

Lymphangiomyomatosis

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Abstract

Lymphangiomyomatosis (LAM) is a disease characterized by cystic lung changes, enlargement of the abdominal and pelvic lymphatics and angiomyolipomas. It occurs in isolation (sporadic LAM), and in patients with tuberous sclerosis complex (TSC). Sporadic LAM occurs only in women with a prevalence of approximately 1:1000,000; in TSC, up to 40% of adult women have evidence of LAM. The disease causes progressive respiratory failure punctuated by recurrent pneumothorax and chylous effusions with a mean survival of 10 – 20 years. Diagnosis is made by a combined computed tomography (CT) and biopsy. Treatment is mainly supportive, but in those with poor or rapidly declining lung function, hormonal manipulation either with progesterone or oestrogen depletion may be tried. Lung transplant may become necessary.

Keywords

Cystic lung disease, LAM cell, hormone treatment

Disease name

Lymphangiomyomatosis (LAM)

Definition

Lymphangiomyomatosis (LAM) is a rare and possibly fatal disease which affects the lungs, axial lymphatics and kidneys. In LAM, there is progressive infiltration of the affected tissues by proliferating smooth muscle cells and subsequent development of cysts within the lung parenchyma. LAM is also associated with angiomyolipomas, which are benign

mesenchymal tumours occurring chiefly in the kidneys. LAM may occur in isolation (sporadic LAM) or be associated with tuberous sclerosis complex (TSC).

Prevalence

The disease is very rare with a prevalence of approximately 1 per million in the general population in the UK [1], France [2] and the USA (data from the LAM Foundation). It is much more common in patients with TSC, with up to 40% of adult women having evidence of LAM when

screened [3-5]. Strikingly, all patients with sporadic LAM (without TSC) and the vast majority of patients with TSC-associated LAM are women in the reproductive age.

Clinical features

Pulmonary

The pulmonary features of LAM usually dominate the clinical picture. Dyspnea is present in 42% of the patients at presentation but is almost universal as the disease progresses. Pneumothorax is the presenting feature in half of the patients and two thirds will develop pneumothorax during disease course, which is recurrent in most cases. Chylous pleural effusions are present in 12% of patients at presentation and occur in over one quarter of patients overall. Other symptoms are cough, hemoptysis, chest pain, wheeze and chyloptysis (see table 1).

Table 1. Incidence of pulmonary and extra pulmonary features of LAM compiled from nine published series [1, 2, 6, 8, 9, 11, 12, 14, 23]. Frequency of extra pulmonary manifestations found by screening of the abdomen with Computed Tomography (CT) scan.

	% of patients	Number of patients evaluated
Pulmonary		
dyspnoea	87	164
cough	51	164
chest pain	34	32
hemoptysis	22	164
pneumothorax	65	213
chylous effusion	28	213
Extra pulmonary		
angiomyolipoma - renal	53	146
angiomyolipoma - extra renal *	4	94
lymphadenopathy	50	115
lymphangioliomyoma	16	94
chylous ascites	10	115

*three hepatic, one pancreatic

Extra-pulmonary

Extra-pulmonary manifestations cause symptoms less often and their true frequency has only been identified recently by using abdominal and pelvic computerised tomography (CT). Lymphadenopathy occurs in half of the patients, commonly in the upper retroperitoneum and pelvis. Larger, fluid-filled cystic masses termed lymphangioliomyomas, found in 16% of patients, may involve the retroperitoneum and extend into the pelvis and mediastinum. Lymphadenopathy and lymphangioliomyomas may be detected clinically and can cause abdominal pain and bloating; larger masses are associated with chylous ascites, present in some 10% of patients [6, 7]. Some patients present abdominal disease before respiratory

manifestations occur. Over half of patients will have angiomyolipoma, a benign neoplasm which occurs mainly in the kidneys but occasionally at other sites including liver and pancreas. Although the majority of angiomyolipomas in LAM are small and asymptomatic (mean diameter equal to 1.3 cm in one series), some enlarge to cause flank pain, hematuria and hemorrhage which can require emergency treatment. Angiomyolipomas may often precede respiratory manifestations [6, 8, 9].

Clinical findings

Clinical examination is generally normal in the early stages of the disease but wheeze, pneumothorax or pleural effusion may be present. Respiratory failure, abdominal masses or ascites tend to be later features. Stigmata of TSC must be sought in all patients. Facial angiofibromas, subungual fibroma, hypomelanotic macules, forehead plaques, shagreen patches and dental pitting are all detectable clinically.

