

Review article

## Lymphangiomyomatosis: A review

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### Abstract

Lymphangiomyomatosis (LAM) is a rare disease, of unknown etiology, affecting women almost exclusively. Microscopically, LAM consists of a diffuse proliferation of smooth muscle cells. LAM can occur without evidence of other disease (sporadic LAM) or in conjunction with tuberous sclerosis complex (TSC). TSC is an autosomal dominant tumor suppressor gene syndrome characterized by seizures, mental retardation, and tumors in the brain, heart, skin, and kidney. LAM commonly presents with progressive breathlessness or with recurrent pneumothorax, chylothorax, or sudden abdominal hemorrhage. Computed tomography (CT) scans show numerous thin-walled cysts throughout the lungs, abdominal angiomyolipomas, and lymphangiomyomas. No effective treatment currently exists for this progressive disorder. The prevalence of lymphangiomyomatosis is probably underestimated based on its clinical latency and the absence of specific laboratory tests. With the utilization of international LAM data registries the “classical” picture of the disorder appears to be evolving as a larger number of patients are evaluated. An increased awareness of LAM and its common clinical presentation may advance the development of new therapeutic strategies and reduce the number of mistakenly diagnosed patients.

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### 1. Introduction

Lymphangiomyomatosis (LAM) is a rare disease of unknown etiology described classically as occurring in women of reproductive age, and occasionally in postmenopausal women [1–4]. The disease often arises spontaneously in patients with no evidence of genetic disease and is present in approximately one third of women with tuberous sclerosis complex [5,6]. The pathology of LAM is represented by the proliferation of immature smooth muscle cells in the walls of airways, venules and lymphatic vessels in the lung [7,8]. Proliferation of these cells results in narrowing of the airways,

obstruction, and air trapping. Damaged alveoli combine, and in time lead to the development of cystic lung lesions and fluid-filled cysts in the lymphatics (lymphangiomyomas) [9]. The disease follows an insidious course and the rate of progression is variable ranging from a few years to over three decades before culminating in respiratory failure [10].

The estimated incidence of LAM is between 1–2.6 cases per 1,000,000 women [9,11]. The true incidence is likely under-reported because LAM is often mistakenly diagnosed for asthma, chronic obstructive lung disease, or bronchitis. The two most common presenting symptoms of LAM are dyspnea on exertion and pneumothorax [1]. Pneumothoraces are often recurrent, even in patients with normal chest X-rays (CXR) [2] and have been reported to occur at a frequency of 40 to 80% in patients with LAM [7]. Other less common presenting symptoms include hemoptysis, non-productive cough, chylous pleural effusion and chylous ascites [1]. While these symptoms are less likely present initially, they often develop with disease progression [1,2].

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## 2. Physical findings

The most common complications of LAM — pneumothorax, chylous pleural effusion, and hemoptysis can be explained at least in part by the proliferation of atypical smooth muscle cells around the bronchioles, lymphatics and venules, respectively [3]. The bronchioles may be circumferentially narrowed by the peribronchiolar proliferating tissue [9]. Airway obstruction and air trapping contribute to the formation of parenchymal cysts and pneumothorax. Focal or diffuse thickening of the walls of air spaces may also occur. Involvement of the venules leads to obstruction of venous flow in the lungs causing venous distension, pulmonary venous hypertension, and hemoptysis, a characteristic in 40% of patients [7]. Hemosiderosis is common and is a consequence of clinically insignificant hemorrhage due to the rupture of dilated and tortuous venules [2]. Lymphatic circulation is directly disrupted by a thickened thoracic duct which is often reduced to multiple narrow channels; infradiaphragmatic lymphatic obstruction may result in retroperitoneal cystic masses [10]. Obstruction leads to chylous pleural effusions in 80% of patients [7] and ascites in up to one third of all patients [10]. Clubbing is uncommon (five percent or less) [2]. Lymph nodes in the abdomen and pelvis may be involved and up to half of all patients have renal angiomyolipomas [10].

