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Review Article

Lymphangioleiomyomatosis: A Review

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Introduction

Lymphangioleiomyomatosis (LAM) is a rare, cystic lung disease that almost exclusively affects women during their reproductive years. The estimated prevalence of this disease worldwide is 5 in 1,000,000 people [1]. There is a massively increased prevalence of LAM in patients with the autosomal dominant neurocutaneous disorder, tuberous sclerosis complex (TSC; a disease marked by multi-organ hamartomas, seizures, and intellectual impairment). Because of a shared molecular mechanism, an impressive 30% of patients with TSC develop LAM. [2] This has led to the distinct classifications of spontaneous LAM (S-LAM) and LAM associated with tuberous sclerosis complex (TSC-LAM). LAM of either variety is often accompanied by extra-pulmonary manifestations as well, including angiomyolipomas of the kidney and abdominal lymph nodes, non-pulmonary cystic lymph angioleiomyomas, chylous ascites, and abdominal/pelvic lymphadenopathy [3]. Patients typically present with spontaneous pneumothorax and are subsequently found to have diffuse cystic lung changes on imaging. They often develop progressive dyspnea and airway obstruction and even chylous pleural effusions and ascites. Treatment of LAM centers around sirolimus (an mTOR inhibitor) to slow disease progression; pleurodesis to prevent the recurrence of pneumothorax, and ultimately lung transplant in patients with the end-stage disease [4].

Etiology

Cysts develop in the lungs of patients with LAM when histologically benign cells of unknown origin enter the bloodstream and preferentially deposit in the lungs where they disrupt the normal lung parenchyma. The cysts have histologic characteristics of smooth muscle cells and melanocytes and functional characteristics similar to lymphatic tissue, capable of producing lymphatic fluid [5]. Due to their presumed distal origins (with respect to the lungs) it is reasonable to consider LAM a low-grade metastatic disease with an unknown primary. This neoplastic classification is most clearly illustrated by the recurrence of LAM in patients who have undergone lung transplant [6,7].

Epidemiology

As with any rare disease, accurate measurements of incidence and prevalence are difficult. LAM is currently estimated to occur in roughly 5 in 1 million individuals worldwide [1]. It demonstrates significant regional variation both between and within countries. It is difficult to assess whether this is the result of disease-specific factors or factors that affect disease recognition (i.e., access to high resolution computed tomography, pulmonologists, pathologists, and/or other LAM specialists). It occurs in a disproportionately large number of patients with TSC mutations, estimated between 15 and 30% [2,8]. The overlap between LAM and TSC is the result of a shared molecular mutation in the TSC1/2 protein. For unknown reasons, the disorder affects almost exclusively women, with case reports of men developing the disease remaining in the single digits [9-13].

Pathophysiology

The primary aberrant molecular pathway in LAM (whether in TSC related or spontaneous LAM) is the mTOR pathway. The mTOR pathway is responsible for cell proliferation, migration, and growth [5]. Patients with TSC have inherited mutations in the genes that produce the proteins comprising the intracellular complex TSC1/2 [14]. This complex attenuates the activity of mTOR via g-protein-coupled cell surface signaling pathways [15]. In the presence of an abnormal TSC1/2 protein complex, the mTOR complex goes unchecked leading to increased cell growth, proliferation, and survival. Patients with S-LAM develop de-novo mutations in the genes that encode TSC1/2 as opposed to a patient with TSC who are born with those mutations. In addition to changes in the mTOR signaling pathway, the abnormal cells that comprise the cystic lesions of LAM also acquire characteristics of lymphatic tissue. These cells develop the de-novo expression of lymphatic endothelial markers such as vascular endothelial growth factor D (VEGF-D) [2].

Histopathology

Histologically, LAM cells display characteristics of both smooth muscle cells and melanocytes. For diagnostic purposes, LAM cells are identified by immunohistochemical staining of the human-melanoma-black cell surface receptor, HMB-45 [16].

History and Physical

Roughly 87% of patients present with pneumothorax (PTX) as their initial manifestation of the disease [8]. Patients can also have progressive dyspnea, cough, hemoptysis, and chylous pleural effusions. Those who harbor underlying renal angiomyolipomas or significant intraabdominal adenopathy can demonstrate urinary obstruction, hematuria, abdominal bloating, and even spontaneous intraperitoneal bleeding [5]. This is a much more common presentation in patients with TSC-LAM as they can have large, multi-organ, angiomyolipomas that grow rapidly [5]

The physical exam is quite variable depending on the underlying manifestation. Patients with TCS-LAM present with obvious phenotypes that are well known before the development of LAM (cognitive impairment, seizures, hamartomas, etc.). Airflow obstruction (increased expiratory/inspiratory time), wheezing, diminished breath sounds (PTX/pleural effusion), or increased abdominal girth and flank pain are common as well. Although not required for diagnosis, pulmonary function testing (PFT) is often ordered in such patients. In these patients, an obstructive airway pattern is observed in nearly 60% of patients at the time of their first presentation [8]

Evaluation

The evaluation of LAM frequently begins with high resolution computed tomography (HRCT). Image findings include diffuse, thin, small, and rounded cysts with healthy-appearing interspersed lung parenchyma [17]. Often cystic changes are accompanied by pleural effusions, pneumothorax, or both. If these characteristic image findings are present a diagnosis of LAM can be confirmed through 1 of 3 major routes: clinically, serologically, or histologically. Clinically, a definite diagnosis is established if patients display any of the following known TSC, chylothorax, chylous ascites, angiomyolipomas, or non-pulmonary cystic lymphangioleiomyomas [4]. For patients who lack confirmatory clinical features, the American Thoracic Society and the Japanese Respiratory Society (ATS/JRS) recommend measuring serum VEGF-D. Levels >800pg/ml carry a specificity of 100% and a sensitivity of 72% [18]. In patients that lack either the classic clinical features or adequate serum VEGF-D levels the ATS/JRS recommends definitive diagnosis with tissue biopsy. As mentioned earlier, biopsied tissue will stain positive for HMB-45 cell surface marker.

