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Tuberous Sclerosis Complex with Lymphangioleiomyomatosis: Case Report with Review of the Literature of A Rare Genetic Disease Presenting as COPD

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Abstract

A 61-year-old African-American female initially presented to a Cardiology Clinic with gradually worsening dyspnea on exertion. Pulmonary function testing was consistent with COPD; however, the patient never had a history of smoking, secondhand smoke exposure, or exposure to volatile organic compounds or other workplace chemicals. Structural or functional cardiac causes of dyspnea were ruled out with a normal Holter monitor and echocardiogram. Further workup, including high-resolution CT scan of the lungs, demonstrated diffuse cystic changes to the lung parenchyma. Physical exam demonstrated multiple dermatologic findings consistent with tuberous sclerosis complex. Imaging of the kidneys and brain confirmed the diagnosis of tuberous sclerosis complex with Lymphangioleiomyomatosis (TSC/LAM), an exceptionally rare genetic disease with fewer than 100,000 confirmed cases globally. This report is centered on the diagnosis of the patient, the diagnostic criteria of TSC/LAM, and speaks to potential treatment options available.

Case Report

A 61-year-old African American female, with a history of hypothyroidism, initially presented to Cardiology Clinic with complaints of worsening dyspnea on exertion and palpitations. An echocardiogram and Holter monitor showed normal findings, except echocardiogram demonstrated mild diastolic dysfunction. Having ruled out a cardiac cause of her symptoms, she was referred to Pulmonology for further evaluation.

She reported gradual onset of dyspnea on exertion over the preceding 6-months, exacerbated by ambulation but relieved with rest, and subjective palpitations with episodes of dyspnea. She also reported a non-productive cough, but denied wheezing during these episodes and was unable to identify any associated environmental factors worsening her dyspneic episodes. The patient denied any history of tobacco use or secondhand smoke exposure, with no past or present occupational or environmental exposures that could lead to significant pulmonary pathology (e.g., volatile organic compounds, silicates, or mold). Her social history also is negative for current or prior drug use and ethanol use is limited to 1-2 glasses of wine per month. She denied any recent travel, sick contacts, or new perfumes or detergents in the house.

The patient's hypothyroidism is controlled with medication, Synthroid. She denied any history of childhood asthma or any congenital diseases in childhood. There is no family history other than hypertension and diabetes, and her surgical history is only positive for Cesarean section and hysterectomy later in life due to fibroid uterus. Of note, she reported a high-school level education, and when prompted, she reported significant difficulty in school as a child and adolescent.

Physical exam at time of initial encounter was only positive for diffusely coarse breath sounds, with bibasilar coarse rhonchi. However, during evaluation, an incidental finding was made of multiple skin lesions, including multiple edematous papules of the face, as well as areas of brown, fibrous plaque formation with surrounding hypopigmentation (Supplementary Figures 1-3). When asked about these lesions, the patient revealed they were present for many years and prior evaluation by a Dermatologist revealed they were non-malignant in nature. Oropharyngeal exam was positive for pitting of dental enamel in all observed teeth.

Based on her history and dermatological findings, PFT was ordered as well as a CT scan of the chest. PFTs demonstrated findings consistent with severe obstructive disease showing some restrictive changes and diminished DLCO. Bronchodilator response during PFT was minimal. CT scan showed diffuse cystic changes to the entirety of the bilateral lungs, and markedly abnormal visualized kidney segments, with fatty replacement of the renal parenchyma (Supplementary Figures 4). A renal ultrasound demonstrated diffuse bilateral abnormalities, with multiple angiomyolipomas in both kidneys, but without obstructive disease. CT of the patient's brain demonstrated calcification along the right

