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An Enigmatic pulmonary manifestation of Tuberous Sclerosis: Spontaneous pneumothorax in a young female with lymphangioleiomyomatosis

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Abstract

Introduction: Lymphangioleiomyomatosis (LAM) is a primary disease of the lung parenchyma typified by abnormal growth of atypical smooth muscle cells in the lung vasculature, lymphatics, and alveoli that leads to the formation of multiple cysts in the lungs bilaterally causing respiratory symptoms, such as fatigue and dyspnoea on exertion. The main involved organs are the lungs. LAM can present sporadically (S-LAM) or can be associated with tuberous sclerosis complex (TSC-LAM). ***Case report:*** A 32-year-old nulligravida presented to the hospital, with sudden onset acute dyspnoea. The patient exhibited distinctive facial features of angiofibromas, hypopigmented macules, hamartomas, subungual angiofibromas. Air entry was significantly reduced on both lung fields. The diagnosis of spontaneous pneumothorax secondary to lymphangioleiomyomatosis was made. The patient was subjected to urgent chest radiograph followed by CT chest which showed bilateral gross to moderate pneumothorax. The patient was immediately subjected to ICD insertion on emergency basis. ***Discussion:*** In LAM spontaneous pneumothorax is a common complication that requires a prompt management. In adults TSC patients, LAM is a major cause of death. With advent of mTOR inhibitors for renal disease, LAM is now second most common cause of death. ***Conclusion:*** Lymphangioleiomyomatosis is a rare multisystem disorder that mostly affects middle aged females. The prognosis is poor and management is based on supportive care, use of sirolimus [11]and managing complications like pneumothorax. Since FDA approved therapy is available, prompt diagnosis of LAM is crucial.

Keywords: Lymphangioleiomyomatosis; Tuberous Sclerosis Complex; Spontaneous Pneumothorax; Angiomyolipoma; Sirolimus.

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a primary disease of the lung parenchyma typified by abnormal growth of atypical smooth muscle cells in the lung vasculature, lymphatics, and alveoli that leads to the formation of multiple cysts in the lungs bilaterally causing respiratory symptoms, such as fatigue and dyspnoea on exertion. The main involved organs are the lungs. LAM can present sporadically (S-LAM) or can be associated with tuberous sclerosis complex (TSC-LAM); however, pathologically, these two types are indistinguishable. LAM primarily affects females particularly of child bearing age group. While sporadic LAM is extremely rare, the prevalence rates in females in TSC range from 26-50 percent. Based on worldwide prevalence, 30 percent of the females with TSC develop cystic changes consistence with LAM. However, the majority of females with TSC-LAM have normal lung function. ***[1]***

Here we present a case of 32-year-old female who presented to us with gradually progressive dyspnoea, facial angiofibromas, hamartomas, subungual angiofibromas, and hypopigmented macules. The pathogenic variant of TSC could not be known due to lack of genetic testing, but it was considered to be De novo, due to absence of any significant family history.

Case Report:

A 32-year-old nulligravida presented to the tertiary care centre, with sudden onset acute dyspnoea since 4 days. The patient exhibited distinctive facial features of angiofibromas, hypopigmented macules, hamartomas at nape of neck and subungual angiofibromas. The patient also had history of diminution of vision since 15 years of age.

The patient had these facial angiofibromas since 4 years of age, when she was diagnosed as ‘epiloia’. Contrary to this diagnosis the patient never had an episode of seizure or no intellectual disability, she was educated till class 10.

On further general examination, patient had hypopigmented macules on lower back, subungual fibromas over both the thumbs and involving greater toe of both the feet along with second and third toe of left foot. Patient also had hypopigmented macules on back, and hamartoma measuring about 8cm *4 cm on nape of the neck. Patient had no perception of light. Fundus examination was within normal limits.

Patient on presentation to the hospital was tachypnic with respiratory rate of more than 30 per minute and her saturation was 80 percent on room air. On auscultation of chest the air entry was significantly reduced on both the sides. Electrocardiogram showed no significant finding. 2d echo showed normal study. The examination of rest of the systems were normal. Based upon these findings diagnosis of spontaneous pneumothorax secondary to lymphangioleiomyomatosis was made. The patient was subjected to urgent chest radiograph followed by CT chest which showed bilateral gross to moderate pneumothorax. The patient was immediately subjected to ICD insertion on emergency basis.

