CASE REPORT

Tuberous sclerosis associated lymphangioleiomyomatosis: A case report

Aiman Mushir, Sohail Akhtar, Mujahid Hussain

Abstract

Lymphangioleiomyomatosis (LAM) is a multisystem disorder that primarily affects the lung. Tuberous sclerosis complex (TSC) is characterized by multiple benign tumours of the skin, brain, eyes, heart, lung, liver, and kidney. LAM can be either sporadic (sporadic-LAM) or in association with Tuberous Sclerosis (TSC-LAM). Many clinical, radiologic, and pathologic features are shared between TSC and sporadic variants. We present a case admitted at The Indus Hospital Karachi with pneumothorax and multiple manifestations of TSC-LAM.

Keywords: Tuberous sclerosis, (Lymphangioleiomyomatosis), Cysticlungdisease, (Pneumothorax), Genetics.

DOI: https://doi.org/10.47391/JPMA.5546

Submission completion date: 14-02-2022

Acceptance date: 26-09-2022

Introduction

Lymphangioleiomyomatosis (LAM) is known to be a disorder affecting multiple systems, however primarily it affects the lungs, while tuberous sclerosis complex (TSC) is another rare entity in which a patient may suffer from benign tumours involving the skin, brain, heart, eyes, liver or kidneys. We mention the two together here as there is a well-established association between the two.

LAM can occur without any association; that is, sporadic (sporadic-LAM) or can be found to be associated with Tuberous Sclerosis (TSC-LAM). Many clinical, radiologic, and pathologic features are shared between the two variants (TSC-LAM and sporadic LAM).

We present a case admitted at The Indus Hospital Karachi with pneumothorax and multiple manifestations of TSC-LAM.

Case Report

A 17-year-old female resident of Dadu Sindh presented to Emergency department of The Indus Hospital, Karachi on 3rd March 2021, with left sided chest pain and shortness of breath for ten days without cough, sputum production, haemoptysis or history of trauma. Clinical examination and chest radiograph confirmed left sided simple pneumothorax. Her past medical history included seizures at the age of fifteen days, recurrent hyperventilation and fainting for one year, self-limiting and lasting few minutes. There were no witnessed true seizures. She did not take any medications. She had no developmental delays in her history, her menstrual cycles were timely and the last cycle ended four days prior to admission. Tube thoracostomy was done and she was admitted for further management.

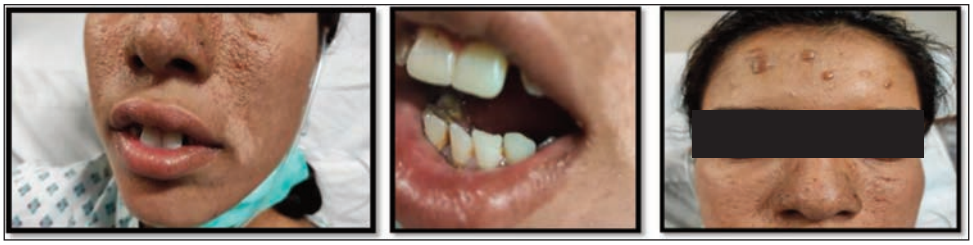

Image A: Facial angiofibromas and hypopigmented ash leaf lesions seen.

Image B: Dental pits.

Image C: Angiofibromas on the forehead.

She had multiple skin lesions; fibrous plaques on the forehead, facial angiofibromas over the nose extending up to cheeks (image A); hypopigmented skin lesion on left upper lip (image C); dental pits (image B). She had similar hypopigmented areas on her back, along with a raised fibrous patch (shagreen patch) (image D).