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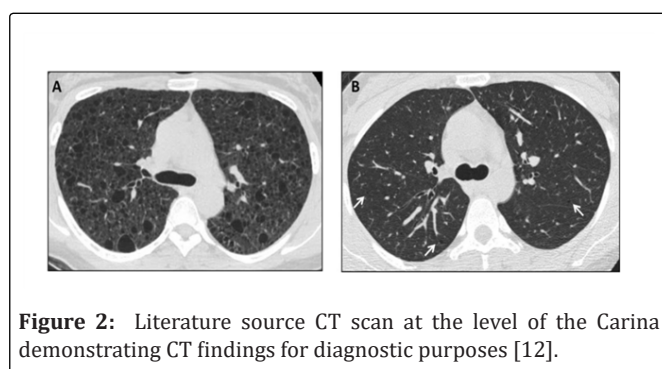
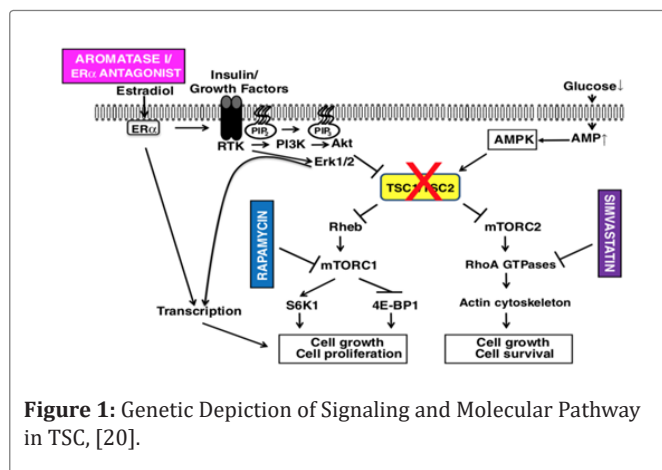
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caudate head of the right frontal horn. Serum ANA was positive, however, reflex cascade of autoantibodies was negative. Total serum VEGF level was low, but due to lack of insurance authorization for the assay, fractionated VEGF-D was not done. Similarly, an order for definitive genetic testing for TSC mutations also was rejected by the patient's insurance company and not done. Her symptoms were controlled with ANORO Ellipta (umeclidinium/vilanterol).

Based on the 2012 International Tuberous Sclerosis Consensus Conference diagnostic criteria, a diagnosis of TSC with LAM was made with three major criteria observed and two minor criteria. Major criteria included multiple dermal hypomelanotic nodules, pulmonary lymphangioleiomyomatosis, and diffuse bilateral renal angiomyolipomas. Minor criteria for this patient included multiple renal cysts and observed dental enamel pits.

Literature Search and Methods

To gather the necessary information, we pulled medical literature doing a PubMed Literature Review and used approximately 46 sources. Key words used in our search included lymphangioleiomyomatosis, TSC/LAM, Pulmonary lymphangioleiomyomatosis, and Tuberous Sclerosis Complex. The literature was comprised from peer reviewed journals, previous case reports, published literature including previous literature reviews, and online clinical support database from 1990 through 2019. Due to the relative rarity of TSC/LAM, we included sources for general information from Pediatric journals and society guidelines.

Discussion

TSC is a rare disease, affecting approximately every 1 in 5000 to 10,000 live births globally. TSC/LAM is exceptionally rare, with estimates of LAM development ranging between 26%-50% of all patients with TSC. LAM development is often associated with TSC2 gene mutations than TSC1 mutations. Diagnosis of LAM is commonly made in the third and fourth decades of life, with 80% of cases diagnosed in females over the age of 40[1]. Based on current population data, it is estimated there are approximately 100,000 cases globally[2]. LAM is more likely to develop in females with TSC

compared to males and with cystic changes consistent with LAM seen 10-15 fold more frequently in females on high resolution CT scan (HRCT) than in males[2]. Although some study populations have been predominantly white, evidence suggests TSC and TSC/LAM affects all race/ethnicities equally.

Disease Presentations

TSC/LAM encompasses a wide spectrum of clinical presentations from mild TSC/LAM with minimal neurocognitive symptoms and some symptoms of cystic lung disease, to severe TSC/LAM with severe congenital neurocognitive delay, seizures, and progressive respiratory failure depending on the severity and location of the mutation. The severity of TSC varies greatly even within families with inherited mutations due to genetic mosaicism; in the case of a newly diagnosed child with a severe form of TSC, parental evaluation occasionally results in one parent diagnosed with a mild form of TSC[3]. Despite the availability of genetic assays to identify TSC1 and TSC2 gene mutations, initial diagnosis of TSC is primarily a clinical diagnosis with major and minor criteria being met[4,5](Table 1).

