Eur Respir J 2006; 27: 1056–1065
DOI: 10.1183/09031936.06.00113303

SERIES "RARE INTERSTITIAL LUNG DISEASES"
Edited by C. Vogelmeier and U. Costabel
Number 1 in this Series

Lymphangioleiomyomatosis

S.R. Johnson

ABSTRACT: Lymphangioleiomyomatosis (LAM) is a rare disease of the lungs and lymphatics, which can occur sporadically or in association with tuberous sclerosis. LAM almost exclusively affects females, generally developing before the menopause.

The disease is characterised by progressive pulmonary cystic change, recurrent pneumothorax, chylous pleural collections and, in most cases, progressive respiratory failure. Abdominal manifestations include lymphadenopathy, cystic lymphatic masses (lymphangioleiomyomas), chylous ascites and angiomyolipoma (a benign tumour). Survival in LAM is ~70% at 10 yrs, although this is highly variable since long-term survivors have been described.

Diagnosis is made by a combination of clinical features and computed tomography scanning or, in cases of doubt, lung biopsy. In patients with rapidly progressive disease, hormone treatment (predominantly progesterone) has been used, although no firm evidence supports its use. Otherwise, treatment is aimed at complications including pneumothorax, chylous collections and extrapulmonary manifestations. The only treatment for severe LAM is currently lung transplantation.

Recent developments in the cell biology of lymphangioleiomyomatosis have shown that these patients have somatic mutations in the genes linked to tuberous sclerosis and that rapamycin may correct the resulting cellular abnormality. Trials of rapamycin in lymphangioleiomyomatosis are currently underway and offer hope of evidence-based treatment for the disease.

KEYWORDS: Angiomyolipoma, interstitial disease, orphan disease, tuberous sclerosis

AFFILIATIONS
Division of Therapeutics and Molecular Medicine, University Hospital, Queens Medical Centre, Nottingham, UK.

CORRESPONDENCE
S.R. Johnson
Division of Therapeutics and Molecular Medicine
University Hospital
Queens Medical Centre
Nottingham NG7 2UH
UK
Fax: 44 1159422232
E-mail: simon.johnson@nottingham.ac.uk

Received:
October 09 2003
Accepted after revision:
March 31 2004

BACKGROUND

Lymphangioleiomyomatosis (LAM) is a disease that predominantly affects young females and generally progresses to respiratory failure. The clinical features result from progressive cystic destruction of the lungs and the accumulation of LAM cells within the lungs and axial lymphatics. The disease is rare (termed sporadic LAM) with a prevalence of ~1 in 1,000,000 people [1, 2] in the whole population, but is much more common in patients with the genetic disease tuberous sclerosis where signs of the disease can be identified in up to 40% of adult females with this condition (tuberous sclerosis-associated LAM) [3–5]. The disease tends to present between the menarche and the menopause, with the mean age of onset being 34 yrs. Occasionally, post-menopausal females will present with the disease; however, these patients are often receiving oestrogen replacement therapy [6]. There are a very small number of case reports describing LAM in males and children with tuberous sclerosis; however, this is extremely unusual and does not appear to occur in sporadic LAM [7].

HISTORY

The first recorded case of LAM was probably the death of a female with tuberous sclerosis from bilateral pneumothoraces described by LUTEMBACHER [8] in 1918. The first case of sporadic LAM was reported in 1937 by VON STÖSSELL [9], who described a young female who died of respiratory failure with diffuse cystic lung disease and dilated thoracic lymphatics; the author called the disease ''muscular cirrhosis''. In 1966, CORNOG and ENTERLINE [10] reviewed 20 cases of abdominal or pulmonary disease caused by LAM, which they termed lymphangiomyoma. In 1975, CORRIN *et al*. [11] reviewed the literature and described the clinical and pathological features and drew attention to a potential link between LAM and tuberous sclerosis. In the 1990s, major series of LAM were reported from the USA [12, 13], South-East Asia [14], the UK [1, 15] and France [2]. Increasing interest in LAM saw the establishment of registries and patient groups and, as a result, research has increased exponentially, resulting in greater understanding in both the clinical and cellular aspects of LAM.

