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LYMPHANGIOLEIOMYOMATOSIS: A REVIEW

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ABSTRACT

Lymphangioleiomyomatosis (LAM) is a cystic lung disease.[1] It is a multisystem disease of women. It is mainly reported in women of child bearing age, most commonly with dyspnea and pneumothorax. It is mainly characterized as proliferation of abnormal smooth muscle-like LAM cells, leading to the formation of lung cysts, fluid-filled cystic structures in the axial lymphatics (eg, lymphangioleiomyomas), and renal angiomyolipomas. The major cause of LAM mutations of the *TSC1* or *TSC2* genes, which encode for hamartin and tuberin, two proteins with a major role in control of the mammalian target of rapamycin (mTOR) signaling pathway. LAM may present with progressive dyspnea, recurrent pneumothorax, or chylothorax.[2] It is extremely difficult to treat and has poor prognosis. Pulmonary function tests indicates reduced flow rates (forced expiratory volume in the first second) and diffusion capacity. Exercise testing shows gas exchange abnormalities, ventilatory limitation, and hypoxemia.[3] Other test for finding out severity and progression of disease include lung histology scores, quantification of computed tomography, pulmonary function testing, 6-minute walk tests, cardiopulmonary exercise testing, and measurement of serum vascular endothelial growth factor D levels. Two mTOR inhibitors that are effective in stabilizing lung function and reducing the size of chylous effusions, lymphangioleiomyomas, and angiomyolipomas are Sirolimus and Everolimus. Combination of Sirolimus and hydroxychloroquine causes ihibition of autophagy and has been proposed as a possible treatment for LAM. Treatment with Simvastatin targets RhoA GTPases. It inhibits Rho GTPases and promotes apoptosis. This targets signaling pathways considered important in the pathogenesis of disease.

KEYWORDS: lymphangioleiomyomatosis, dyspnoea, Sporadic LAM, TSC1 and TSC2 mutations, Sirolimus.

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a lung disease which is caused by the abnormal growth of smooth muscle cells especially in lungs and lymphatic system.[1] This abnormal growth causes formation of holes or cysts in the lungs. LAM is a diffuse cystic lung disease. It is an indolent, progressive growth of smooth muscle cells throughout the lungs, pulmonary blood vessels, lymphatics and pleura. It is a rare progressive and systemic disease that result in cystic lung destruction.[2] LAM can be mainly classified into two: Sporadic LAM and Tuberous Sclerosis Complex-LAM(TSC-LAM). These are mainly caused by mutation in TSC1 and TSC2 genes. TSC-LAM is a hereditary form of disease where as Sporadic LAM is due to genetic mutation and not an hereditary process hence cannot be passed on to children.[4]

LAM predominately affects females of childbearing age. Women who have LAM are usually diagnosed between the age of 20 and 40. Aproximately around 30% of women who have tuberous sclerosis have LAM.[5] LAM can be mainly characterised by cystic lung disease which result in progressive dyspnoea, renal angiomyolipomas and lymphatic complications. Pneumothorax occurs frequently that is 70% and definitive management with pleurodesis is recommended as the risk of recurrence is high.[7] CT scan shows a characteristic thin-walled cysts and the presence of elevated serum levels of a vascular endothelial growth factor-D has good diagnostic specificity (figure 1). Currently, no single clinical or serological factor has been shown to predict prognosis. In general, pulmonary manifestations predominate but are often mistakenly diagnosed as other respiratory disorders such as asthma, emphysema or COPD, leading to diagnostic and treatment delays and thus increasing the risk.[8]