Differential Diagnosis

As with many pulmonary diseases, the differential based on imaging alone is extensive. The most common cystic lung diseases that warrant consideration in any patient with cystic changed noted on HRCT include Langerhans-cell histiocytosis, emphysema, and Birt-Hogg-Dube. Other disorders to keep in mind include Sjogren's, amyloidosis, lymphoid interstitial pneumonia, and desquamative interstitial pneumonia [17].

Treatment and Management

Various treatments have been studied for the management of LAM since it was first described in 1918 by Lutembacher [19]. Unfortunately, given the relatively low prevalence of the disease many studies have been hampered by low enrollment and lack of randomized or controlled studies. Arguably, the most successful pharmacologic treatment identified thus far are mTOR pathway inhibitors. In 2011 the New England Journal of Medicine published a randomized, placebo-controlled trial of sirolimus in patients with LAM and moderately reduced FEV1 (mean 48%). Patients were randomized to 12 months of sirolimus vs. 12 months of placebo. After 12 months both sirolimus and placebo were discontinued, and patient outcomes were followed for another 12 months. The study demonstrated that patients who received sirolimus had stabilization of FEV1, increases in FVC, and improvements in quality-of-life metrics compared to placebo during the 12 months of active treatment. Unfortunately, during the subsequent 12 months in which therapy was suspended, the rate of decline in FEV1 equalized between the two groups suggesting that no long-term disease modifying changes had occurred with exposure to sirolimus [20]. Although sirolimus is currently recommended by the American Thoracic Society as first-line treatment for LAM, patient-centered discussions must still take place which respects the degree of functional impairment, the rate of decline in lung function, the adverse effects of sirolimus therapy and the indefinite duration of drug therapy.

Before sirolimus the most commonly studied treatments were hormone therapies, undoubtedly driven by the almost exclusive female predominance of the disease. Various hormonal modification treatment including progesterone [21,22], oophorectomy [23], GnRH agonists [24,25], SERM [26] or some combination of the above [27] have been studied in LAM. As mentioned previously, the vast majority of these studies are either case reports, case series, or retrospective cohort studies. Currently, the ATS/JRS recommend against using of any of these interventions however they do endorse further research with high quality, large scale, randomized trials.

Lastly, lung transplant is a viable option for patients with end-stage disease. 5-year survival rates range from 65%-80% [28,29] with single lung transplant showing surprisingly good results in a recent single center review at a large Japanese quaternary medical center [29]. The most common complications following single lung transplant were contralateral PTX and chylothorax occurring in 24% and 20% respectively [29].

Complications and Their Management

In addition to causing progressive airway obstruction and loss of diffusion capacity, LAM exhibits several other classic clinical complications. These include pneumothorax, chylothorax, and angiomyolipomas. As mentioned earlier, the majority of new cases present with spontaneous pneumothorax [8]. For many years, the

standard of care was to postpone pleurodesis in these patients for as long as possible. This was guided by the fact that subsequent lung transplantation was technically more challenging, as surgeons had to dissect around extensive scar tissue and often dealt with increased bleeding [4]. In 2017 ATS/JRS guidelines published their recommendation to perform pleurodesis after the first PTX based on the high rate of reoccurrence [4]. This recommendation is based on the high prevalence of recurrent pneumothorax in the population and evidence that recurrence occurs less frequently in those who undergo pleurodesis (65% vs 32%) [30]. Additionally, the ATS/JRS guidelines recommend that pleurodesis should not be seen as a contraindication for lung transplant [4] citing observational evidence that while rates of bleeding were certainly increased (48% vs 7%) there were no significant differences in mortality, hospital stay or lung function [30-33].

Prognosis

As cysts become more widespread in the lungs, patients developing ever-worsening degrees of airway obstruction and diminished DLCO. In the majority of cases, severe dyspnea on exertion develops within 10 years of symptom onset. The progressive loss of FEV1 seen in patients with LAM has been estimated to be anywhere from 75-143ml reduction in FEV1 per year [34,35] Following the onset of symptoms about half of patients progress to dyspnea while walking on flat ground by 10 years. Mortality is estimated at 10-20% 10 years after the onset of symptoms [5].

Conclusion

Lymphangioleiomyomatosis is a rare, cystic lung disease that affects almost exclusively women, primarily during their reproductive years. It is a slowly progressive disease that can lead to lung transplant or death. Not every provider needs to be aware of the nuances of disease presentation, natural history, and treatment, however, a basic familiarity with the HRCT images changes as well as the extra-pulmonary manifestations can greatly improve the time from symptom onset to a final diagnosis.

A high index of suspicion should be maintained in any young, non-smoking, female that presents with diffuse, thin-walled cysts on HRCT. A cursor medical history and ROS can help eliminate some of the more common causes of cystic lung changes (i.e. smoking and rheumatologic disease) as well as uncover any of the other classic associated conditions, such as chylothorax, pneumothorax, and angiomyolipomas. The presence of any of these should prompt a quick referral to a local specialist; including pulmonologists, pathologists, and potentially thoracic surgeons who have experiences with diagnosing and treating this rare but potentially devastating disease.

Conflict of Interest

No conflict of interest.

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