Lymphangioleiomyomatosis

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Abstract

Although the diagnosis of tuberous sclerosis complex-lymphangioleiomyomatosis (TSC-LAM) is rare in adolescents, emerging data suggest that its true incidence, particularly among females with TSC, may be underestimated. High-resolution CT of the chest is critical for identifying characteristic pulmonary cysts, while abdominal imaging plays a supportive role by detecting associated renal angiomyolipomas. Given the progressive nature of LAM, early recognition is essential for guiding management and improving outcomes. Clinicians should maintain a high index of suspicion for LAM in adolescents with TSC2 gene mutations.

Keywords: pulmonary, lung, congenital

Case Summary

An adolescent female with tuberous sclerosis complex (TSC) underwent screening chest CT.

Imaging Findings

Initial chest CT (Figure 1) demonstrated multiple small, thin-walled cysts predominantly located in the right lower lobe, consistent with early findings of lymphangioleiomyomatosis (LAM). Follow-up chest CT (Figure 2) performed 12 years later showed mild progression in the number and size of pulmonary cysts. Abdominal MRI (Figure 3) revealed multiple renal angiomyolipomas (AMLs), most of which were lipid-poor. The largest lesion was in the lower pole of the right kidney.

Diagnosis

TSC-LAM.

Differential diagnosis includes sporadic LAM, emphysema, Sjögren syndrome, pulmonary Langerhans cell histiocytosis, follicular bronchiolitis, lymphoid interstitial pneumonia, amyloidosis, light-chain deposition disease, and Birt-Hogg-Dube syndrome.

Discussion

LAM is a rare, progressive multisystem disease that primarily affects women of childbearing age, with an estimated prevalence of 3.4-7.8 per million women worldwide.[1] It is characterized by the proliferation of abnormal smooth muscle—like cells that infiltrate the lungs and lymphatics, leading to progressive cystic destruction, impaired pulmonary function, and, ultimately, respiratory failure.[2]

LAM occurs in 2 forms: a sporadic form, which typically presents in adulthood, and a form associated with TSC, which may present in childhood.[2] TSC-LAM is increasingly recognized as a significant cause of morbidity in women with TSC. Among adult women with TSC, approximately 30-40% will develop LAM. The condition is significantly more common in those with TSC2 mutations than in those with TSC1 mutations, with one study reporting a prevalence of 55% vs 0%, respectively.[3] Serum VEGF-D levels are also typically higher in patients with LAM and TSC2 mutations and may serve as a useful biomarker for the presence of LAM.[3] In a study by Cudzilo et al, the prevalence of LAM in females under the age of 21 with TSC was 27%, suggesting that disease onset may occur earlier than previously recognized.[4] Another study showed that lung cysts were present in 12% of patients with TSC who had received a chest CT, including 20% of women.[5] Nevertheless, diagnosis in adolescents remains rare, likely due to a combination of factors, including the absence of respiratory symptoms, lack of universal screening protocols in the pediatric populations, and the subtle, nonspecific appearance of early pulmonary changes on imaging.[4,6]

In adolescents, TSC-LAM is often asymptomatic, but when symptoms do occur, they may include exertional dyspnea or spontaneous pneumothorax. Imaging, chest CT, plays a central role in diagnosis. According to the 2017 American Thoracic Society/Japanese Respiratory Society guidelines, LAM can be diagnosed

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Figure 1. (A, B) Sequential images from chest CT showing several small cysts (arrows) with imperceptible walls.

