Lymphangioleiomyomatosis (LAM) is a rare idiopathic interstitial lung disease predominately affecting women. Although Van Stossel first described pulmonary LAM in 1937, the natural history of LAM remains poorly understood [1]. Patients with LAM develop peribronchial, perivascular, and lymphatic proliferation of smooth muscle-like cells in the lungs, resulting in vascular and airway obstruction and cyst formation. A progressive decline in lung function occurs over time. The true incidence and prevalence of LAM are unknown, although current worldwide registries report LAM as a disease of women with no geographic preference (Table 1). LAM has been reported to occur in patients with tuberous sclerosis complex (TSC), alpha-1 antitrypsin deficiency, Langerhans’ cell histiocytosis, thyroid carcinoma, bronchoalveolar carcinoma, and in association with renal angiomyolipomas (AMLs) [2–6]. More than 400 citations are listed currently in the literature for LAM. This article reviews and updates the expanding knowledge about LAM.

**Lymphangioleiomyomatosis: clinical, radiographic, and pathologic features**

Patients diagnosed with LAM are primarily women of child-bearing age who present with a spontaneous pneumothorax, chylous pleural effusion, progressive exertional dyspnea, cough, or occasionally hemoptysis [7]. Most patients experience progressive dyspnea on exertion in the fourth and fifth decades of life. The average interval between onset of symptoms and time of diagnosis is approximately 3 to 4 years [8]. Most of the delay in diagnosis results from misdiagnosis and the lack of early specific clinical findings. Common misdiagnoses include asthma, emphysema, and chronic bronchitis [9]. No infectious cause has been identified to date, including agents such as herpes and papilloma viruses.

**Radiographic features**

Radiographic findings include hyperinflation, an interstitial pattern that may be reticular, reticulonodular, or associated with cysts (wall thickness <4 mm and diameter <10 mm), bullae, and pneumothoraces [10]. In most patients with LAM, high-resolution chest CT shows numerous thin-walled cysts throughout the lungs without any particular distribution. There are, however, other diffuse cystic lung diseases that can be confused with LAM, including Langerhans’ cell histiocytosis, honeycomb lung associated with advanced fibrosis, and, rarely, metastatic disease [11]. Other radiographic findings that occur in patients with LAM include renal AMLs and meningiomas of the brain [12].

**Pulmonary function studies**

Pulmonary function studies demonstrate a combination of obstructive and restrictive changes including an elevated total lung capacity, increased residual volume, and a reduced forced expiratory volume...
in 1 second [13]. Diffusion of carbon monoxide is reduced in these patients, and arterial blood gas analysis often reveals hypoxemia without hypocapnia [9,14]. Cardiopulmonary exercise testing demonstrates a decreased maximal work load [9]. Ventilatory limitation seems to be responsible for poor exercise performance in patients with LAM [9].

### Pathology

Macroscopically, the lung of a patient with LAM has a honeycomb appearance [15]. Cysts, measuring 0.5–2 cm in size are often filled with air, serosanguinous fluid, or chylous material. Microscopically, enlarged airspaces are seen with abnormal proliferation of smooth muscle–like cells in their walls [16]. These spindle-shaped “LAM cells” contain eosinophilic cytoplasm, abundant rough endoplasmic reticulum, and rare mitotic figures. LAM cells are found in the walls of the cysts along the pulmonary lymphatics as well as in the blood vessel wall where they grow in an infiltrative, disorganized, and non-concentric pattern forming obstructive cell bundles [16]. LAM cells stain positively for anti-smooth muscle α-actin and, therefore, have been described as smooth muscle-like cells [3]. They also display features of myofibroblasts [17] and stain positively for a variety of fibroblast markers, including fibroblast antigen.