TSC diagnosis is an independent risk factor for the development of LAM, with symptoms of TSC/LAM presenting similarly to patients with sporadic LAM without TSC [6,7]. Similar to our patient, adult female patients may present initially with pulmonary symptoms and diagnosed with COPD or asthma. The TSC/LAM diagnosis is made later despite the patient meeting criteria for TSC diagnosis years prior[6].

It is rare to have a diagnosis of TSC/LAM before the age of 20. The average age of diagnosis is approximately 35[8]. Initial complaints can range from dyspnea, wheezing, or resting hypoxia to severe complications of spontaneous pneumothorax or chylothorax[7]. In one study analyzing data from the US NHLBI LAM registry, approximately one-third of patients entering the registry reported spontaneous pneumothorax as a sentinel event leading to an eventual diagnosis of LAM. In patients with combined TSC/LAM, the most common presenting symptom was dyspnea[1]. However, in contrast to sporadic LAM, patients with TSC/LAM were slightly more likely to have normal spirometry results at time of initial registry entry, with both spontaneous LAM and TSC/LAM patients demonstrating obstructive spirometry results if an abnormality was observed. Because of the relative rarity of TSC and the significant phenotypic variation of patients with TSC1/2 mutations, the diagnosis of TSC and TSC/LAM may be missed for years resulting in a misdiagnosis of COPD due to disease presentation.

Physical Exam/Screening

When diagnosing LAM in patients with a known diagnosis of TSC, a HRCT scan is performed as part of the initial screening process for pulmonary involvements of TSC. However, as in our patient, it sometimes becomes difficult to distinguish cases of LAM from other more common pulmonary diseases without a more detailed workup. Similarly, the incidence of patients presenting with LAM typically is limited without a known diagnosis of TSC first. Subsequently, patients with TSC typically present with a slow onset of pulmonary symptoms that may not be clinically relevant until more advanced cystic lung disease is present at a later stage in life. At the most basic level, physical examinations including a full dermatologic and skin examination should be performed, especially with the suspicion of TSC[9]. Furthermore, along with a strong physical exam, a thorough and detailed family history also should be obtained for diagnostic and family planning purposes because of the Autosomal dominant nature of this disease and the gravity for infants born to those carrying a disease of TSC.

Another more serious initial and physical exam presentation for individuals presenting with symptomatic disease is pneumothorax. Regarding diagnostic imaging, an X-Ray typically is not sufficient for diagnosis and management, yet Primary Spontaneous Pneumothorax can be misinterpreted from underlying cystic lung disease and LAM. This is seen most in Japan, as CT scans are more readily used in imaging and management for Pneumothorax[8]. Globally, screening

Diagnostic Criteria for TSC from the 2012 Tuberous Sclerosis Consensus Conference	
Genetic Diagnostic Criteria:	Identification of any TSC1 or TSC2 pathogenic mutation in normal tissue, with a pathogenic mutation being defined as one that leads to an inactive protein established by functional assessment, or a mutation leading to the loss of protein synthesis. Other TSC1 and TSC2 variants whose effects on protein function are less certain are not enough to make a diagnosis of TSC.
Clinical Diagnostic Criteria:	
Major Features	1. Hypomelanotic macules (≥ 3, at least 5mm in diameter) 2. Angiofibromas (≥ 3) or fibrous cephalic plaque 3. Ungual fibromas (≥ 2) 4. Shagreen patch 5. Multiple retinal hamartomas 6. Cortical dysplasia, including tubers and cerebral white matter radial migration lines 7. Subependymal nodules 8. Subependymal giant cell astrocytoma 9. Cardiac rhabdomyoma 10. Lymphangioleiomyomatosis 11. Angiomyolipomas (≥ 2).
Minor Features	1. "Confetti" skin lesions 2. Dental enamel pits (≥ 3) 3. Intraoral fibromas (≥ 2) 4. Retinal achromic patch 5. Multiple renal cysts 6. Nonrenal hamartomas
Definite Diagnosis:	Two major features, or one major feature with ≥ 2 minor features
Possible Diagnosis:	-One major feature or $\geq$ minor features
NOTE:	The presence of angiomyolipomas and LAM alone are not sufficient to make the diagnosis of TSC without other features

Table 1: Diagnostic Criteria for TSC/LAM per 2012 TSC Consensus Conference Guideline Updates [5].

for LAM typically takes place after the diagnosis of TSC has been made.