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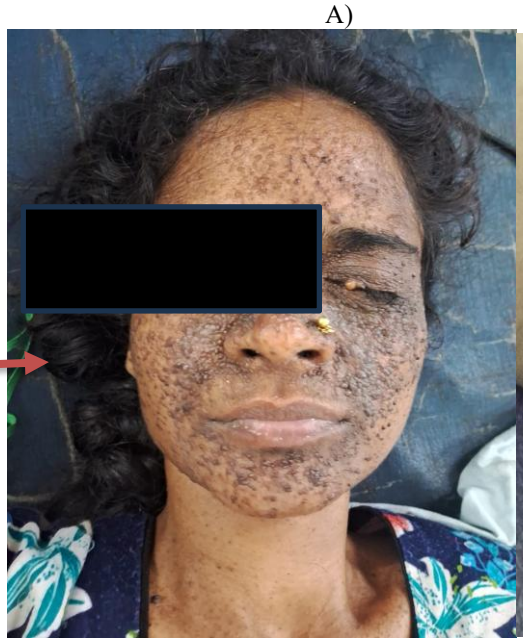

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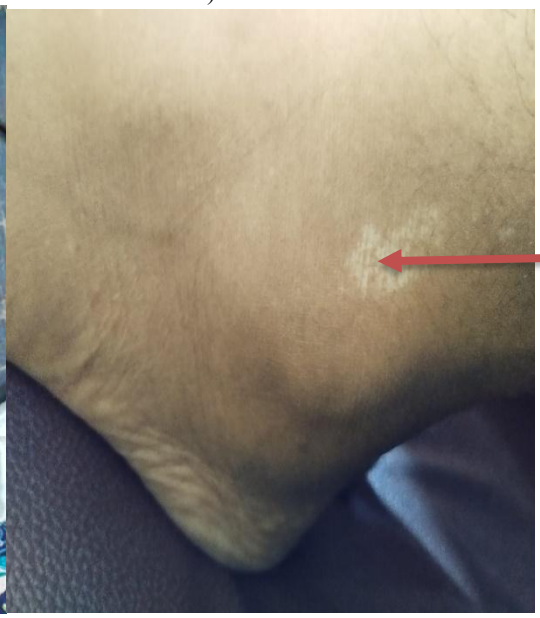

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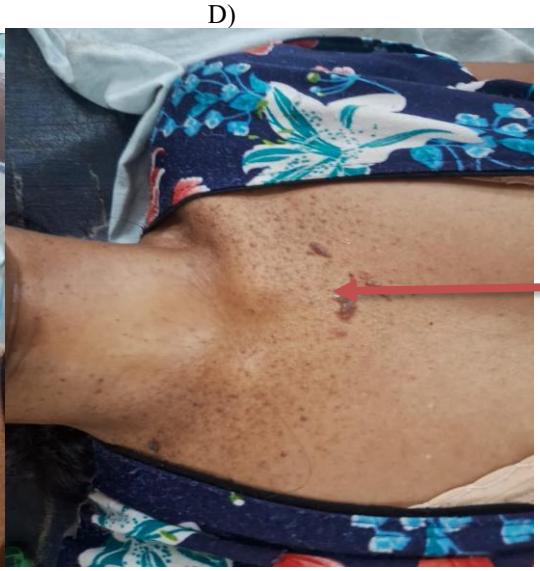