LAM cells may exhibit specific immunostaining with the human melanoma black (HMB-45) antibody [18,19], an antibody that reacts with a glycoprotein (gp 100) found in immature melanocytes. HMB-45 staining, however, is variable and is not detectable in all LAM biopsies or on all cells in a specific LAM lesion [13,18]. There seem to be two types of LAM cells: large and small. Most large, epithelioid cells, which are at the periphery of the LAM lesion, stain with HMB-45, whereas most small, spindle-shaped cells are located in the center of the lesion and do not stain with HMB-45 [18]. The central cells also show immunoreactivity for matrix metalloproteinases and proliferating cell nuclear antigen, a marker of cell proliferation. This evidence suggests that the proliferating central cells may be involved in the turnover of the extracellular matrix [18,20]. Although melanogenesis has been suggested to occur in the large peripheral cells of the LAM lesions, mature melanosomes have not been found [18].

Two pathologic entities may be confused with LAM: lymphangioma and lymphangioleiomyoma. Lymphangiomas are congenital, benign neoplasms of lymphatic vessels that are associated with lymphoid tissue and bundles of smooth muscle that stain positively for smooth muscle actin and negatively with HMB-45. Most lymphangiomas occur in the head and neck region of children, but they can occur in adults. On the other hand, lymphangioleiomyomas are acquired or congenital lesions that contain smooth muscle and stain positively with HMB-45. Lymphangioleiomyomas affecting more than one organ system have been referred to as lymphangioleiomyomatosis. Lymphangioleiomyomas may occur as part of a LAM lesion. The terms lymphangioleiomyomatosis and lymphangioleiomyomatosis (LAM) have been used interchangeably, promoting confusion in the literature.
**Lymphangioleiomyomatosis and tuberous sclerosis complex**

There are three groups of patients that develop LAM-like lung disease: S-LAM patients who do not have any clinical features of TSC or AMLs; S-LAM with AMLs; and TSC-LAM patients who have TSC as their primary disease and also can have large AMLs. Most cases of S-LAM and TSC-LAM are reported in women (4;11;22) [4,21,22].

In early studies, LAM was reported in only 2% to 3% of patients with TSC [23]. In a retrospective cohort study of 78 women with TSC, Costello et al [24] reported that 26% of the women had TSC-LAM although LAM was biopsy-confirmed in only seven cases. A more recent survey of 38 women with TSC revealed a 10-fold higher prevalence of LAM (34%) in this population [21]. The authors of this study concluded that there may be an unrecognized subclinical population of patients with TSC at risk for pulmonary complications [21]. Recent radiographic data indicate that up to 39% of women with TSC have LAM-like diffuse cystic lung disease [21,24,25].

In addition to LAM, male and female patients with TSC may also develop multifocal micronodular pneumocyte hyperplasia (MMPH) [25,26]. MMPH is characterized by nodular proliferations of alveolar type II cells and may also occur in the lungs of patients with S-LAM and as an isolated finding. The significance of this pathologic subtype is unclear.

AMLs, which occur in up to 70% of patients with TSC, may be found in up to 60% of patients with LAM [13,27]. Meningiomas, also described in association with TSC, have been reported in patients with LAM [12]. Although most patients with LAM do not develop the central nervous system and skin changes of TSC, the similarities in the lung and kidney manifestations of the two diseases have led some investigators to postulate that they may have a common origin.

TSC, an autosomal dominant neurocutaneous disorder, is a member of a group of hamartomatous diseases known as the phakomatoses and is characterized by hamartomas of the skin, eye, heart, kidney, and brain accompanied by seizures and mental retardation [28]. TSC is genetically linked to two tumor suppressor genes, TSC1 and TSC2, that encode two proteins, hamartin (TSC1) and tuberin (TSC2). As members of the P13K/PKB (Akt)/S6K signaling pathway, they are important in regulating cellular size and growth [29–34]. Tuberin binds to mTOR (mammalian target of rapamycin), a protein involved in stimulating cell growth. Phosphorylation of tuberin by Akt dissociates the tuberin/hamartin complex that regulates mTOR [32,35]. The activation of mTOR leads to the activation and phosphorylation of S6 [32]. Overactivation of these signaling pathways caused by defective tuberin could contribute to dysregulation of cell growth and the formation of hamartomas.