Disease course

Increasing airflow obstruction and cyst formation cause progressive dyspnea which is punctuated by pneumothorax and chylous effusions. The mean rate of decline in FEV₁ (forced expiratory volume) was 118 ml/year in one series but this is highly variable [10]. Symptomatic chylous ascites may occur, usually later in disease course. Although no prospective data on survival in LAM exists yet, the mean survival appears to be around ten years. However, longer term survivors are recognized [10]. It is difficult to predict which patients will decline more rapidly but provisional data suggest that low DLCO (diffusing capacity) and younger age of onset predict a poor outcome.

Investigations

Lung function is normal in early disease but patients generally develop progressive airflow obstruction and impaired gas transfer with preserved lung volumes. Restrictive changes are usually the result of pleural complications or surgery [11-13]. The chest radiograph, normal in early disease, shows interstitial changes with preserved lung volumes. Pneumothorax or effusions may be present. The high resolution computed tomography (HRCT) shows multiple thin-walled cysts distributed evenly throughout the lung fields with normal intervening lung parenchyma [14]. CT of the abdomen is helpful to detect angiomyolipomas (which have a characteristic appearance), lymphadenopathy or lymphangioliomyomas. Their presence is helpful both for diagnosis of LAM and for management of abdominal symptoms.

Diagnosis

There are no universally agreed criteria for the diagnosis of LAM although lung biopsy remains the gold standard. In some cases diagnosis can be made with transbronchial biopsy and immunostaining for smooth muscle actin and HMB-4515. In early disease, LAM cells are sparse and the diagnosis may be difficult to make unless an experienced respiratory pathologist is consulted. When HRCT scan shows the classical features of LAM (multiple thin-walled cysts distributed evenly throughout the lung fields with normal intervening lung parenchyma), lung biopsy may not be necessary. The classical appearance may not be present in all cases and then other conditions such as emphysema, Langerhans cell histiocytosis and cystic metastases from an occult tumor need to be considered. For these reasons, we consider that diagnosis of LAM can be made without lung biopsy only when the history and HRCT are classical and other diseases unlikely. The presence of lymphadenopathy, lymphangioliomyomas, angiomyolipomas and chylous collections is highly supportive of the diagnosis of LAM and should be sought. In practice, some patients will not be suitable for lung biopsy due to poor lung function and therefore diagnosis of probable LAM should be made whilst looking for supportive features and excluding other diseases. Biopsy of abdominal lesions may be safer in patients with advanced lung disease. In the absence of a consensus, the strategy we use is summarized in table 2.

Table 2: Suggested diagnostic criteria for sporadic LAM

Lung biopsy showing characteristic LAM cell infiltration (with HMB 45 immunostaining usually positive)
Or
Compatible clinical manifestations with characteristic HRCT scan plus one or more of CT or histological evidence of angiomyolipoma
Or
Chylous pleural or abdominal collection
Or
Abdominal / pelvic lymphangioliomyoma with histological evidence of LAM cell infiltration (with HMB 45 immunostaining usually positive)

In all patients with LAM, TSC should be excluded by careful clinical examination and if indicated by appropriate imaging and genetic testing. Only a minority of patients with TSC have the classical triad of seizures, mental

retardation and facial angiofibromas, and in those with milder manifestations of TSC the diagnosis could be overlooked. In women with TSC, cystic pulmonary disease is highly likely to be LAM and, unless HRCT is highly atypical and other diseases likely, biopsy is not routinely required. The 2000 NIH (National Institutes of Health) consensus conference on TSC recommended screening asymptomatic women for LAM with HRCT at 18 years. Although this approach may not be of direct benefit to all patients, HRCT should be performed in any patient with respiratory symptoms.

Etiology

The organs affected by the disease are all infiltrated with LAM cells. LAM cells are of smooth muscle origin but also express oestrogen and progesterone receptors [16] and contain inclusions typical of pre-melanosomes which can be labelled with the antibody HMB-45 [17]. Although the cell of origin is unknown, this unusual phenotype is also shared by the smooth muscle elements of angiomyolipomas and the rare clear cell tumor of the lung. LAM cells are also present in TSC-associated LAM and mutations in the *TSC-2* gene have been demonstrated in the lungs, lymph nodes and angiomyolipomas of women with sporadic and TSC-associated LAM18. Unlike women with TSC-associated LAM, patients with sporadic LAM neither have other features of TSC nor germ line mutations in *TSC-2* [19]. However, it is not known if *TSC-2* mutations are present in all women with LAM and other mechanisms may exist. The *TSC-2* gene codes for the protein tuberlin which inhibits mTOR (mammalian target of rapamycin). mTOR is a key signalling molecule activated in response to growth factor stimulation via Pi3-OH kinase and other inputs. Cells without tuberlin have constitutive activation of mTOR and proliferate more rapidly than normal cells. Importantly rapamycin, a drug normally used for immunosuppression, can inhibit mTOR and increased growth in tuberlin deficient cells [24] and trials in LAM and angiomyolipoma are underway. Recently, the observation that identical mutations are shared between the renal and pulmonary lesions have led to the hypothesis that the pulmonary LAM cell may have originally metastasized from a distant site and that pulmonary LAM is a metastatic disease [25, 26].