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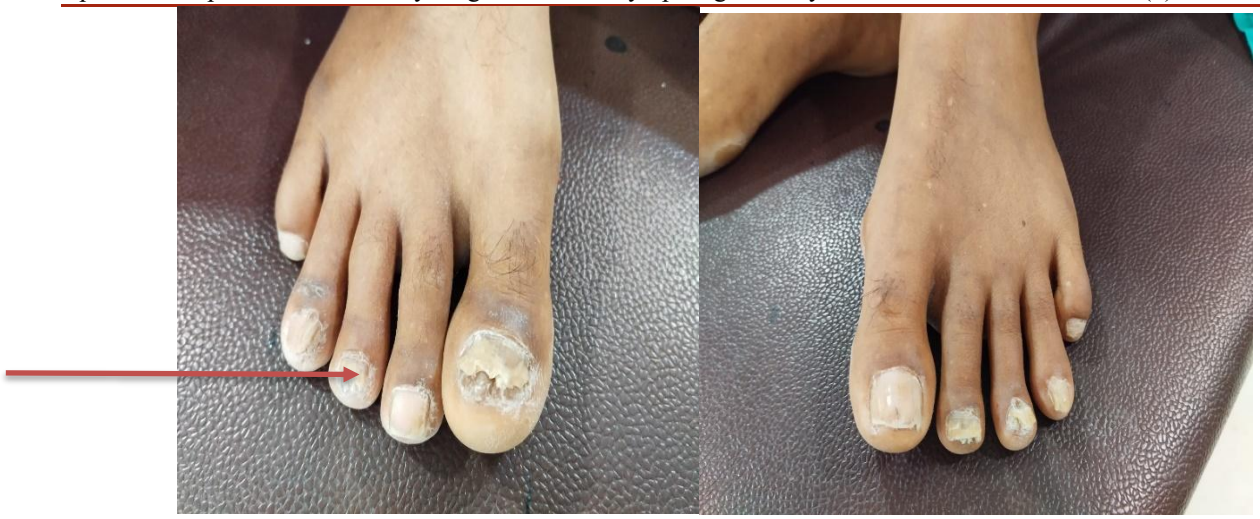

Clinical photographs of the patient showing various clinical features.
A) Facial angiofibromas B) Ash leaf macules
C) Tuber D) Confetti skin lesions
E) Subungual angiofibroma

Radiological investigations:
The patient was subjected to various radiological investigations like ultrasonography of the abdomen and pelvis which showed bilateral renal angiomyolipomas and hepatic angiomyolipoma, which was later confirmed by contrast enhanced CT of the abdomen.

Contrast scan of the thorax showed left sided gross (maximum thickness 10.1 cm) and right sided moderate (maximum thickness 8.3 cm) pneumothorax with underlying lung collapse. Multiple well-defined round to oval thin-walled cysts of average size 2cm noted in bilateral lung parenchyma suggestive of lymphangiolieomyomatosis.

MRI plain and contrast scan of brain showed, cortical and subcortical tubers and radial bands, subependymal nodules in bilateral lateral ventricles, subependymal giant cell astrocytoma (SEGA) with moderate obstructive hydrocephalus.

Haematological investigations were normal except for the thrombocytosis.

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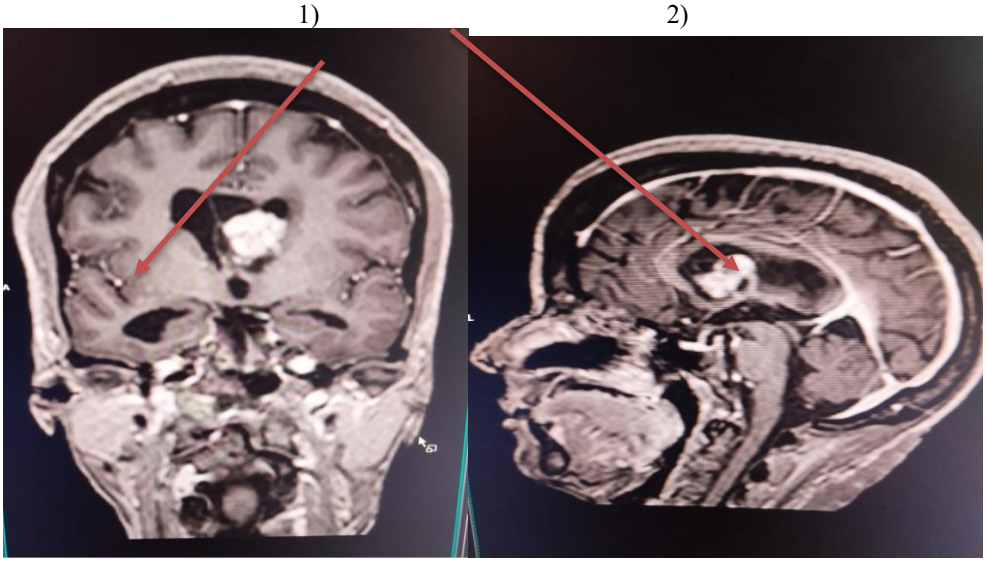