In TSC lesions, there is a germline mutation in one of two genes (TSC1 or TSC2) and a second somatic mutation (or hit), known as loss of heterozygosity (LOH). The result of LOH is loss of protein function (hamartin or tuberin) in that cell. Thus, two hits have occurred: germline mutation and LOH. In patients with TSC, germline mutations and LOH have been identified in renal tumors [30] but not in the majority of brain lesions [30]. Recently, a novel mechanism of posttranslational inactivation of tuberin by physiologically inappropriate phosphorylation has been demonstrated in TSC-associated brain lesions [30].

A vast array of mutations and polymorphisms in TSC1 and TSC2 has been reported in patients with TSC [22]. Patients with TSC also have a diverse clinical course, and the severity of clinical disease does not correlate with the degree of genetic abnormalities. Inheritance of germline mutations is seen in familial TSC, but most cases of TSC represent de novo mutations. Mother–daughter transmission of TSC-LAM has been reported [22].

Current studies of LAM are hampered by the lack of an animal model that develops lung disease. The predominant animal models of TSC, the Eker rat, a rodent lacking TSC1 or TSC2, and TSC1 +/− and TSC2 +/− mice, have not been reported to develop any LAM-like lung disease. The mice develop renal cystadenomas and liver hemangiomas. Data generated from cells isolated from Eker uterine leiomyomas (ELT3 cells) have been utilized to further the understanding of the lung disease of LAM. A better model for LAM lung disease awaits further development.

Data from studies in humans also question the evidence that the lung lesions in LAM are exactly the same as in TSC-LAM. Loss of tuberin or hamartin expression is found in most TSC lesions [36]. Some brain lesions with TSC2 germline mutations may express tuberin [37]. Johnson et al [38] have demonstrated that tuberin is strongly expressed in LAM cells, and to date a mutant tuberin has not been reported in LAM. It is possible that an abnormally functioning tuberin may exist in LAM as the result of a mutation in functionally related proteins or another undetermined mechanism. There may also be tissue variability of tumor suppressor gene phenotypes or variable levels of mosaicism in LAM tissue.
 Nonetheless, genetic studies have demonstrated several provocative findings establishing a link between LAM and TSC. The first reports of a genetic relationship between LAM and TSC appeared in 1998. Smolarek et al [39] reported LOH for TSC2 in 7 of 13 AMLs from patients with S-LAM. Mutations in TSC2 were not detected in peripheral blood cells in these patients. Two years later, Carsillo et al [40] examined LAM lung lesions, AMLs, and normal lung and kidney tissue in seven patients with S-LAM and described LOH for TSC2 in five of the seven AMLs. In four patients, the same mutation was found in LAM tissue, with no mutations noted in the surrounding nondiseased tissue. An additional study also reported LOH for TSC2 in both involved lung and AML tissue in two patients with S-LAM [41]. These data suggest that somatic mutations occur in S-LAM. To determine if germ-line mutations in TSC2 occur in S-LAM, Astrinidis et al [42] completed a mutational analysis of TSC2 in 21 patients with S-LAM. Three silent TSC2 polymorphisms and no germ-line mutations were found. Sato et al [43] have reported one TSC1 germ-line mutation in 1 of 22 Japanese S-LAM patients. Pan et al [44], however, demonstrated no TSC1 or TSC2 mutations in an additional Japanese patient with S-LAM. These studies suggest an association between LOH for TSC2 and the presence of AMLs.

Fig. 1. A 62-year-old woman who has had dyspnea for 5 years. At the time of her hysterectomy at age 48 years, the chest radiograph was read as suggestive of hyperinflation. She had been treated with estrogen replacement therapy since age 49 years. She developed (A) persistent chylous effusion and at age 60, a wire was placed in the thoracic duct for management of the effusion. A lung biopsy was performed demonstrating LAM. No angiomyolipomas or meningiomas were detected on CT scans of the abdomen or brain, respectively. (A) Posterior-anterior chest radiograph: hyperinflated lung at the time of the hysterectomy. (B) CT scan of chest demonstrating large right pleural effusion. (C) Cellular infiltrates diagnostic of LAM in section from video-assisted thorascopic biopsy. (D) Pulmonary function tests with severe obstructive changes not responsive to bronchodilators and decreased diffusion capacity. Arterial blood gas on room air and at rest (7.43/PCO2 42/PO2 52/87%) demonstrates significant hypoxemia.
and LAM. The failure to detect mutations in all patients may result from limitations in technique or mosaicism. Germline mutations do not seem to occur in S-LAM, supporting the lack of familial cases of LAM.

