorax. Chylothorax and hemoptysis are less frequent appearances. Occasionally, LAM presents with extrapulmonary symptoms, most often bleeding from AMLs.[3] However, most often, the diagnosis is made by abdominal and pelvic masses.[13,21] In rare presentations, abdominal symptoms may appear years before respiratory symptoms appear, and final diagnosis is determined with the appearance of respiratory symptoms.

TSC-LAM patients present with clinical manifestations of TSC which includes delayed development, seizures, hamartomas of central nervous system, and skin manifestations, such as Shagreen patches and ash-leaf macules.

Whereas S-LAM patients have progressing dyspnea during exertion, persistent cough without expectoration, spontaneous chylothorax, or pneumothorax and often presented with renal AMLs.[22] Dyspnea is the most prevalent symptom (75%) due to chylous pleural effusion in 20% of patients and pneumothorax in 50% of the patients. Spontaneous pneumothorax occurring in 60–70% of the patients with 70% of recurrence rate is the most common among chronic pulmonary diseases.[23]

Patients with TSC associated LAM often present with breathlessness which is gradually progressive, but patients with sporadic LAM have dyspnea which is more acute in onset often as spontaneous pneumothorax. Our case has initial manifestations of nervous system like multiple seizure episodes from childhood and subsequently, she developed pneumothorax, most often due to tear of pre-existing cystic lung lesions.

Our patient would have TSC-LAM as she had symptoms like seizure episodes since childhood, neurocutaneous markers such as ash-leaf macule and Shagreen patch, facial angiofibromas, and recurrent spontaneous pneumothorax, and breathlessness.

Premenopausal women who use oral contraceptives[22,24] have been observed to have LAM, and the incidence rises during pregnancy.[25,26] Therefore, it has been suggested that estrogen plays a part in its etiopathogenesis. The patient in our instance was a young woman who was premenopausal and had never used oral contraceptives before.

Diagnosis

In diagnosing a patient with LAM, reticulonodular or reticular pattern with hyperinflated lung is typically visible on a plain X-ray chest image. On a standard chest X-ray, cysts and bullae are visible. But only on high-resolution computed tomography (HRCT) their precise anatomical delineations are visible.[9,23,27] Based on the cyst type, their distribution pattern, and other coexisting lesions, cystic lung diseases can be easily distinguished from one another.[28]

In 2012, the International Tuberous Sclerosis Complex Consensus Conference updated the TSC diagnosis criteria (Tables 1 and 2). Definitive TSC – two major features or one major feature plus two or more minor features. Two major criteria were met by our young female patient.

The existence of distinctive and compatible HRCT chest and lung biopsy, or distinctive features on lung HRCT with any combination of TSC or renal angiomyolipoma, are the definite

Table 1: The diagnostic criteria 2012 by International Tuberous Sclerosis Complex Consensus Conference – Major criteria

Facial angiofibromas or fibrous cephalic plaque	Nontraumatic ungual or periungual fibromas	Subependymal giant cell astrocytoma
Cortical dysplasias	Subependymal nodules	Lymphagioleiomyomatosis
Renal angiomyolipoma	Hypomelanotic macules at least 5 mm diameter	Cardiac rabhdomyomas
Shagreen patch	Multiple retinal hamartomas	

Table 2: The diagnostic criteria 2012 by International Tuberous Sclerosis Complex Consensus Conference – Minor criteria

Multiple dental enamel pits	Retinal achromic patch
Intra oral fibromas	Confetti skin lesions
Non renal hamartomas	Multiple renal cysts

diagnostic criteria for LAM.[29] However, in this case, histological diagnosis of pulmonary LAM was not made because our patient was not willing for lung biopsy. However, in the presence of a clinical setting, our patient's HRCT findings confirmed the diagnosis.

Treatment

The definitive treatment for pulmonary LAM is none. Bronchodilators are employed in the treatment of symptoms. Intercostal chest tube drainage can be used for management of pneumothorax. nonetheless, in order to treat lung bleb, resection and to prevent recurrence pleurodesis or occasionally video-assisted thoracoscopic surgery (VATS) are frequently needed.[30] Regarding hormonal therapy progesterone, anti-estrogen, such as tamoxifen and oophorectomy have been explored but not very successful. Sirolimus, mTOR pathway blocker were used as a promising treatment for LAM. Sirolimus significantly reduced the volume of angiomyolipoma and improved forced vital capacity (FVC), residual volume (RV), and forced expiratory volume (FEV1).[31] When a patient has severe hypoxemia, repeated refractory pneumothorax, or deteriorating pulmonary function (FEV1 < 30% of expected FEV1), lung transplantation is considered usually. End-stage pulmonary LAM may benefit from lung transplantation; yet, recurrence may also happen because of LAM cell migration into the new transplanted lung.

Conclusion

Being an extremely rare disease, knowing that LAM can induce spontaneous recurrent pneumothorax, particularly in young girls, primary care physicians might benefit from as this information can aid in the diagnosis. Women with LAM are typically of reproductive age. Lymphangioleiomyomatosis ought to be considered in the differential diagnosis of recurrent pneumothorax and cystic pulmonary diseases.

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