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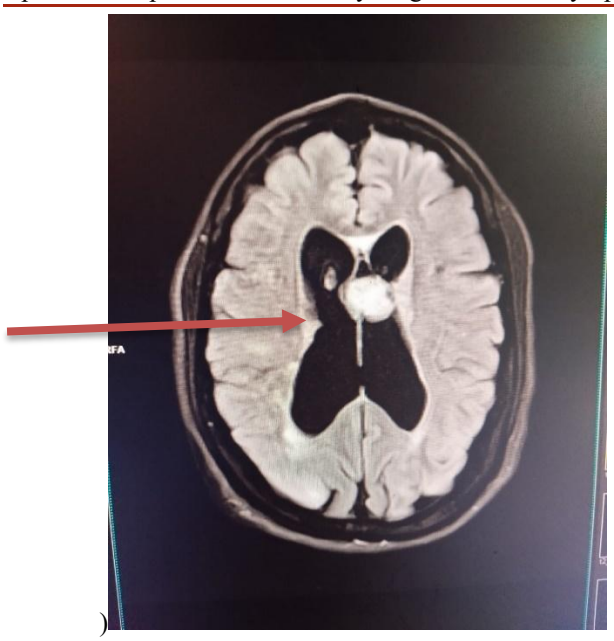

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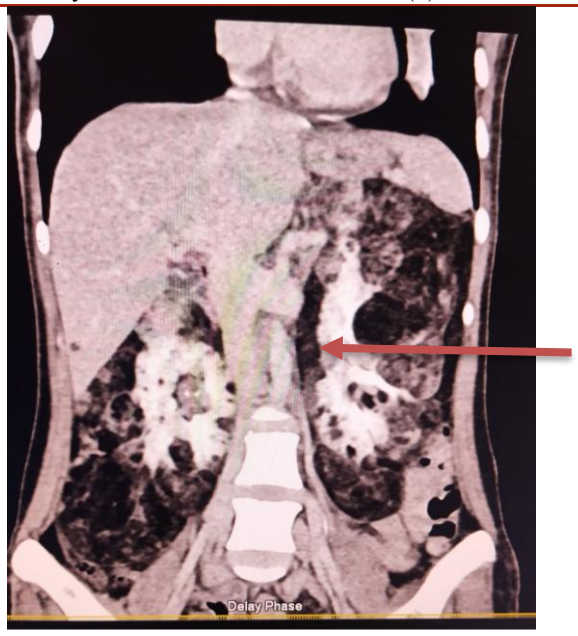

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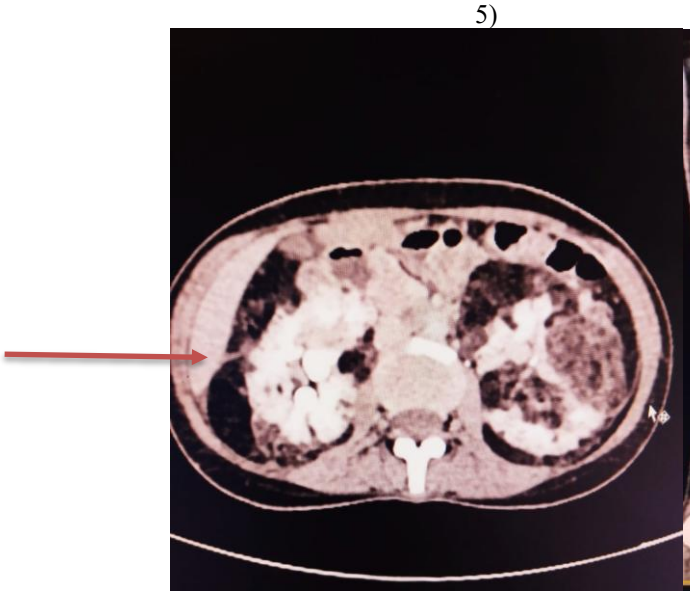