In contrast, mutation analysis in patients with TSC-LAM has shown germline mutations. Strizheva et al [45] reported seven TSC2 mutations and one TSC1 mutation in 14 women with TSC-LAM. In Japan, Sato et al [43] found TSC2 germline mutations in two of six patients with TSC-LAM. This group also reported LOH in three of four TSC-LAM patients, in four of eight S-LAM patients, and in microdissected cells from other tissues. These findings suggest a possible metastatic capability of mutated cells to travel and migrate to different organs within the same host [43].

These genetic studies also explain the recurrence of LAM in the donor lung of a few patients with LAM who have undergone lung transplantation [46–49]. In a single case report, patient-derived LAM cells with a somatic 1-base pair deletion in TSC2 were reported in the allograft from a single lung transplant patient who did not have AMLs. This report demonstrates that LAM cells can arise or migrate from sites other than AMLs or perhaps from a circulating growth factor [50]. Many studies are currently underway to investigate the etiology of LAM and recurrence after lung transplantation (Figs. 1–3).

**Hormonal features of lymphangioleiomyomatosis**

Some reports suggest that a puzzling disparity exists in the clinical course of LAM that may be related to age at diagnosis [51,52]. Patients who are diagnosed with LAM at a younger age of onset seem to have a more aggressive course than patients diagnosed at an older age [8]. To date, nine cases

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Fig. 2. A 61-year-old woman with dyspnea on exertion who was diagnosed with an angiomyolipoma of the kidney at age 34 years. Twenty-five years later, she developed her first pneumothorax. Ultimately, a lung biopsy showed LAM. (A) High-resolution CT of the chest showing multiple cysts of varying sizes. (B) CT of the abdomen demonstrating angiomyolipoma (arrow). (C) LAM cellular infiltrate with large cystic air spaces. (D) Pulmonary function tests demonstrating severe obstructive changes without response to bronchodilators. Arterial blood gas on room air and at rest: 7.45/PCO2 36/PO2 81/96% with mild respiratory alkalosis.
of LAM affecting postmenopausal women have been reviewed in the literature [51,52]. These reports include cases of postmenopausal women receiving hormone replacement therapy and those not receiving hormonal replacement therapy who subsequently developed symptoms. All prior reports have observed that the clinical course may be longer and more benign following menopause[52,53].

LAM is one of many pulmonary diseases that seem to worsen during the onset of menses [8], during pregnancy [14,54,55], and with oral contraceptive use [8,56], further suggesting an association between hormones and clinical deterioration. One study showed that in LAM patients the overall incidence of complications of pregnancy was 11 times higher during pregnancy than at other times [51]. In a single case report of LAM presenting during pregnancy, the patient’s lung function improved postpartum but never returned to baseline [54]. These observations have led some physicians to recommend that patients with LAM avoid pregnancy [7,55], although many successful pregnancies have been reported.

Despite the identification of estrogen and progesterone receptors in LAM tissue and in AMLs [57,58], the role of hormones remains unclear. Recently, Finlay et al [59] have shown that in the ELT3 uterine tuberin-null cells, estrogen (17b-estradiol [E2]) promotes growth through estrogen receptor-alpha and is associated with increased expression and activation of platelet-derived growth factor receptor-beta (PDGFR-beta) and extracellular signal-regulated kinase 1 and 2. When tuberin was expressed in ELT3 cells, there was less E2-induced growth, and activation of PDGFR-beta and extracellular signal-regulated kinase was inhibited. These studies indicate that hormones have a pivotal role in the regulation of all growth in the uterus. Whether these data are applicable to the lung and will help explain the role of hormones in LAM awaits further investigation.