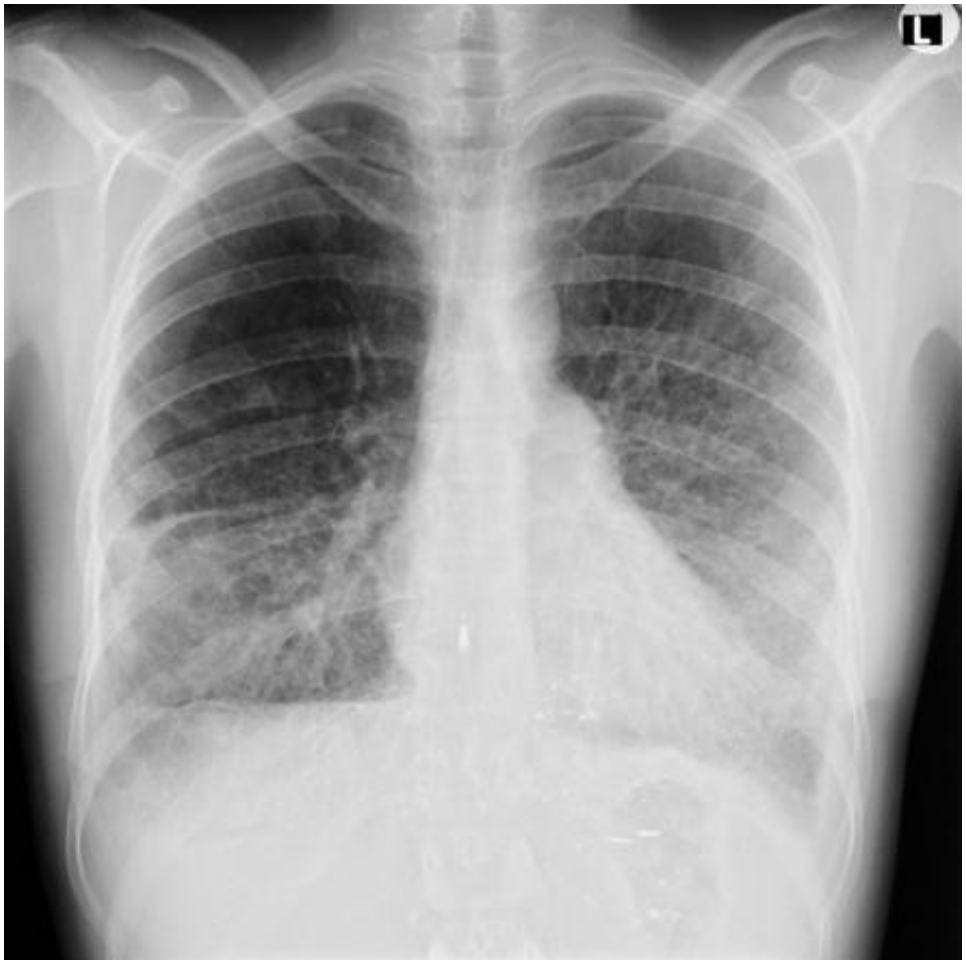

Figure 1: Chest radiograph in advanced lymphangioleiomyomatosis showing a combination of left pneumothorax, interstitial changes and pleural shadowing due to a chylous effusion.

EPIDEMIOLOGY

LAM is a rare disease that affects mainly women of childbearing age. Approximately 3.4-7.8 per million women worldwide may be affected by LAM.[9] Clinically significant S-LAM occurs almost exclusively in women. Reports of radiological and histologically confirmed LAM have not been found in men. In one study, approximately 10% of men with TSC had cystic lung disease changes, though were rarely symptomatic.[7] Two-thirds of patients at presentation are pre-menopausal females, but the age range can extend from pre-adolescent to elderly. Only one study suggested that S-LAM was more common in white females with a higher socioeconomic status; however, this has no definite evidence.

PATHOPHYSIOLOGY

Parenchymal destruction and cystic disease is caused by deposition of smooth muscle-like neoplastic cells from an unknown origin circulate in blood and lymphatic vessels which further deposit in the lungs.[12] This can be assumed as the basic pathology of LAM as only minor knowledge is available as evidence. Mutations also leads to LAM which include mutation in the tumour suppressor genes TSC1 and TSC2 which lead to inappropriate signalling through the mTOR pathway, and can be seen in both S-LAM and TSC-LAM (figure 2).[10] These pathways has an important role in regulation of cellular functions including growth, motility and survival. LAM cells also express lymphangiogenic growth factors which includes vascular endothelial growth factor (VEGF)-C and VEGF-D. These are involved in the metastatic spread of LAM cells, and breakdown of the extracellular matrix by matrix metalloproteinases (MMPs), eventually contributing to cyst formation.[15] MMP-2 and MMP-9 have been found in cystic areas in the lung. Female sex hormones also play an important role in pathogenesis of LAM, demonstrated by predominance of LAM in females and exacerbations of LAM during exposures to surges in female sex hormones, i.e. pregnancy, hormonal contraception and during menstruation. Observation shows that in the post-menopausal period, patients with LAM often experience stabilisation of their disease.