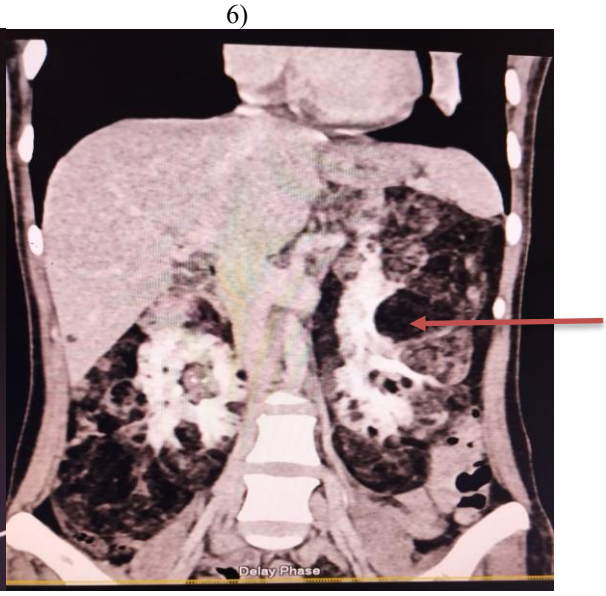

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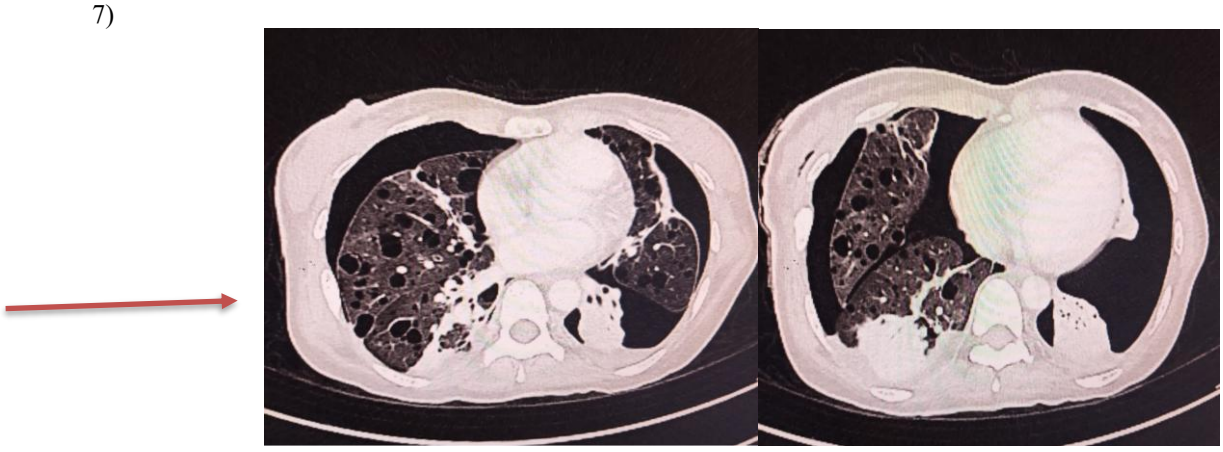