## 3. Pathogenesis and tuberous sclerosis complex (TSC) association

LAM and the Tuberous Sclerosis Complex may share a common genetic relationship. TSC is caused by germline mutations of either the TSC1 or TSC2 gene located on chromosomes 9q34 and 16p13, respectively. Both of these genes are tumor suppressor genes encoding hamartin (TSC1) and tuberlin (TSC2) [23]. Tumor in either condition is associated with a loss of heterozygosity (LOH) at one of the two genes [14,45]. The tumor suppressor gene TSC2 has been implicated in the etiology of LAM, as mutations and LOH in TSC2 have been detected in LAM cells [45]. The exact pathogenesis of LAM is unidentified, but the accumulating data supporting the role of somatic mutation of the TSC2 gene suggest a spontaneous mutation in a normal resident pulmonary cell [50] that facilitates the lack of expression of certain cellular enzymes resulting in tumor suppression dysfunction and aberrant local proliferation [14]. The mutation has also been shown to influence proteins involved in the synthesis of catecholamines [10]. The varying expression of growth factors and their receptors in LAM may result in cell-specific functions which facilitate the fibrogenic, proliferative, and matrix-regulating actions of LAM cells [14]. It is not entirely clear how defects in these proteins or in catecholamine synthesis may potentially produce the LAM phenotype.

Somatic mutations of the TSC2 gene are identified in approximately one-half of renal angiomyolipomas in patients with either LAM or tuberous sclerosis [40]. DNA examina-

tion of sporadic LAM angiomyolipomas yields TSC2 mutation [45]. These observations suggests that somatic mosaicism for TSC2 mutations within the lungs and kidney may result in foci of disease superimposed upon a milieu of normal functioning cells within these tissues [38]. The role of environmental factors in the development of clinically apparent LAM is under debate [38]. Nevertheless, the notion that LAM represents dissemination of angiomyolipomatous tissue to the lung in a manner comparable to the syndrome of benign metastasizing leiomyoma cannot be excluded [39].

Tuberous Sclerosis, a neurocutaneous disorder, is an autosomal-dominant tumor suppressor gene syndrome involving the brain, skin, kidneys, bones, heart and lungs. Pulmonary LAM is histologically indistinguishable from the pulmonary lesions observed in TSC, and McCormack reports that LAM has a prevalence as high as 39% in TSC [49]. Clinically, TSC is characterized by the triad of mental retardation, seizures, and adenoma sebaceum. The diagnosis of TSC is usually made clinically based on somatic feature recognition; the presence of mental retardation, together with adenoma sebaceum, shagreen patches and depigmented areas on the limbs and trunk which characteristically fluoresce under Wood's Light. The presence of multiple well-defined pulmonary cysts, bilateral fatty renal tumors, and bony sclerosis is pathognomonic of tuberous sclerosis complex. Many other sites may be involved, including the liver, pancreas, and lymph nodes in the retroperitoneum and mediastinum.

It should be emphasized that LAM and tuberous sclerosis are distinct syndromes. TSC demonstrates clear Mendelian inheritance and will also affect the skin and central nervous system. The clinical, radiologic, and histological features of pulmonary involvement in TSC are impossible to differentiate from lymphangiomyomatosis. Both pulmonary TSC and LAM are characterized by hamartomatous proliferation of smooth muscle in the walls of airways, venules, and lymph vessels within the lung [7]. Pulmonary involvement is said to occur in 1 to 2.3% of patients with TSC [15,16] and often these patients have a lower incidence of epilepsy and mental retardation [17]. Interestingly, TSC affects both sexes equally but pulmonary involvement, like LAM, almost exclusively affects women of childbearing age. Imaging holds a critical role in the detection of associated pulmonary or extrapulmonary pathology in patients with LAM, with or without TSC.