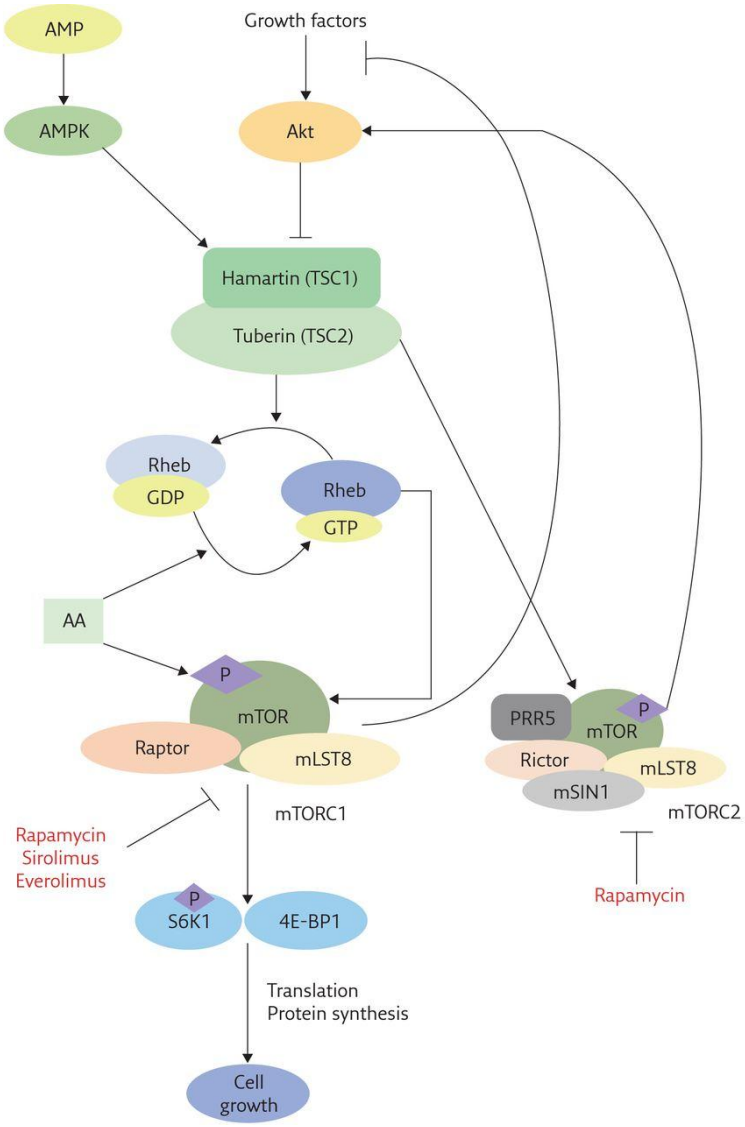

Figure 2: mTOR signalling pathways and sites of action of mTOR inhibitors.

CLINICAL FEATURES

Clinical feature of LAM is mostly considered in females of reproductive age with unexplained dyspnea. It is strongly considered in those with a primary spontaneous pneumothorax.[16] In LAM, progressive dyspnea is the major clinical feature in two-third of patients, while 25% patients show respiratory symptoms such as cough, infection and chest pain. Some patients show haemoptysis, chyloptysis (due to reflux of chyle from the axial lymphatics into the pulmonary lymphatic circuit) and fatigue to varying degrees.[18]

Patients with LAM are misinterpreted as having asthma, emphysema or COPD as dyspnea is common to a range of respiratory condition. Along with this due to diagnostic delay, one third of women with LAM have reversible airflow obstruction. The major indication of LAM is appearance of diffuse pulmonary cysts (figure 3).[20] Conditions that can mimic LAM includes pulmonary Langerhans cell histiocytosis (LCH), emphysema, follicular bronchiolitis, Birt– Hogg–Dubé syndrome (BHD), lymphoid interstitial pneumonia, light chain deposition disease and advanced interstitial lung disease.[21] For proper diagnosis and specification of clinical features a thorough smoking and occupational history should be recorded in all patients. When physical examination is done it would be often normal but depending on the clinical presentation wheeze, crackles, abdominal masses or features suggestive of TSC may be present.