Treatment

General measures

Like in other chronic respiratory diseases, patients with LAM should refrain from smoking and receive influenza and pneumococcal vaccinations. Patients with airflow obstruction

may benefit from bronchodilators. Like patients with other orphan diseases, these patients may feel isolated and lack information and support of others, once told they have a rare and possibly fatal disease. Patients support groups are helpful for some patients, particularly soon after diagnosis.

Hormone therapy

No treatment has proved to be effective for LAM. As the disease is likely to be hormone-dependent to some extent, treatment has been aimed at oestrogen depletion and progesterone supplementation. Practices vary from country to country but progesterone is the drug most commonly used in Europe and the USA. Compiling three larger case series, progesterone appeared to be effective in 15 of 32 patients taking 10 mg or more daily [10-12]. In one retrospective analysis, progesterone was associated with a reduction in decline in TLCO (carbon monoxide transfer factor) and may have slowed decline in FEV₁ also [10]. However all these studies were retrospective and prone to selection bias. Oophorectomy has been used in a smaller number of patients but is often combined with other treatments such as progesterone; its efficacy is hard to assess and it is now abandoned. Gonadotrophin-releasing hormone agonists can trigger reductions in oestrogen levels similar to oophorectomy, but their use is not supported by evidence. Various other treatments including interferon α and somatostatin have been reported, but such reports are difficult to evaluate. As no treatment is of proven efficacy, it is suggested that hormone treatment may be tried in patients with severe or rapidly progressive disease, with progesterone (400-800mg/month intramuscularly or 10-20 mg/day orally) being the first-line treatment [20].

Pneumothorax

Pneumothorax is frequent in LAM, and frequently recurs following conservative treatment (aspiration or chest drain) [1]; surgical treatment should be considered early in these patients.

Chylous effusions

Chylous effusions occur in about 20% of patients. Some are small and require no treatment. Other may respond to aspiration, but many continue to accumulate and require surgical treatment with pleurectomy and, occasionally, thoracic duct ligation. Anecdotal reports suggest that progesterone may be more helpful in women with chylous collections [12]. Reduction of lymphatic accumulation by a low-

fat or medium-chain triglyceride diet may also be helpful.

Angiomyolipoma

Angiomyolipomas are present in half of the patients. They are generally small (mean diameter equal to 1.3 cm) and asymptomatic [6]. Those greater than 4 cm are at greater risk of bleeding manifesting as haematuria or flank pain [21]. Treatment of symptomatic or large angiomyolipomas should aim to conserve renal tissue; embolisation and nephron-sparing surgery are the options of choice. As angiomyolipomas may be bilateral and continue to develop during disease course, treatment by nephrectomy may result in a dangerous loss of renal function, should a contralateral tumour require treatment in the future. It is suggested that all patients with LAM are screened for angiomyolipoma by CT or ultrasound to allow for planned treatment when necessary, and to avoid nephrectomy.

Pregnancy

Pregnancy may be associated with increased risk of pneumothorax and, possibly, acceleration of disease course in some cases, although others have uncomplicated pregnancies [1]. Patients should be informed of this possibility, ideally before conception.

Lung transplantation

Transplantation is the only effective treatment for advanced LAM with respiratory insufficiency. Over 100 patients have received transplants, usually of single lung. Complications specific to LAM include post-operative chylothorax (usually in patients with previous chylous collections), and pneumothorax in the native lung [22]. Recurrence of the disease has been reported in three patients following transplantation. The overall survival after transplantation is similar to that for other lung diseases.

Unresolved questions

The most pressing need in LAM is for an effective treatment. Although hormone treatment is used, it is of unproven efficacy. Rapamycin is a promising therapy for LAM and the results of clinical trials are eagerly awaited. Other questions such as survival and the possible effects of pregnancy are important questions for patients. In the laboratory, the mechanism of loss of *TSC-2* function and how this leads to the LAM phenotype are important.

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