## 4. Radiography

The chest radiographic findings may be normal or may show diffuse reticular or miliary changes throughout all lung zones with overexpansion of the lungs. Ground glass opacities may be noted corresponding to pulmonary hemosiderosis and/or relatively diffuse proliferation of immature smooth muscle cells [2]. A pattern of reticulation results from the coalescence of numerous pulmonary cysts [18]. An alternative cause of this pattern on CXR is Langerhans' Cell Histiocytosis (LCH), from which LAM

must be differentiated. The two conditions share similar potential findings of chylous pleural effusion, pneumothorax, pulmonary nodules and cysts [19].

Chest CT scans often demonstrate multiple well-defined thin-walled cysts, homogeneously distributed and present throughout all lung zones with relative apical sparing [18]. Thin-section CT has a higher diagnostic yield than plain radiography and may demonstrate parenchymal cysts even in the presence of a normal CXR [18,20–22]. The intervening lung parenchyma is often normal but as the disease progresses the cysts enlarge and may coalesce resulting in distortion of adjacent lung tissue. While cystic lung lesions are not pathognomonic for LAM, the combination of diffusely scattered thin-walled cysts on chest CT and clinical symptoms compatible with LAM are often highly suggestive of the diagnosis, and may warrant biopsy of lung tissue for confirmation.

Further explanation of CT findings calls for the differentiation of LAM, LCH and  $\alpha$ -1 Antitrypsin emphysema. In contrast to LAM, LCH is predominantly characterized by nodules and cyst walls of variable thickness [18] which typically exist in the middle and upper lung zones, sparing the costophrenic angles [23]. Although nodular densities have previously been reported in LAM [2], such nodules were not observed in a recent study of 35 patients by Chu et al. These findings may be of particular interest in the differentiation of LAM from LCH. In contrast,  $\alpha$ -1 Antitrypsin emphysema is characterized by diffuse bullous and emphysematous changes on both standard and high resolution CT. Such findings should easily be differentiated from the diffusely scattered, thin walled cystic pattern observed in LAM [20]. LAM is one of the few interstitial diseases in which lung volumes are maintained or increased. Large lung volumes and interstitial disease on plain film also can be seen with Langerhans Cell Histiocytosis, sarcoidosis, Cystic Fibrosis and extrinsic allergic alveolitis. Occasionally, emphysema presents with a similar pattern as a result of summation of widespread small bullae.

Bronchiectasis has been described as demonstrating a cystic pattern which can be observed radiographically. While less likely to be considered in the differential diagnosis based on history, the classic manifestations of bronchiectasis are cough and daily mucopurulent sputum production, the radiological findings warrant differentiation. Cystic or saccular bronchiectasis will typically demonstrate ulceration with bronchial neovascularization and as a result a ballooned appearance that may potentially demonstrate air-fluid levels [48]. Classic epidemiologic teaching suggests that persons aged 60–80 years have the highest frequency of bronchiectasis, in contrast to the younger population which is diagnosed with LAM.

## 5. Hormone association

LAM classically occurs in women of childbearing age and its presentation in postmenopausal women is generally considered unusual. It is likely that estrogen plays a fundamental

role in disease progression. The disease is never seen before menarche, known to accelerate during pregnancy and observed to subside after oophorectomy. In addition, receptors of estrogen and progesterone have been located in a sub-population of the atypical smooth muscle cells that are characteristic of the disease [29,40,41]. These receptors can be identified on the smooth muscle cells even when the disease affects males [42].

Taylor et al. have presented evidence suggesting that when the disease does present in the post menopausal female often times, these women were taking estrogen containing hormone replacement therapy [1]. These reported findings correspond with evidence suggesting that estrogen administration [24,25] and pregnancy [26–28] may accelerate disease progression. Generally speaking, patients with LAM should be cautioned to avoid pregnancy because of the impression that the disease progresses during pregnancy and because patients with LAM often suffer from a higher incidence of respiratory complications [26,27].

Previous investigators have reported the initial presentation of LAM or its progression while patients were taking oral contraceptives [7,31]. Despite these reports, in a case control study performed by Wahedna et al. no association was found between the use of oral contraceptives and LAM [32]. Further, only 1 of the 46 LAM patients described by Kitaichi et al. had used oral contraceptives before the onset of symptoms [2]. Matsui et al. report that the estrogen and progesterone receptors may be subsequently down regulated as a result of the administration of hormonal therapy [41]. These reports highlight the variable association between hormone administration and our knowledge of the onset, progression and treatment of LAM.