Extra pulmonary manifestations of LAM can be mainly denoted as lymphadenopathy, large cystic lymphatic masses, chylous abdominal collections in approximately half of patients, the coexistence of a benign tumour of smooth muscle, blood vessels and fat (termed angiomyolipoma), which occurs chiefly in the kidneys.[23] Computed tomography (CT) scanning shows enlarged abdominal lymph nodes, either retroperitoneal, retrocrural or occasionally pelvic, in approximately one third of patients. Larger cystic masses called lymphangioleiomyomas most commonly occur in the abdomen, retroperitoneum and pelvis.[25] These may occasionally occur in the mediastinum and neck.

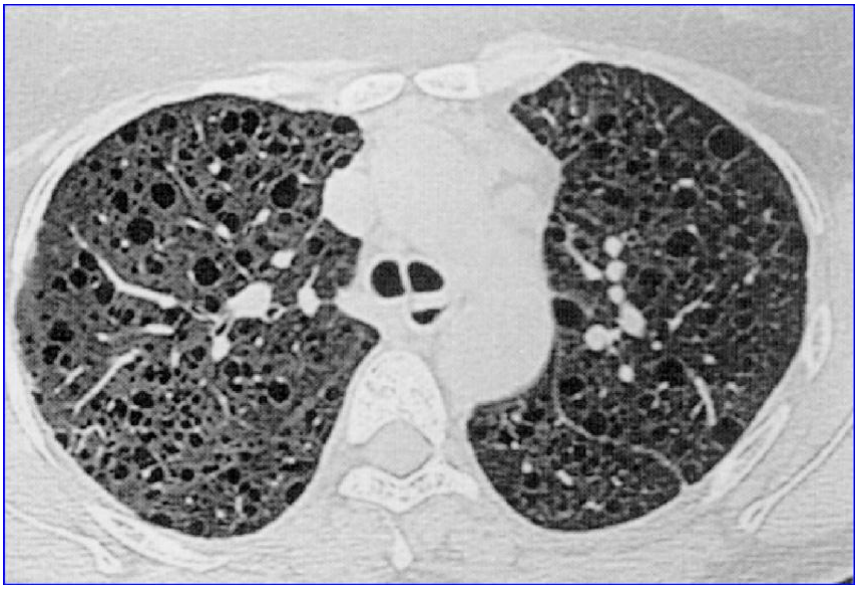

Figure 3: Chest CT scan of patient with lymphangioleiomyomatosis showing multiple cysts throughout the lung parenchyma.

Symptoms in accordance with lymphangioleiomyomas are nausea, bloating, abdominal distension, peripheral oedema and urinary symptoms.[26] These symptoms may worsen during the day. This finding has been correlated with an increase in the size of lymphangioleiomyomas in the afternoon, mostly due to increased lower limb lymph accumulation due to standing throughout the day.[23] Less commonly, localised swellings or pressure effects can cause symptoms at other sites. Around 10% of patients will develop chylous ascites due to lymphatic obstruction. Ascites are associated with lymphatic obstruction and chylous collections in the thorax[6] and more advanced lung disease.[23] Angiomyolipoma is the most common abdominal manifestation of LAM. CT scan shows that it is present in up to 50% of patients.

DIAGNOSTIC EVALUATION

High Resolution Computed Tomography (HRTC) helps to diagnose patients with LAM before they become symptomatic with characteristic cysts noted, which is found when checked for another indication.[26] Causes of cystic lung disease can be found by certain blood work, including α1-antitrypsin and connective tissue disease screen (anti-Ro/ La, anti-cyclic citrullinated peptide, rheumatoid factor and antinuclear antibody). This will help identify other causes of cystic lung disease. To make a confident diagnosis of LAM a stepwise approach is suggested, using a combination of clinical, radiological and serological tests (figure 4).