Apart from the left pneumothorax, a computerized tomographic (CT) scan of chest showed randomly

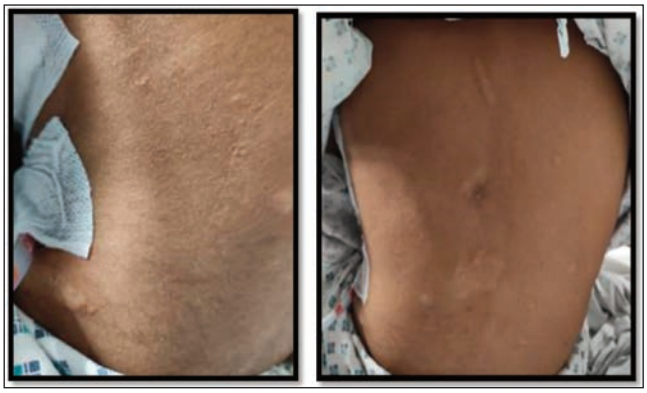

Image D-1: Shagreens Patch.

Image D-2: Shagreen patch and hypopigmented lesions on the back.

Department of Pulmonology, The Indus Hospital, Karachi, Pakistan.
Correspondence: Aiman Mushir. e-mail: aimanmushir@live.com

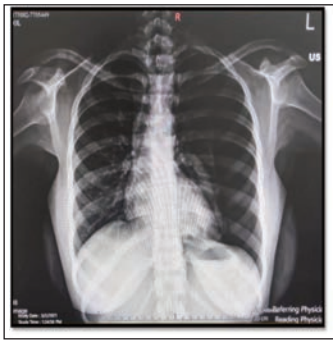

Image E: Chest Xray showing left sided Pnemothorax.

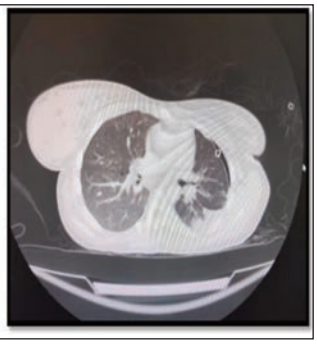

Image F: Left residual pneumothorax, a computerized tomographic (CT) scan of chest showed randomly scattered, well defined sub-centimeter cysts of varying sizes in both lung fields.

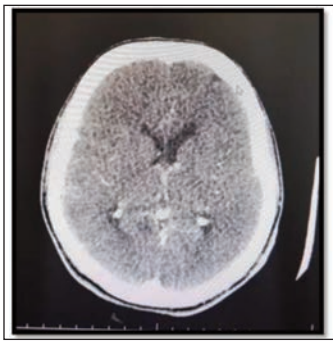

Image G: CT brain showed multifocal calcification along the lateral margins of both lateral ventricles as well as the left cerebellum, suggestive of hamartoma.

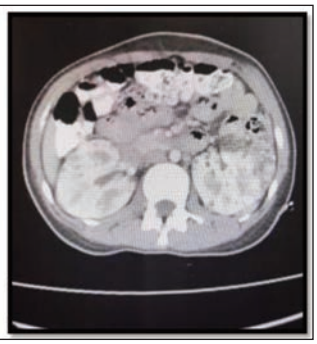

Image H: CT scan of abdomen revealed few hypodense lesions in both kidneys suggestive of angiomyolipoma both kidneys. A well-defined abnormal soft tissue lesion was seen in the left hypochondrium inseparable from the left kidney measuring 8.4 x 3.9 cm.

scattered, well defined sub-centimeter cysts of varying sizes in both lung fields (F). CT scan of abdomen revealed few hypodense lesions in the liver with largest in segment VI measuring 1.7 cm with evidence of mixed density including fat density suggestive of angiomyolipoma in liver and (in) both kidneys. Another well-defined abnormal soft tissue lesion was seen in the left hypochondrium inseparable from the left kidney measuring 8.4 x 3.9 cm and left adrenal gland appeared bulky (image H). CT brain showed multifocal calcification along the lateral margins of both lateral ventricles as well as the left cerebellum, suggestive of hamartoma (image G).

On the basis of her history, physical findings and image findings, she was diagnosed as secondary spontaneous pneumothorax secondary to lymphangioleiomyomatosis (LAM) with TSC (tuberous sclerosis complex). Her pneumothorax required negative suction and the lung eventually expanded.