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

In 2000, somatic mutations in the tuberous sclerosis complex (TSC)2 gene were described in sporadic LAM [16] and, since then, significant advances have been made in determining the biology of its protein product tuberin [17] to the extent where biological therapies are now being tested in clinical trials.

CLINICAL FEATURES

The pulmonary symptoms tend to dominate the clinical course, with the most common features being pneumothorax, progressive dyspnoea and chylous pleural effusions [2, 6, 11–14]. Other respiratory symptoms include cough, haemoptysis and chyloptysis (table 1). Dyspnoea is suffered by the vast majority of patients with LAM and is the result of airflow obstruction and replacement of the lung parenchyma by cysts. Approximately two thirds of patients will have a pneumothorax at some point in their clinical course, which are recurrent in most and a cause of significant morbidity [6]. Chylous pleural effusions are less common, but again can be difficult to treat conservatively and tend to recur after simple aspiration [6, 18]. Haemoptysis and chyloptysis are due to LAM cell obstruction of pulmonary capillaries and lymphatics, respectively, and both occur in a small number of patients. Extrapulmonary manifestations of LAM are lymphadenopathy, large cystic lymphatic masses (termed lymphangioleiomyomas), chylous abdominal collections [19, 20] and, 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 (table 1) [20–22]. Enlarged abdominal lymph nodes, either retroperitoneal, retrocrural or occasionally pelvic, are visible by computed tomography (CT) scanning in approximately one third of patients, but alone tend not to cause abdominal symptoms [20]. Lymphangioleiomyomas are larger cystic masses; these most commonly occur in the abdomen, retroperitoneum and pelvis but occasionally in the mediastinum and neck. Symptoms associated with lymphangioleiomyomas are nausea, bloating, abdominal distension, peripheral oedema and urinary symptoms [23]. These symptoms may worsen during the day, and this finding has been correlated with an increase in the size of lymphangioleiomyomas in the afternoon, presumably due to increased lower limb lymph accumulation whilst 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 [20]. The most common abdominal manifestation of LAM is angiomyolipoma, which is present in up to 50% of patients when screened by CT; however, the majority of these tumours are asymptomatic [20–22]. Multiple tumours and those >4 cm are more likely to grow and cause symptoms [24, 25], which, if present, are predominantly due to haemorrhage resulting in flank pain, haematuria and occasionally life-threatening bleeding [26].

TABLE 1 Symptoms and clinical findings

	At presentation	During course of disease
Dyspnoea	42 (256)	87 (164)
Cough	20 (221)	51 (164)
Chest pain	14 (152)	34 (32)
Haemoptysis	14 (138)	22 (164)
Pneumothorax	43 (256)	65 (213)
Chylous effusion	12 (256)	28 (213)

Data are presented as % (n). Data from [2, 6, 11–14, 20–22].

PRESENTATION

The first symptom in most patients is either dyspnoea or pneumothorax. Less common presentations are cough, haemoptysis or chylous pleural effusions. Occasionally, extrapulmonary manifestations will be the first symptom of LAM, most commonly bleeding from angiomyolipomas [2], but occasionally abdominal and pelvic masses will lead to the diagnosis [19, 27]. Rarely, abdominal symptoms can pre-date lung disease by many years with the final diagnosis only being made with the onset of respiratory symptoms.