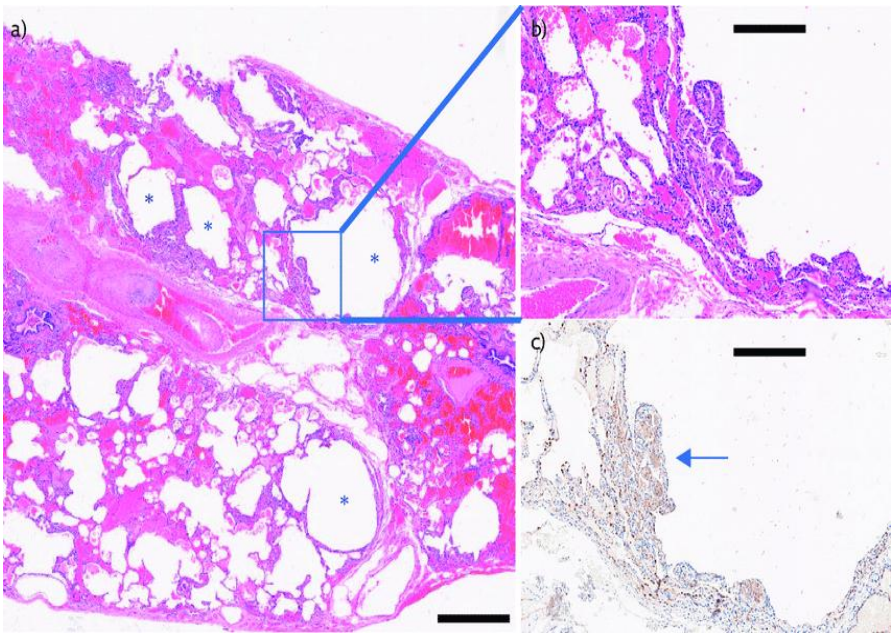

Figure 4: Lung biopsy in LAM. a) Lung parenchyma showing multiple cysts (arrows) with proliferation of b) spindle cells that are c) Human Melanoma Black 45 positive. Scale bars: a) 1000 µm; b and c) 100 µm.

Pulmonary function

Pulmonary function tests (PFTs) are useful to establish the baseline severity of pulmonary disease and to facilitate monitoring over time even though they are non specific.[28] Common features are airflow obstruction (25–66%), restrictive/mixed (<25%) and no abnormality in up to 60%. Diffusing capacity of the lung for carbon monoxide (DLCO) is reduced in majority of cases and is a more useful indicator of possible LAM. 30% of patients shows reversible airflow obstruction and is related to prognosis.

Radiology

In early cases, chest radiographs are often normal. Later, reticular or nodular opacities, hyperinflation, pneumothorax or lymphadenopathy may occur. HRCT of the thorax demonstrats thin-walled cysts. Features on CT may also be used to differentiate LAM from other causes of cystic lung disease which includes LCH or emphysema.[29] A definitive diagnosis of LAM based on current guidelines can be based on the presence of multiple characteristic cysts on lung HRCT and any of the following: kidney AML, thoracic or abdominal chylous effusion, lymphangioleiomyomas or lymph nodes involved in LAM, TSC, and elevated VEGF-D (figure 4).

Vascular endothelial growth factor-D

VEGF-D is a growth factor that binds to VEGF receptor 3. It is found to be elevated in 70% of patients with LAM.[30] When present at levels >800 pg·mL−1 in patients having characteristic lung cysts on HRCT, the specificity approaches 100% for the diagnosis of LAM. Moreover, VEGF-D can be specifically used to distinguish LAM from other causes of cystic lung disease.