Discussion

TSC, an autosomal dominant condition which can occur in about one in five thousand to ten thousand live births and has high incidence especially in those who are diagnosed with LAM.[1-3] Several studies report predominantly higher prevalence rates of TCS in females (mostly TSC2 mutations) from 26 to 50 percent.[4] These rates are reported to increase with age, with the highest rates (up to 80 percent) reported in females over the age of 40 years and lowest rates (27 percent) in those <21 years.[5,6]

Exact prevalence of TSC-LAM is not well determined as the data are derived from small retrospective observational studies that mostly report CT evidence of cystic lung disease which aid the diagnosis.[7] Based upon the worldwide prevalence of over one million people and a conservative projection that 30 percent of females with TSC develop cystic changes consistent with LAM, it is estimated that the number of females with TSC-LAM and/or cystic changes consistent with LAM is over 100,000. Lung functions can be normal in majority of the females affected by TSC-LAM.

TSC-LAM being predominantly female-gender associated disease, can affect males as well. According to data males can have cystic lung disease with prevalence of 10% up to 40%, but the disease tends to follow a milder course, with less symptoms and deterioration in lung function.

Young females are commonly affected by LAM.[8] Most common presenting complaints include gradually worsening dyspnoea along with dry cough. Apart from the common complaints, patients can also present with pleural effusion, most likely chylous and spontaneous pneumothorax. Such patients are frequently misdiagnosed as other pulmonary diseases, like asthma or emphysema, which results in late diagnosis of the disease. One of the complications noted is pulmonary hypertension, which occurs usually after more than 5 years of disease manifestation. It occurs due to hypoxia and progressive decline pulmonary arterial capacitance (PAC). Pedal oedema can be an indicative sign to show the presence of pulmonary hypertension. According to studies, 5-years survival rate of LAM varies from 50 to 97%. Patients with TSC LAM may also frequently present with neurological symptoms like fits, or have predominant features related to hamartomas.[8]

Radiology has a key role in LAM diagnosis. A chest X ray may show various presentations like hyperinflated lung, reticulonodular pattern, cystic lung disease, or pneumothorax and pleural effusion, which are well known complications of LAM.[8] High resolution CT scan chest shows well circumscribed thin wall cysts, which in

advanced stages can involve the whole lung parenchyma.

Cystic lung disease can be graded based on HRCT findings. Less than 10 cysts is considered to be minimal disease whereas, if there are more than 10 cysts and less than one third of the lung is involved, it is considered mild disease. Up to two thirds of lung involvement is graded as moderate disease and involvement of more than two thirds is characterised as severe disease. Most of the TSC-LAM patients have minimal or mild lung involvement as compared to sporadic LAM. The following table aids the diagnosis of LAM which was created by European Respiratory Society in 2010 and ATS/JRS guidelines 2016.[9,10]

Criteria for a definite diagnosis of lymphangioleiomyomatosis according to guidelines:

LAM patients are usually young patients and can benefit greatly with preventive measures like vaccination (pneumococcal and influenza) and pulmonary rehabilitation. Anti-oestrogens and progesterone have some role in slowing disease progression however their role is still considered controversial. Patients with pneumothorax are treated with tube thoracostomy, while pleurodesis an option for recurrent pneumothorax. Respiratory failure may follow severe and advanced disease, and in such cases lung transplant can be considered. Since younger population is usually affected, they are the preferred candidates for transplant with optimistic results. Sirolimus works as an immunosuppressant and inhibits T-cell proliferation. It is an mTOR inhibitor and has shown promising results in slowing LAM disease progression. It has also been found to be effective in reducing size of angiolypomas which are seen in TSC. Matrix metalloproteinase inhibitor is also being considered to be marketed as a management option for LAM.

Table-1.1: Diagnosis criteria for LAM.

ERS guidelines 2010	ATS/JRS guidelines 2016
Characteristic HRCT scans and one of the following: (multiple cysts on CT, 10 or more than 10, thin walled, diffuse, no basal sparing)	
Tuberous sclerosis complex	Tuberous sclerosis complex
Chylous pleural effusions	Chylous pleural effusions
Angiomyolipomas/Skin involvement	Angiomyolipomas/Skin involvement
Lymphatic system involvement	Lymphatic system involvement
	Serum VEGF-D ≥800 pgml

ERS: European Respiratory Society; ATS/JRS: American Thoracic Society/ Japanese Respiratory Society.[9,10]

Table-1.2: Clinical features of TSC are divided into major and minor features.