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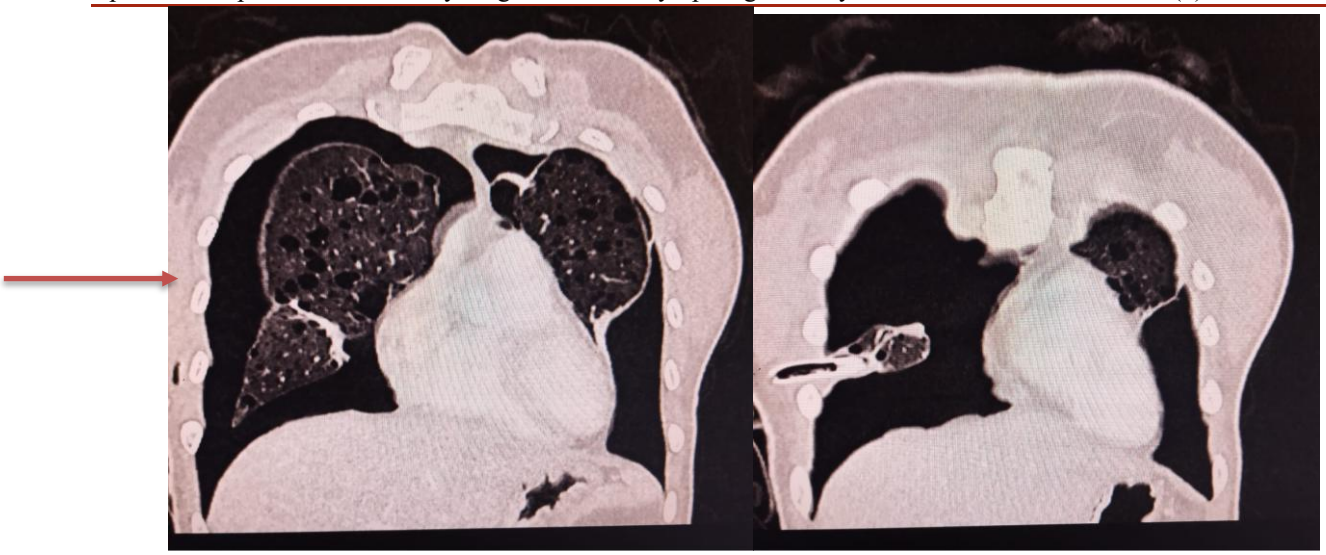

Based on clinical criteria, definite diagnosis of tuberous sclerosis was made.
1),2),3) subependymal giant cell astrocytoma.
4),5),6) renal angiomyolipomas.
7),8) lymphangioleiomyomatosis in lungs with pneumothorax.

DISCUSSION

TSC is an autosomal dominant genetic disorder, has an incidence of approximately 1 in 5000 to 10000 live births with high prevalence of LAM among adults. Several studies report prevalence rates in females with TSC (mostly TSC2 mutations) that range from 26 to 50 percent. Rates increase with age after 15 years with highest rates (up to 80 percent) reported in females over the age of 40 years and lowest rates (27 percent) in those <21 years. [Harrison 21 edition, neurocutaneous disorders],[1]

Unlike sporadic LAM, which is extremely rare in males, LAM can occur in males with TSC. The rates of cystic lung disease in males with TSC range from 10 to 38 percent. [1]

The high prevalence of LAM in TSC has led to the identification of a critical role for mutations in the TSC genes, particularly in the TSC2, in the smooth muscle cell proliferation which is characteristic of LAM lesions. In support of this hypothesis LAM mostly occurs among patients with TSC2 mutations and is rare in patients with TSC1 mutations. [1]

The primary histopathologic abnormality in LAM is the proliferation of atypical smooth muscle-like cells. Reports from several groups support a dominant role for loss of function of the tuberous sclerosis proteins, tuberin or hamartin, in the pathogenesis of LAM. Tuberin is the protein product of the TSC2, which is located on chromosome 16p13. Tuberin complexes with hamartin, a sister protein that is encoded by TSC 1 gene located on chromosome 9q34. The tuberin-hamartin complex hetero-oligomer functions as tumour suppressor complex that inhibits mechanistic target of rapamycin(mTOR), which in turn integrates and controls cellular signals that regulate cell growth, cell size, cell survival and autophagy. Pathogenic loss-of-function variants in TSC1 or TSC2, leads to destabilization of the hamartin-tuberin complex, the main negative modulator of the mTOR signalling pathway. This complex normally functions via GTPase activating protein activity to cleave GTP from RAS homolog enriched in brain (Rheb), a regulator of mTOR, and inhibit Rheb activity. mTOR interacts with raptor (regulatory protein associated with mTOR) and other components to form mTOR complex 1. When activated via Rheb mTORC 1 leads to phosphorylation of downstream targets that regulate protein and lipid synthesis, cellular growth, mitochondrial proliferation, and autophagy. [2],[3]

Thus, pathogenic TSC1 or TSC2 variants lead to inactivation of tuberin-hamartin complex, loss of GTPase activity, an increase of GTP-activated Rheb, and hyperactivation of mTORC1 activity thereby releasing an inhibitory influence on the cell cycle. [2],[3]

The patient presented with progressive dyspnoea and with classic TSC features except for cognitive disability and seizures. She had bilateral renal angiomyolipomas (AML), which are more frequent in TSC-LAM (>80 percent) when compared with TSC LAM.