Physical examination is often normal early in the disease unless a pneumothorax or chylous effusion is present. Crackles and wheezes are present in a minority of patients [13, 14]. In the occasional patient presenting with abdominal disease, lymphangioleiomyomas may be palpable; however, in most cases, abdominal manifestations will not be detectable by clinical examination alone [19]. All patients with LAM should undergo a careful clinical examination for stigmata of tuberous sclerosis. Subungual fibromas, facial angiofibromas and shagreen patches are all detectable clinically but may be misdiagnosed or overlooked in milder cases, and hypomelanotic patches require examination under Woods (ultraviolet) light for reliable detection. The diagnosis of tuberous sclerosis is not always straightforward as an increasing number of patients with mild disease are being identified in adulthood, including some with LAM as an initial presentation. Furthermore, two thirds of cases occur as a result of sporadic mutations and will have no family history of the disease. If there is a clinical suspicion of tuberous sclerosis, then full evaluation by a clinical geneticist is warranted to confirm the diagnosis, for genetic counselling and management of potential complications [28].

As pulmonary symptoms and findings in LAM are common to other lung diseases, such as primary spontaneous pneumothorax, asthma and emphysema, the diagnosis of LAM is often delayed, sometimes for many years. Clinical situations that should raise the suspicion of LAM are the following: pneumothorax (especially recurrent) in a young female with proceeding breathlessness or haemoptysis; and emphysema in a young female with minimal smoking exposure and airflow obstruction with interstitial changes.

INVESTIGATIONS AND DIAGNOSTIC STRATEGY

Routine investigations can be supportive but not diagnostic in LAM. The chest radiograph often appears normal in early disease, although may show a pneumothorax or pleural effusion. The most common abnormalities are reticulonodular shadowing and cysts or bullae (fig. 1; table 2). The lung volumes are generally preserved and the combination of preserved lung volumes and interstitial changes occurs in a small number of

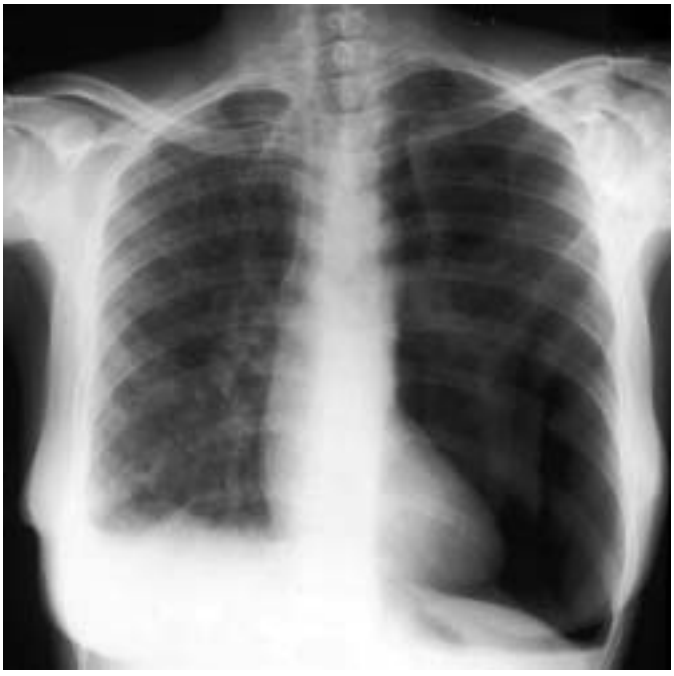

FIGURE 1. Chest radiograph in advanced lymphangioleiomyomatosis showing a combination of left pneumothorax, interstitial changes and pleural shadowing due to a chylous effusion and pleural surgery.

conditions including LAM, Langerhans' cell histiocytosis, sarcoidosis and chronic hypersensitivity pneumonitis.

Pulmonary function tests may be normal in patients with early disease, although the majority have airflow obstruction and, in a third of cases, a modest improvement after β_2-agonist inhalation. The total lung capacity is preserved but the gas transfer is generally markedly reduced (table 2) [12].