Major features	Minor features
Facial angiofibromas/forehead plaques	Confetti skin lesion
Shagreen patch	Gingival/introral fibromas
Three or more hypomelanotic macules	Multiple randomly distributed pits in dental enamel (more than three)
Two or more ungal fibromas	Hamartomatous rectal polyps
Lymphangioleiomyomatosis	Multiple renal cysts
Renal angiomyolipoma (two or more)	Non-renal hamartomas
Cardiac rhabdomyoma	Bone cysts
Multiple retinal hamartomas	Retinal achromatic patch
Cortical tubers/dysplasias	Cerebral white matter radial migration lines
Sub-ependymal nodules	
Sub-ependymal giant astrocytoma	

Definite TSC: 2 major features or 1 major + 2 minor features
Probable TSC: 1 major or 1 minor features
Possible TSC: 1 major feature or 2+ minor features

Diagnosis of table TSC can be done using the following criteria as shown in table 1.2; (Reference: https://www.researchgate.net/figure/Clinical-diagnostic-criteria-for-TSC_tbl1_51687755).

Conclusion

LAM associated with TSC is still an under investigated entity and can have a variable disease course. TSC-LAM presenting with pneumothorax as an initial presentation is a rare event. Early recognition of the disease and preventive management can greatly improve the disease outcome.

Patients Consent: The guardian's written consent was obtained to publish this case report.

Declaimer: None.

Conflict of Interest: The person who signed ethical review statement is also a co-author of the same manuscript.

Funding Disclosure: None.

References

1. von Ranke FM, Zanetti G, e Silva JL, Araujo Neto CA, Godoy MC, Souza CA, et al. Tuberous Sclerosis Complex: State-of-the-Art Review with a Focus on Pulmonary Involvement. Lung 2015; 193: 619-27.
2. Afshar Saber W, Sahin M. Recent advances in human stem cell-based modeling of Tuberous Sclerosis Complex. Molecular Autism 2020; 11: 16.
3. Riaz A, Chaudhry R. Tuberous Sclerosis Complex: A Case Report. Pak J Ophthalmol 2018; 34: 295
4. Adriaensen ME, Schaefer-Prokop CM, Duyndam DA, Zonnenberg BA, Prokop M. Radiological evidence of lymphangioleiomyomatosis in female and male patients with tuberous sclerosis complex. Clin Radiol 2011; 66: 625-8.
5. Zak S, Mokhallati N, Su W, McCormack FX, Franz DN, Mays M, et al. Lymphangioleiomyomatosis mortality in patients with tuberous sclerosis complex. Ann Am Thorac Soc 2019; 16: 509-12.
6. Kristof AS, Li PZ, Major P, Landry JS. Lymphangioleiomyomatosis and Tuberous Sclerosis Complex in Quebec: Prevalence and Health-care Utilization. Chest 2015; 148: 444-9.
7. Escalon JG, Richards JC, Koelsch T, Downey GP, Lynch DA. Isolated cystic lung disease: an algorithmic approach to distinguishing Birt-Hogg-Dubé syndrome, lymphangioleiomyomatosis, and lymphocytic interstitial pneumonia. AJR Am J Roentgenol 2019;1-5. doi: 10.2214/AJR.18.20920. Online ahead of print.

8. Ferreira Francisco FA, Soares Souza A Jr, Zanetti G, Marchiori E. Multiple cystic lung disease. Eur Respir Rev 2015; 24: 552-64.

9. McCormack FX, Gupta N, Finlay GR, Young LR, Taveira-DaSilva AM, Glasgow CG, et al. Official American Thoracic Society/Japanese Respiratory Society clinical practice guidelines: lymphangioleiomyomatosis diagnosis and management. Am J Respir Crit Care Med 2016; 194: 748-61.

10. Johnson SR, Cordier JF, Lazor R, Cottin V, Costabel U, Harari S, et al. European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. Eur Resp J 2010; 35: 14-26.