Diagnostic criteria requirement

Based on current society guidelines the diagnostic workup should include: 1. Single high resolution CT scan at 18 years and again at 30 for patients with known diagnosis of TSC, with emphasis and approximate sensitivity at an image slice at the level of the carina[9,10]; and 2. HRCT screening for LAM completed in females at least once after the age of maturity[11]. Once the diagnosis of cystic lung disease is confirmed, the next step is to determine if confirmatory testing is needed. Current guidelines show a CT scan with greater than four cysts at the level of the carina for TSC diagnosis, with co-symptoms of TSC, angioliomatosis, and positive dermatologic findings consistent with TSC can be considered diagnostic for TSC/LAM[8]. Further diagnostic work up can involve laboratory data, including serologies, ANA, anti-CCP, SSA and SSB as well as a work up for connective tissue disease, alpha 1- antitrypsin. The literature is equivocal if VEGF and VEGF-D should be included in diagnostic criteria; at this time, these lab tests are not included in society guidelines[11-15].

Genetics/Mutations

Tuberous Sclerosis Complex mutations are a familial disorder or the result of de novo mutation usually during gametogenesis and less often after fertilization. TSC2 mutations are mainly seen among de novo mutations and occur four times as often as TSC1 mutations. In familial cases, TSC1 and TSC2 gene mutations are equally prevalent. As mentioned previously, there is exceptional variability in phenotypic expression of TSC mutations, owing to frequent somatic mosaicism, and the presence or absence of a second somatic mutation related to TSC in the affected individual[16].

The TSC2 is located on chromosome 16p13.3 and encodes the

protein tuberin. Tuberin combines with hamartin, the encoded product of the TSC1 gene, to produce the tuberin-hamartin complex. Missense TSC2 mutations resulting in function loss are the most commonly observed mutations giving rise to TSC[17]. Currently, data suggest the lack of a functional tuberin-hamartin complex removes an inhibitory force on the cell cycle through the mTOR pathway, resulting in continuous growth and proliferation of the cell[13,14]. Loss of cellular regulation results in the growth of the characteristic tumors seen with TSC as well as the abnormal proliferation of smooth muscle cells within the lung giving rise to LAM. Of note, genetic analysis performed on tissue samples from patients with sporadic LAM demonstrated loss of function mutations in the TSC2 gene, reinforcing the role that TSC2 plays in LAM development[18,19] (Figure 1).

Diagnostic imaging guidelines

The European Respiratory Society recommends screening CT scans at age 17 and then repeat at 30 in patients already diagnosed with TSC, with four characteristic cysts at the level of the carina being diagnostic[12], a recommendation in line with the 2012 TSC Alliance recommendation on HRCT[11]. One study examined the use of Society guidelines versus conservative cyst counts to diagnose LAM in patients undergoing screening CT scans. In this study, 47.5% of patients scanned met criteria for TSC/LAM using the current society guideline of identification of four or more lung cysts at the level of the carina. Conservative screening, using a cutoff of 10 or more lung cysts, resulted in 45% of screening patients being positive[12].

CT confirmed cyst presence is directly correlated with the age of the patient, with more cysts developing as the patient ages. Cystic lung disease is present in greater than 81% of patients with TSC by 40 years of age, with a diagnosis made using a single CT scan slice at the level of the carina, thereby decreasing radiation exposure to the patient.(Figure 2)

Current findings on CT scan that would otherwise be rare in LAM include ground glass opacities, cysts that contain an internal structure, pulmonary hemorrhage, lymphatic congestion, and hilar and mediastinal lymphadenopathy, all of which can be used as possible rule out criteria for LAM [8].

Treatment

One current therapy mainstay includes Sirolimus[21,22]. Sirolimus was found to decrease and resolve pleural effusions and lymphangiomas in patients presenting symptomatic LAM in rapidly progressing disease. In this same trial, after a mean of 2.6 years being on Sirolimus therapy, FEV1 function actually increased by 1.8%[23]. Both short- and long- acting bronchodilators have been used to relieve symptoms of TSC/LAM, however bronchodilators have not been shown in studies to improve PFTs or slow disease progression[24]. Some authors have proposed using statins as a part of combination therapy based on an observed inhibition of abnormal cell growth in animal and cell culture models with statin therapy[20]; however, no preclinical or clinical trials are available currently to determine effects in humans with TSC or TSC/LAM.