Fig. 3. A 29-year-old woman with mild dyspnea. She developed a right pneumothorax, and lung biopsy done at the time of chest tube placement demonstrated LAM. No angiomyolipomas or meningiomas were detected on CT scans. (A) Chest radiograph with right pneumothorax. (B) High-resolution CT scan showing right pneumothorax and multiple small cysts throughout the lung. (C) Fragments of residual alveolar walls with bundles of LAM cells that protrude into cysts. (D) Pulmonary function tests with restrictive pattern and markedly reduced diffusion capacity.
Current approaches to treatment of lymphangioleiomyomatosis

Because LAM is found almost exclusively in women, the disease has been managed with anti-estrogen therapies. No randomized, clinical trials have been conducted in newly diagnosed LAM. Eliasson et al [60] conducted the only meta-analysis of therapeutic options in LAM, which found progesterone or oophorectomy to be the most effective therapies. The latter observation suggests a potential therapeutic option by the induction of menopause [60]. Most women with LAM have been empirically placed on some form of progesterone therapy during the course of their disease. Progesterone can be given by intramuscular injection monthly or bimonthly at a dose of 400 mg. Medroxyprogesterone may also be taken orally, 10 to 20 mg/day. Tamoxifen, a partial estrogen receptor agonist, was used for many years but was reported to exacerbate disease in some women [8]. Other treatment modalities used in the past were bilateral oophorectomies and radiation therapy of the ovaries [8]. No definitive improvements have been reported from any of these treatments. Rapamycin, an immunosuppressant peptide that binds and inactivates mTOR, is currently being investigated in a clinical trial in patients with TSC in the United States and Europe. The purpose of this initial trial is to test the hypothesis that inhibition of mTOR may retard the growth of AMLs in patients with TSC. Additional aspects of these studies are focused on the growth of AMLs in patients with TSC-LAM and S-LAM.

Another important challenge in the treatment of patients with LAM is the management of pneumothorax. Most case series report the predominant finding of pneumothorax in LAM patients. Sahn and colleagues have recently reviewed the clinical history of 395 LAM patients (Sahn S, personal communication, 2004). At the most recent LAM 2004 Symposium, they presented data demonstrating that, compared with other lung diseases, LAM has the highest rate of both initial and recurrent secondary spontaneous pneumothorax. In a case series of patients with LAM in Japan, 84% of patients reported pneumothorax; there were fewer reports of pneumothorax in patients receiving hormonal therapy. Management of pneumothorax has been complicated by concerns related to lung transplantation. Current recommendations include ipsilateral pleural

![Image of graphs](A) Silverstein (1974)  
![Image of graphs](B) Corrin (1975)  
![Image of graphs](C) Kyoto Congress (1993)  
![Image of graphs](D) Kyoto Congress (1993)

Fig. 4. Kaplan-Meier survival data from four different reported studies [14,62,63,65] of LAM patients (A–D). Earlier studies revealed a poorer survival than more recent studies that show higher 5-year survival rates.
symphysis at the time of the initial pneumothorax in patients with LAM. Bilateral pleurodesis should be considered when pneumothorax develops in the contralateral LAM lung.

Supportive therapy is essential and includes supplemental oxygen 24 hours/day, pulmonary rehabilitation, and early evaluation for lung transplantation. To date, more than 100 lung transplants have been performed for LAM (www.ishlt.org). Transplant remains an important alternative for women with end-stage disease despite reports of LAM occasionally recurring in the transplanted organ (Fig. 4) [46–48].

Survival in LAM

There have been six reported series of patients with LAM that focus on survival (see Fig. 4). The older studies reveal a survival at 5 years of 50% (Fig. 4A). In 1993, the Kyoto Congress published a survival of 8.5 years of 38% (see Fig. 4A and B). The most recently reported series from France and Spain showed a higher survival at 5 years of 90% (see Fig. 4C and D). The large range and disparity in survival data may reflect the small numbers of patients with LAM included in these reports as well as the variability in clinical characteristics.

Summary

Our knowledge about LAM has expanded over the past decade. Many studies have focused on hormonal aspects of LAM, although the role of estrogens in the pathogenesis of LAM remains unknown. Elucidation of the mechanism for formation of the cystic lesions characteristic of LAM will be critical in the development of therapies for LAM. It is important for clinicians to be familiar with LAM as we approach the next decade and new treatments.

References

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