## 6. Diagnosis of LAM

Any young woman who presents with emphysema, recurrent pneumothorax, or a chylous pleural effusion should raise suspicion for LAM. High resolution CT scan can often confirm the diagnosis, and tissue confirmation may not always be necessary [19]. However, lung tissue is often obtained through either thoracoscopic or open lung biopsy. Transbronchial lung biopsy can provide adequate tissue sample for pathologic evaluation. LAM can be readily diagnosed by its characteristic histological findings. Immunohistochemical stains specific for smooth muscle components (actin, desmin, or HMB-45) have been employed to increase the diagnostic sensitivity and specificity of pathologic evaluation [12]. Open-lung biopsy and histological examination using the monoclonal antibody HMB 45, which specifically stains LAM smooth-muscle cells is considered the diagnostic gold standard [12]. Biopsy confirmation is often required if these patients are to be considered, which they often are, for lung transplantation [13]. Laboratory results including complete blood count, serum chemistries, and liver enzyme levels, and urinalysis generally reveal no abnormalities that are judged to be informative in diagnosis [44].

## 7. Pulmonary function testing

The lungs of patients suffering from LAM are often hyperinflated. Typically patients demonstrate an increased total lung capacity (TLC). Pulmonary function tests frequently reveal an “obstructive” or “mixed” pattern [1,2,20]. An increase in residual volume (RV) and RV/TLC ratio as a result of the air trapping is generally present. Patients will demonstrate limitations to airflow and pulmonary function tests often show reduced flow rates (FEV1). Twenty per cent of patients have positive bronchodilator responses [45]. Lung function suffers from diminished elastic recoil as well as an increase in airway resistance, both contributing to the observed airflow limitations. Poor gas exchange results in a significantly reduced diffusion capacity (DLCO) in conjunction with an elevation in the alveolar–arterial oxygen gradient [19]. Exercise testing shows gas-exchange abnormalities, ventilatory limitation, and hypoxemia that may occur with near-normal lung function. Disease progression is best assessed by measurements of DLCO and FEV1 [45].

## 8. LAM in men

Of the four reported cases of LAM occurring in males, the report that indicates the occurrence of LAM in a chromosomally normal man unaffected by TSC is of particular interest [42]. Schiavina et al. reported the case of a phenotypically and karyotypically (TSC1 and TSC2 germ line mutations were not detected at DNA analysis) normal man with left pneumothorax and massive pulmonary collapse with widespread thin-walled cysts throughout both lungs. Interestingly, the HMB-45-positive cells lining the cysts of the male patient also showed strong reactivity for estrogen and progesterone receptor proteins [42]. Mesenteric LAM has been reported occurring in an adult male affected by Klinefelter syndrome. In contrast to the before mentioned case the tumor cells were negative for estrogen, progesterone, and androgen receptors [43]. The association between LAM and Klinefelter syndrome has yet to be described but could represent an area of interest in the uncertain pathogenesis of this disease [43]. Even in the absence of signs of TSC the possible diagnosis of LAM should be entertained when diffuse cystic lung disease occurs in a man [42].

## 9. Treatment

Although Taylor et al. found no therapeutic benefit from oophorectomy or anti-estrogen therapy with tamoxifen, progesterone was reported beneficial in at least some patients leading to their recommendation of its use in all symptomatic patients [1]. However, these findings have not been demonstrated consistently and a recent retrospective analysis performed by Taviera-DaSilva et al. reported that progesterone therapy did not slow decline in lung function and may have limited use in the treatment of patients with LAM [30].