The gold standard for the diagnosis of LAM is a tissue biopsy of lung or involved lymphatics, which will show nodular infiltration by abnormal smooth muscle cells, termed LAM cells. Immunohistochemical staining for the smooth muscle marker actin and the melanoma-related antigen HMB45 will be positive in LAM [31]. Immunohistochemical staining is an important adjunct in analysing lung biopsies, especially transbronchial biopsies [32], as the LAM cells may be sparse and difficult to identify in the early stages of the disease. Not all patients with LAM require tissue biopsy for a definitive diagnosis as the disease has a characteristic CT appearance in the majority of cases. CT scanning shows multiple thin-walled cysts scattered throughout the lung fields in an even distribution with normal intervening lung parenchyma. The cysts have thin walls that are usually visible on CT (fig. 2) and when the CT appearance is classical in the presence of other typical manifestations of LAM, such as an angiomyolipoma, lymphangioleiomyoma or chylous pleural or abdominal collection, a tissue biopsy is not normally required. Therefore, patients with suspected LAM should have a high-resolution CT of the thorax and a CT of the abdomen to examine for the presence of angiomyolipomas and other lymphatic involvement. Where the CT scan is not characteristic of LAM, a lung biopsy should be obtained for a definitive diagnosis. In patients unable to undergo a lung biopsy due to poor lung function, abdominal CT may reveal a target for tissue biopsy in the abdomen or associated features of LAM, which may negate the need for tissue biopsy. A suggested diagnostic strategy is shown in figure 3. In a small number of patients, on CT, the cysts will not have walls and be indistinguishable from emphysema [33]. Other cystic lung diseases may occasionally be confused with LAM, particularly Langerhans' cell histiocytosis. However, in this disease, nodules are often present particularly in the early stages of the disease, and the cysts are more irregular with thicker walls and tend to occur predominantly in the upper and mid zones. Although cystic metastases generally have thicker walls and are less numerous than LAM cysts, those from smooth muscle tumours, particularly uterine sarcomas, occasionally have a very similar appearance to LAM [32].

Angiomyolipoma can usually be identified by CT scanning without the need for tissue biopsy. The tumour is of mixed mesenchymal origin, containing smooth muscle, blood vessels and fat. The presence of fat in these lesions gives a characteristic CT appearance (fig. 2); diagnostic difficulty may arise in the small number of angiomyolipomas that do not contain fat. If the diagnosis of LAM is secure, these lesions are likely to be angiomyolipomas and can be followed by repeat imaging; however, in some cases, tissue biopsy may be required to differentiate them from renal cell carcinoma. Although more often solitary in sporadic LAM, angiomyolipomas can be multiple, most commonly in patients with tuberous sclerosis-associated LAM.

PATHOLOGY

During the course of the disease, LAM cells progressively accumulate in the lungs and lymphatics. LAM cells express smooth muscle actin, desmin and vimentin consistent with a smooth muscle lineage, although also have features that are not typical of normal muscle cells, namely electron-dense granules, which contain melanoma-related proteins including glycoprotein 100 (the target of the antibody human melanoma black (HMB)45) and tyrosinase [35] and receptors for oestrogen and progesterone [36, 37]. LAM cells tend to proliferate in nodules, the centres of which contain predominantly spindle-shaped LAM cells, which have a high proliferative capacity, whereas the periphery is comprised of epithelioid LAM cells, which have a lower proliferative capacity but a higher expression of HMB45 [35]. These nodules line the airways and cysts and are the hallmark lesion in LAM (fig. 4). Cystic change is associated with smooth muscle proliferation in the lung and it is likely to be due to tissue destruction from LAM cell-derived matrix metalloproteinases (MMPs). MMP-2 is upregulated particularly in regions of degraded extracellular matrix lining the cysts [38, 39]. In addition to these findings, LAM lesions are lined with type II pneumocytes, and a significant proportion of patients also have airway inflammation (bronchiolitis) in airways surrounded by LAM cells [40]. Due to obstruction of pulmonary capillaries, haemosiderin deposits may also be prominent in biopsies [11]. In the lymphatics, LAM cells form haphazard clumps of cells, leading to thickening of lymphatic walls and, variably, obliteration of the vessel lumen and cystic dilatation. The unusual HMB45-positive LAM cell phenotype also comprises the muscular elements of angiomyolipomas (fig. 4) and has been termed the perivascular epithelioid cell [41]. In addition, perivascular