Conclusions

Currently, there are estimated to be 100,000 people in the world with concurrent TSC/LAM, with many cases going undiagnosed and under reported[2]. Onset of LAM symptoms in patients with TSC follows a parabolic distribution, with the most common time of onset in the fourth or fifth decade of life. Although genetic tests and serum factor assays exist to assist in diagnosing TSC/LAM[4], the diagnosis largely remains a clinical process, with set major and minor criteria for TSC[5]. Despite the rarity of TSC with LAM, TSC alone is significantly more common, occurring once in every 5000 to 10,000 live births as a result of either heredity or random germ-line mutation[12].

In summary, with the aid of available diagnostic screening criteria, a thorough physical exam, strong clinical suspicion of respiratory disease, especially those refractory to traditional respiratory treatments should prompt the clinician to perform a thorough workup of secondary causes including TSC and TSC/LAM. On physical exam, TSC and its associated skin findings can further guide the clinician into more diagnostic work. In those diagnosed at earlier ages, one time screenings at the age of 18 with single CT scan imaging at the level of the Carina helps diagnose lung manifestations of TSC/LAM. This can be followed up with repeat imaging at the age of 30. Finally, confirmation can be performed although not technically necessary, with serology including vascular endothelial growth factor - D. Treatment options currently consist of Sirolimus which shows promising improvement in FEV1 when started early, hence early screening guidelines. New treatment modalities tend to be promising with newer understanding of molecular pathways in rare genetic diseases such as Tuberous Sclerosis Complex with associated Lymphangiomyomatosis.

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Conflicts

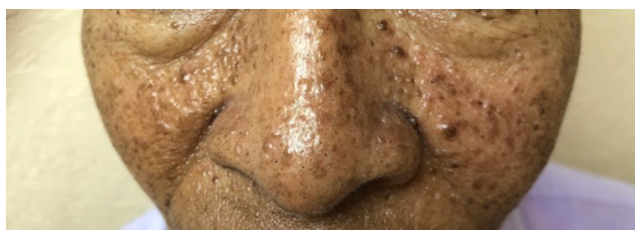
The authors all affirm that they have no competing interests or conflicts of interest relating to this manuscript or its contents.

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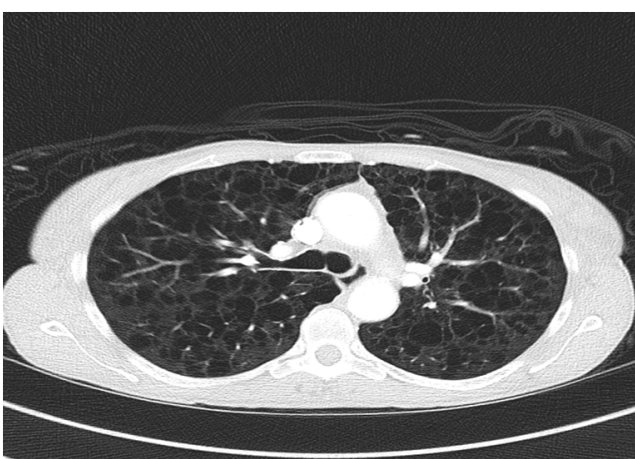
Supplementary Figure 1: Nasal Bridge showing typical skin manifestations of TSC. Patient lived with these skin findings her whole life without a diagnosis.



Supplementary Figure 2: Closer Imaging of Nasal Folds with skin manifestations of TSC.



Supplementary Figure 3: Further skin findings present throughout her body, diagnostic of TSC.



Supplementary Figure 4: CT Scan of the Chest showing diffuse cystic disease of the lungs, indicative of LAM.



Supplementary Figure 5: CT scan of the Abdomen showing diffuse cystic involvement of the renal architecture including angioliipomas.



Supplementary Figure 6: CT Scan of the Abdomen showing further renal angioliipomas.