Lung biopsy

Biopsies are considered in cases were a definitive diagnosis is required. The decision to proceed with biopsy should be made in an institute familiar with the care and management of LAM patients. It should take into account the benefit and risk of diagnosis.[31] The most important features of pulmonary LAM are lung cysts and LAM cells, which are positive for oestrogen receptors and an immunopositive reaction to the Human Melanoma Black (HMB)-45 antibody (figure 4). Other biopsy techniques are surgical lung biopsy (SLB) and transbronchial lung biopsy. High diagnostic yield is found in SLB nearly 100%) but it has significant morbidity and mortality.[35]

Other investigations

Acute Myelogenous Leukemia (AMLs) can be assesed using abdominal–pelvic imaging which are found in 33% of patient with S-LAM. This can be achieved via CT or magnetic resonance imaging (MRI). This imaging also help to find out lymphangioleiomyomas, abdominal or retroperitoneal lymphadenopathy, or other lymphatic manifestations.[33]

MANAGEMENT OF LAM

The most important step in the management of LAM is education. Patients should be educated about their disease, its effect and potential therapies.[44] Weight loss, physical activity, smoking cessation and seasonal vaccinations are recommended for initial and mild disease condition. Patients with large AMLs should avoid heavy sports due to a risk of trauma and bleeding.

Pharmacotherapy

Confirmed LAM patients and an FEV1 <70% predicted should be treated with an mTOR inhibitor, either Sirolimus or everolimus.[46] In other selected groups, i.e. patients with normal spirometry but other markers of severity (rapidly reducing FEV1, elevated residual volume, reduced diffusing capacity, exercise induced desaturation or resting hypoxaemia), mTOR therapy should be considered. Doses of Sirolimus maintaining a trough level as low as 5 ng·mL−1 is more effective and improves tolerability.[48] Duration of treatment is unclear. function and may not require treatment with mTOR inhibitors. VEGF-D levels can be used to monitor treatment response and allow dose adjustments.

Even though Sirolimus is mostly well-tolerated, the common side-effects include mucositis, gastrointestinal symptoms, high cholesterol, acne and lower-limb oedema.[42] Rarer side-effects include ovarian cyst formation, dysmenorrhoea, proteinuria, deranged liver function, drug-induced pneumonitis and infection risk.

Reversibility on spirometry is seen in up to 30% of patients. These patients should be given a trial of an inhaled β-agonist.

Pulmonary complications

The initial approach to pneumothorax in LAM is done in the same way as other lung disorders. Thoracic surgeon should be involved when a second pneumothorax or a persisting air leak occurs. Even if after a surgical treatment, pneumothorax may recur and result in chest pain and a gurgling sensation within the chest. Treatment of pneumothorax in patients who require lung transplantation should avoid radical pleural procedures, especially if bilateral pneumothorax has occurred.

Chylothorax may be associated with symptomatic dyspnoea in LAM.[33] It occurs by one of three mechanisms: 1) obstruction of the thoracic duct and its tributaries; 2) leakage from pleural lymphatics; and 3) transdiaphragmatic flow from chylous ascites. Treatment mainly focusses on obliterating the pleural space and thereby prevent lymphatic accumulation or ligation of the thoracic duct. Re- accumulation is seen after simple aspiration or chest tube drainage. Patients with persisting effusions after aspiration have been treated by pleurodesis, pleurectomy and, in some cases, thoracic duct ligation.

Hormone therapy

Various antioestrogen strategies have been used in the treatment of LAM. As LAM generally presents in pre-menopausal females and may be exacerbated by exogenous oestrogen.

Progesterone is the most commonly used hormone treatment for LAM.[36] Progesterone shows a nonsignificant reduction in the rate of decline in FEV1 and a significant reduction in the rate of decline in carbon monoxide diffusing capacity of the lung . These effects were small and there was a wide variation in rates of decline in FEV1. Common side-effects of progesterone include bloating, fluid retention and nausea. Progesterone treatment may be associated with the increased incidence of meningiomas in LAM. Medroxyprogesterone is another hormonal treatment for LAM.[34] Tamoxifen, a partial agonist of the oestrogen receptor, has been used; the more selective full oestrogen antagonists may be more effective but have not yet been evaluated for LAM.

Lung transplantation

The first transplant procedure for LAM was performed in 1983. Transplantation may be done in patients with progressive disease and severe disability and those dependent on oxygen. Survival following transplant is similar to other lung diseases.[28] Acute lung injury, haemorrhage and sepsis, with later deaths predominantly due to obliterative bronchiolitis and sepsis may cause early post-transplant deaths. Specific complications related to LAM are native lung pneumothorax following single lung transplant and postoperative chylothorax.