TABLE 2 Physiological and radiological findings from published series

	At presentation	During disease course
Pulmonary function [11, 12, 14, 29, 30]		
Normal[#]	10 (42)	4 (97)
Obstructive[¶]	29 (42)	63 (97)
Restrictive[+]	26 (42)	10 (97)
Combined obstructive/restrictive	36 (42)	15 (97)
Low gas transfer[§]	96 (31)	91 (89)
Hypoxaemia[f]	83 (42)	76 (81)
Chest radiograph [2, 13, 14]		
Normal	5 (147)	0 (32)
Reticulonodular infiltrate	68 (147)	94 (32)
Cysts/bullae	47 (147)	41 (32)
Pleural effusion	5 (78)	28 (32)
Pneumothorax	35 (78)	81 (32)
Hyperinflation	27 (147)	25 (32)
Thoracic CT [2, 12, 14]		
Cysts	100 (104)	100 (35)
Ground-glass opacities	29 (104)	
Nodular densities	9 (104)	
Pneumothorax	16 (38)	6 (35)
Pleural effusion	13 (38)	14 (35)
Hilar/mediastinal adenopathy	6 (104)	
Dilated thoracic duct		11 (35)
Pericardial effusion		6 (35)
Abdominal CT [20–22]		
Normal		5 (80)
Renal angiomyolipoma		53 (111)
Lymphadenopathy		36 (80)
Lymphangioleiomyoma		16 (80)
Ascites		9 (80)
Hepatic angiomyolipoma		3 (80)

Data are presented as % (n). CT: computed tomography. [#]: all values >80% predicted; [¶]: forced expiratory volume in one second (FEV_1) <80%, FEV_1/forced vital capacity (FVC) <70% predicted; [+]: FVC <80%, FEV_1/FVC >70% predicted; [§]: all values <80% predicted; [f]: <10.6 kPa.

epithelioid cells form the rare, benign, clear cell tumour [42], which can also be associated with both sporadic LAM and tuberous sclerosis [43]. The smooth muscle cells of angiomyolipomas are clonal [44], as are some of the blood vessels [45] and possibly fat, suggesting the three elements of the tumour may derive from a common mesenchymal precursor or stem cell. In patients with tuberous sclerosis, focal proliferations of type II pneumocytes (termed multifocal micronodular pneumocyte hyperplasia (MMPH)) may occur [46]. MMPH in tuberous sclerosis occurs both independently of and in association with LAM [3]. This finding can be seen as nodules on high-resolution CT, but is not thought to be clinically significant.

CLINICAL COURSE

Patients with sporadic LAM generally develop progressive airflow obstruction. Two studies have recently shown that forced expiratory volume in one second (FEV_1) declines rapidly in LAM at ~120 $mL \cdot yr^{-1}$, although the variation about this mean value was very large in both studies [1, 47]. Typically, in addition to worsening airflow obstruction, patients may have intermittent pneumothorax, chylous collections or other complications as mentioned previously. The clinical course of LAM is highly variable, and it is difficult to be accurate about the prognosis of individual patients at the onset of the disease. Studying a cohort of patients, it has been shown that after 10 yrs, 55% of 77 patients would be more breathless than their peers or have to stop when walking at their own pace on the flat, and ~10% would be housebound due to dyspnoea [48]. There are no prospective data on survival; early studies based on case reports and *post mortem* series have suggested survival is in the order of 4 yrs, although more recent data have suggested that 10-yr survival is of the order of 55–71% [2, 13]. However, in one study, one third of patients were alive at 15 yrs and almost a quarter at 20 yrs after the onset of symptoms [48]. At present, there is no good way of predicting the prognosis of individual patients at diagnosis. However, this variability is likely to be due to polymorphisms in modifier genes and identification of such polymorphisms, which may predict the clinical course of patients, is ongoing.