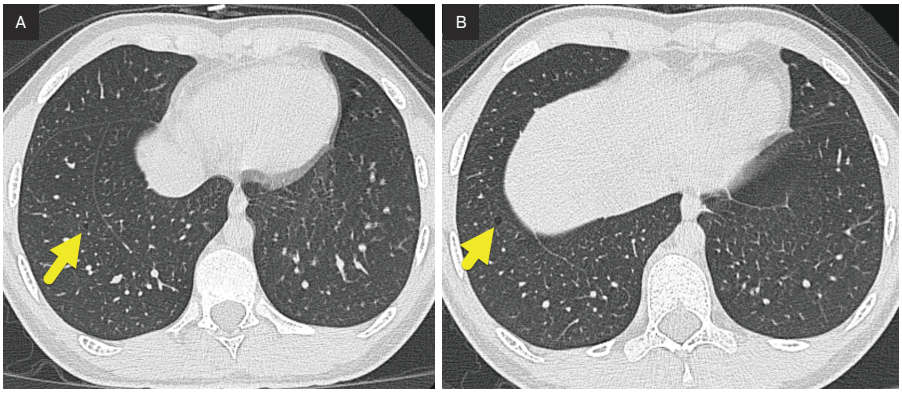
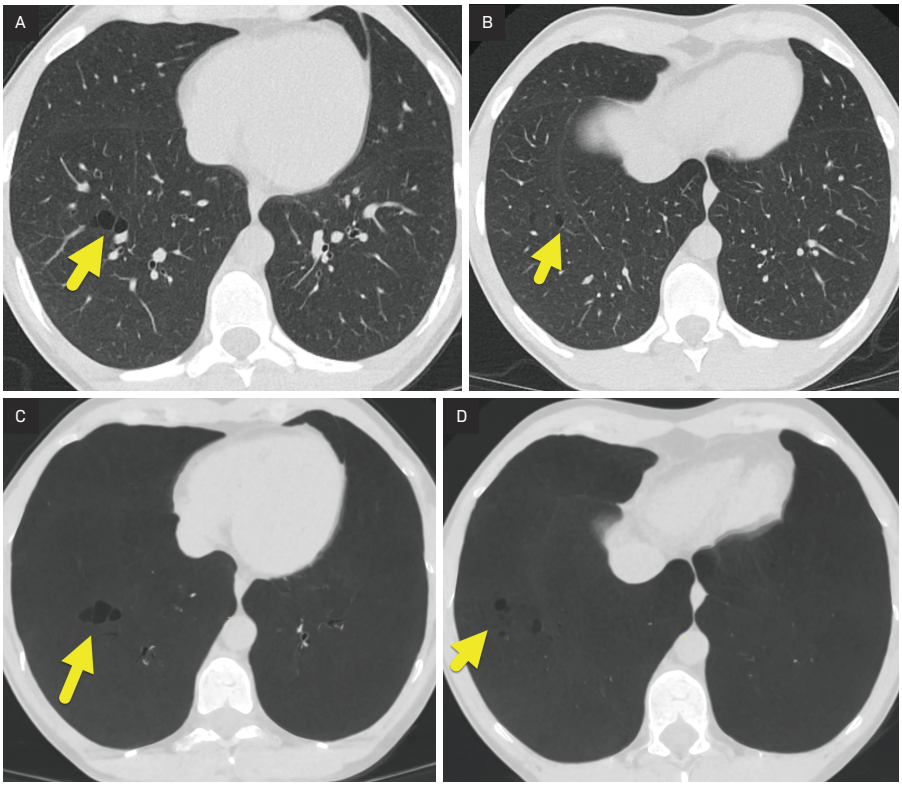


Figure 2. (A, B) Sequential images from chest CT performed 12 years later showing that the small cysts (arrow) have increased in size and number. (C, D) Minimum intensity projection images at the same levels highlighting the extent of the small cysts.

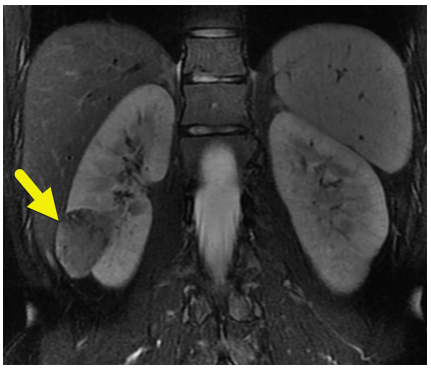


based on the presence of characteristic diffuse, thin-walled, round pulmonary cysts, in conjunction with one or more supportive features, such as TSC, renal AML, cystic lymphangioleiomyoma, chylothorax, or chylous ascites.[7]

Chest radiographic findings vary depending on disease severity: patients with early-stage disease may have a normal radiograph or may have mildly increased interstitial markings. Patients with advanced disease may demonstrate reticular opacities, pleural thickening, lymphadenopathy, and hyperinflation.[1,2]

Current TSC guidelines recommend baseline chest CT for all females and symptomatic males, starting at 18 years of age.[8] On chest CT, TSC-LAM is characterized by numerous thin-walled, round, or oval cysts distributed throughout the lungs.[1] In early disease, cysts are fewer and smaller, with intervening normal lung parenchyma. At this stage, the cysts may be more visible on minimum intensity projection images. As the disease progresses, cysts become more numerous and larger, gradually replacing healthy lung tissue. Additional CT findings may include focal ground-glass opacities, lymphatic congestion, septal thickening, chylothorax, pericardial effusion, and thoracic duct dilation.[1,2] TSC-LAM may also be associated with multifocal micronodular pneumocyte hyperplasia.[1] Certain imaging features help distinguish LAM from other diffuse cystic lung diseases. For example, thick, irregular upper lobe cysts are more typical of pulmonary Langerhans cell histiocytosis.[1]

Figure 3. Coronal T2-weighted MRI showing a dominant lipid-poor angiomyolipoma in the lower pole of the right kidney. There are many tiny angiomyolipomata throughout both kidneys, giving the cortex a striated appearance.