Pregnancy

Females having LAM are less likely to plan pregnancy compared to women without LAM. It is found that women with LAM are less fertile and have fewer children in comparison to general population.[26] Women with LAM may have a higher risk of pregnancy complications including pneumothorax, chylous effusions, worsening dyspnoea or bleeding from AMLs. Pneumothorax or increased dyspnoea can be present for the first time in pregnancy with LAM. This may be due to hormonal changes in pregnancy or whether there is an unmasking of the disease due to the changes experienced with pregnancy physically.[21] Those with advanced LAM should be advised commence Sirolimus rather than delay and to avoid pregnancy. The use of Sirolimus in pregnancy and its safety is unclear.

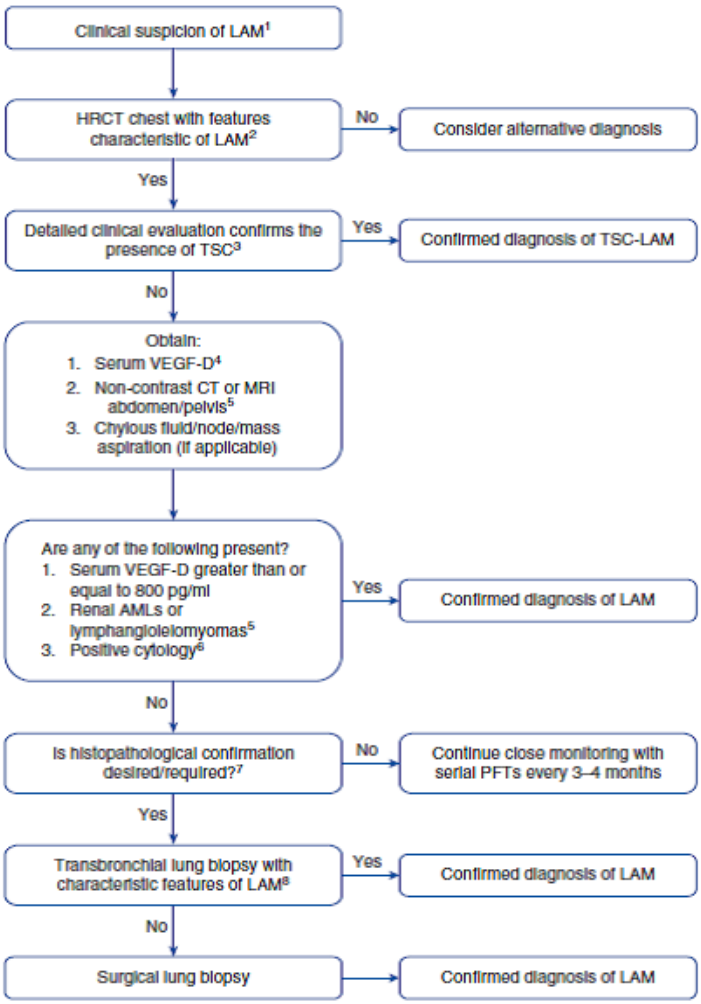

Figure 5: treatment algorithm for LAM.

CONCLUSION

LAM is a rare diffuse cystic lung disease. It is a multisystem disease of women. It is mainly reported in women of child bearing age, most commonly with dyspnea and pneumothorax. It is mainly characterized as proliferation of abnormal smooth muscle-like LAM cells It is mainly characterised by proliferation, metastatic spread and infiltration of tissues, most commonly lung parenchyma by abnormal smooth muscle-like LAM cells. The most common clinical manifestation is dyspnea. Prolongation of the disease condition may lead to respiratory failure. First line diagnostic marker for LAM is Vascular endothelial growth factor (VEGF)-D. When tested it would be elevated in 70% of patients with LAM, and should be measured in all suspected cases of LAM.[22] Other diagnosis methods include pulmonary function test, radiology, lung biopsy etc. treatment options for LAM include treatment with an mTOR inhibitor, either Sirolimus or Everolimus, hormonal therapy with anti-oestrogen, progesterone and methoxyprogesteron. For crutial cases, lung transplantation is done. The chances of pregnancy in women with LAM is poor when compared with normal women. Pregnancy in LAM patient is often risky.

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