Clinical criteria for Tuberous Sclerosis: [4][8]
The clinical diagnostic criteria for TSC include 11 major and 7 minor features.
Major features: The following are the major clinical features of TSC:

- Hypomelanotic macules (>3, at least 5 mm diameter)
- Angiofibromas (>3) or fibrous cephalic plaque.
- Ungual fibromas (>2)

- Shagreen patch
- Multiple retinal hamartomas
- Multiple cortical tubers and/or radial migration lines
- Subependymal nodules (>2)
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma
- Lymphangiolieomyomatosis (LAM)*
- Angiomyolipomas (>2) *

*A combination of LAM and angiomyolipomas without other clinical features does not meet criteria for a definite diagnosis.

Minor features: The following are the minor features: [4][8]

- Confetti skin lesions (1 to 2mm hypomelanotic macules)
- Dental enamel pits (>3)
- Intraoral fibromas (>2)
- Retinal achromic patch
- Multiple renal cysts
- Non renal hamartomas
- Sclerotic bone lesions

Diagnostic certainty – The diagnostic certainty of TSC depends upon the number of major and minor features: [4]

- Definite TSC requires two major features or one major and two or more minor features.
- Possible TSC requires either one major feature or two or more minor features.

The diagnosis of TSC-Lam is typically made by identifying characteristic high resolution computed tomography findings in patients with established diagnosis of TSC [6][7][10][11]. The presence of an angiomyolipoma (as in our case) and/or elevated vascular growth factor-D and/or other features of LAM such as chylous effusion confirm the diagnosis of LAM but their absence does not preclude it. This patient had multiple well-defined round to oval thin-walled cysts of average size 2cm noted in bilateral lung parenchyma on contrast scan of the thorax, suggestive of lymphangiolieomyomatosis. A definitive diagnosis can be made via lung tissue obtained by lung biopsy but definitive histopathological diagnosis is generally not necessary. [6],[7]. In LAM spontaneous pneumothorax is a common complication that requires a prompt management. This patient was managed in the acute setting with placement of an anterolateral left followed by right sided chest tube, with under water seal. Because the recurrence of pneumothorax is frequent, pleurodesis is often recommended. Supplemental oxygen was indicated in this patient during the rest due to desaturation. The patient may have signs and symptoms of reasonably associated with desaturation such as erythrocytosis or pulmonary hypertension. General measures used to treat TSC-LAM include avoidance of oestrogen containing medications and contraceptives, avoidance of smoking, supplemental oxygen for hypoxemia and bronchodilators.[6][7]

The mTOR inhibitor sirolimus, is the first line therapy for patients who have severely reduced lung function. For patients with those refractory to mTOR inhibitors, clinical trials or lung transplantation are main options. [6][7][10][11]

Patients with TSC-LAM should be monitored for progressive lung function decline with pulmonary function testing and for the development of any complications.

In adults TSC patients, LAM is a major cause of death together with renal disease and sudden death from epilepsy (SUDEP). With advent of mTOR inhibitors and aggressive approaches for renal disease, a single centre retrospective study suggests that fewer patients are dying from renal complications and LAM is now second most common cause of death after SUDEP [6]. Some case series report that presentation with dyspnoea on exertion, as opposed to pneumothorax, is associated with worse prognosis. This is intuitively plausible, because a sentinel pneumothorax may reveal LAM in early stages. Conversely it is believed that good prognostic features include older age, post menopausal status, initial presentation with pneumothorax, and normal or mild dysfunction on pulmonary function tests. [6][9]

CONCLUSION

Lymphangioleiomyomatosis is a rare multisystem disorder that mostly affects middle aged females. Here we have discussed the case of TSC-LAM. The prognosis is generally poor and management is based on supportive care, use of sirolimus [11]and managing related complications like pneumothorax. Since FDA approved therapy is available, prompt diagnosis of LAM is crucial.

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