Abdominal and pelvic imaging with CT or MRI is essential, as over 90% of patients with TSC-LAM and approximately one-third of those with sporadic LAM have renal AMLs.[9] On CT, AMLs typically involve the renal cortex and often contain macroscopic fat. However, in patients with TSC-LAM, up to one-third of AMLs may be fat-poor, making detection more challenging.[10] On MRI, classic AMLs demonstrate signal loss on fat-suppressed sequences. Chemical shift MRI can also detect small amounts of fat by revealing signal loss within voxels that contain both fat and water, often

producing an "India-ink" artifact at the fat-water interface of the lesion.[11]

Management of LAM focuses on alleviating symptoms and slowing disease progression. Recurrent or complicated pneumothoraces may be treated with pleurodesis, and lung transplantation is considered in patients with advanced respiratory failure. More recently, mTOR inhibitors such as sirolimus have emerged as a key therapy, shown to stabilize lung function and reduce the size of associated tumors in patients with LAM.[1,2]

Conclusion

Although the diagnosis of TSC-LAM is rare in adolescents, emerging data suggest that its true incidence, particularly among females with TSC, may be underestimated. High-resolution CT of the chest is critical for identifying characteristic pulmonary cysts, while abdominal imaging plays a supportive role by detecting associated renal AMLs. Given the progressive nature of LAM, early recognition is essential for guiding management and improving outcomes. Clinicians should maintain a high index of suspicion for LAM in adolescents with TSC2 gene mutations.

References

1) McCarthy C, Gupta N, Johnson SR, Yu JJ, McCormack FX. Lymphangioleiomyomatosis: pathogenesis, clinical features, diagnosis, and management. *Lancet Respir Med*. 2021;9(11):1313-1327. doi:10.1016/S2213-2600(21)00228-9

2) O'Mahony AM, Lynn E, Murphy DJ, Fabre A, McCarthy C. Lymphangioleiomyomatosis: a clinical review. *Breathe*. 2020;16(2):200007. doi:10.1183/20734735.0007-2020

3) Tian X, Glass JE, Kwiatkowski DJ, et al. Lymphangioleiomyomatosis association with underlying genotype in patients with tuberous sclerosis complex. *Ann Am Thorac Soc*. 2021;18(5):815-819. doi:10.1513/AnnalsATS.202008-911OC

4) Cudzilo CJ, Szczesniak RD, Brody AS, et al. Lymphangioleiomyomatosis screening in women with tuberous sclerosis. *Chest*. 2013;144(2):578-585. doi:10.1378/chest.12-2813

5) Ritter DM, Fessler BK, Ebrahimi-Fakhari D, et al. Prevalence of thoracoabdominal imaging findings in tuberous sclerosis complex. *Orphanet J Rare Dis*. 2022;17(1):124. doi:10.1186/s13023-022-02277-x

6) Johnson J, Somerfield W, Johnson SR. Lymphangioleiomyomatosis in patients with tuberous sclerosis: a national centre audit. *Orphanet J Rare Dis*. 2024;19(1):137. doi:10.1186/s13023-024-03115-y

7) McCormack FX, Gupta N, Finlay GR, et al. Official American thoracic society/Japanese respiratory society clinical practice guidelines: lymphangioleiomyomatosis diagnosis and management. *Am J Respir Crit Care Med*. 2016;194(6):748-761. doi:10.1164/rccm.201607-1384TH

8) Northrup H, Aronow ME, Bebin EM, et al. Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. *Pediatr Neurol*. 2021;123:50-66. doi:10.1016/j.pediatrneurol.2021.07.011

9) Avila NA, Dwyer AJ, Rabel A, Moss J. Sporadic lymphangioleiomyomatosis and tuberous sclerosis complex with lymphangioleiomyomatosis: comparison of CT features. *Radiology*. 2007;242(1):277-285. doi:10.1148/radiol.2421051767

10) Silverman SG, Israel GM, Herts BR, Richie JP. Management of the incidental renal mass. *Radiology*. 2008;249(1):16-31. doi:10.1148/radiol.2491070783

11) Thiravit S, Teerasamit W, Thiravit P. The different faces of renal angiomyolipomas on radiologic imaging: a pictorial review. *Br J Radiol*. 2018;91(1084):20170533. doi:10.1259/bjr.20170533

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