Hormonal management provides the foundation of treatment in LAM, based on the recognition that female hormones play an etiologic role in the pathogenesis of the disease. Oophorectomy, progestin therapy (high dose medroxyprogesterone acetate given as IM depot or PO), tamoxifen (20 mg/day), and luteinizing hormone-releasing hormone (LHRH) analogs [31,33–35] have been employed. However, only oophorectomy and treatment with progesterone appear to provide reliable improvement or stabilization of the disease in a subset of patients [34]. It should be noted that response to hormonal manipulation is not universal; in one series of 57 patients who received hormonal therapy, only 4 manifested an improvement in FEV1 of greater than 15 percent [36]. Trials with rapamycin (sirolimus) are currently ongoing and offer hope of evidence-based treatment for the disease [46].

Pneumothorax is often an early associated finding and should be managed conventionally. Surgical assistance may be warranted as the disease pathology predisposes to pneumothoraces that are more likely to be recurrent, bilateral, and less responsive to conservative measures. Recurrent pneumothorax will require management typical of such a condition and should be followed by pleural abrasion, talc or chemical pleurodesis. Patients with lymphangioleiomyomatosis and airflow obstruction are frequently helped by inhaled beta agonists and a therapeutic trial of these agents is reasonable in early management efforts [10]. Treatment outcomes reported by Johnson and Tattersfield included an element of reversibility of greater than 10% in more than half of the patients undergoing treatment with a beta agonist [47].

Lung transplantation offers the only hope for cure in pulmonary LAM. One retrospective international survey evaluated 34 patients who underwent lung transplantation: 27 received single-lung transplants; 6 bilateral lung transplants; and 1 a heart-lung transplant [13]. Boehler et al. report the FEV1 having improved from 24 percent of the predicted value before transplantation to 48 percent six months after transplantation [13]. Patient survival was reported as 69 percent at one year and 58 percent at two years.

## 10. Emerging clinical picture

Recent work by Cohen et al. has revisited the clinical presentation via the utilization of multiple large registries including international groups of LAM patients [37]. Their comprehensive survey suggests that older women (50% without pneumothorax) are now being diagnosed with LAM. The mean age of diagnosis appears to be increasing over time. With the identification of more patients and the utilization of data registry the typical presentation is becoming equally a disease of women 45–60 years of age, with Cohen et al. reporting a mode of 44 years [37]. We suggest that the age distribution of LAM should be broadened to include women in their reproductive years and beyond. The association of dyspnea and unexplained airflow obstruction in a female patient who does not smoke should prompt a search for LAM even in the absence of pneumothorax or known diagnosis of



TSC. In addition, the prototypical symptomatology requires the inclusion of subjective patient complaints. The subjective reports of fatigue have been largely overlooked as a significant symptom of LAM while appearing across the complete range of pulmonary function [37].

## 11. Conclusion

Lymphangiomyomatosis is the result of disorderly smooth muscle proliferation throughout the bronchioles, alveolar septa, perivascular spaces, and lymphatics, resulting in the obstruction of small airways leading to pulmonary cyst formation and pneumothorax. Lymphatic obstruction leads to chylous pleural effusion, leading to pulmonary cyst formation pneumothoraces. LAM occurs in a sporadic form which predominantly affects females often in the childbearing age. A patient who presents with recurrent pneumothoraces, unexplained dyspnea, or chylous effusion should prompt a search for LAM. In addition, the association between LAM in patients with TSC is of note.

## 12. Learning points

- Pulmonary lymphangiomyomatosis (LAM) is a rare lung disease that afflicts young women of childbearing age
- Chest CT often demonstrates multiple well-defined thin-walled cysts, homogeneously distributed and present throughout all lung zones with relative apical sparing
- Thin-section CT has a higher diagnostic yield than plain radiography and may demonstrate parenchymal cysts even in the presence of a normal CXR
- Estrogen administration and pregnancy may accelerate disease progression given that receptors for estrogen and/or progesterone are found on LAM cells
- Characterized pathologically by the proliferation of atypical pulmonary interstitial smooth muscle and by cyst formation
- Often misdiagnosed as asthma or chronic obstructive pulmonary disease (COPD) because of significant airflow limitation
- A diagnosis of LAM should be entertained when diffuse cystic lung disease occurs in a man.

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