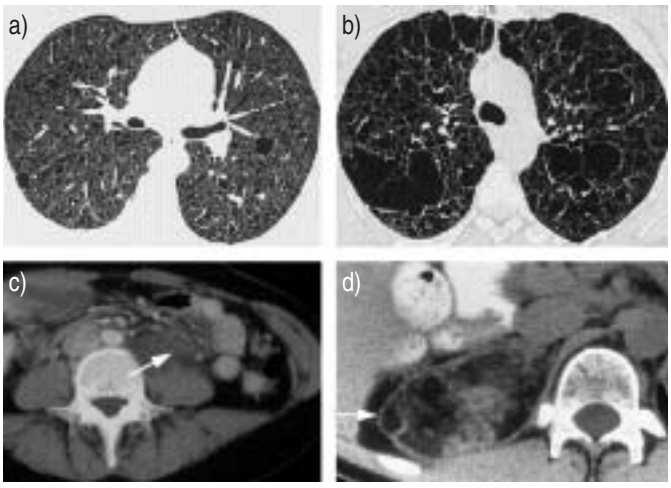

FIGURE 2. Computed tomography (CT) appearances in lymphangioleiomyomatosis (LAM). a) High-resolution CT showing a moderate degree of pulmonary cysts. The cysts have thin walls and the intervening lung parenchyma is normal. b) Advanced LAM where cysts have coalesced, there is minimal normal lung and the appearance is less characteristic. c) Abdominal CT showing a retroperitoneal lymphangioleiomyoma. The low-density centre of the lesion (arrow) representing fluid appeared cystic using ultrasound scanning (not shown). d) CT appearance of a renal angiomyolipoma (arrow) showing mixed CT density, with the characteristic low attenuation areas representing fat.

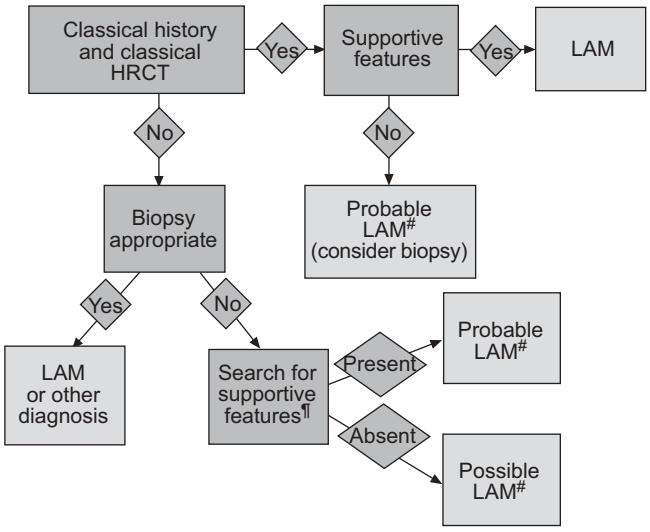

FIGURE 3. Flow chart for suggested diagnostic strategy in lymphangioleiomyomatosis (LAM). HRCT: high-resolution computed tomography. #: consider/exclude other diseases; ¶: supportive features, *i.e.* angiomyolipoma, lymphangioleiomyoma, chylous collection.

LAM IN TUBEROUS SCLEROSIS

In tuberous sclerosis-associated LAM, the spectrum of disease is greater. Only 2–3% of patients with tuberous sclerosis will develop symptoms of LAM [49, 50]; however, if screened, cystic lung disease consistent with LAM is present in 40% of adult females with tuberous sclerosis [4, 5, 51]. This suggests that a large number of these patients do not develop significant lung disease or it may be overlooked in view of severe involvement of tuberous sclerosis in other organ systems. In those patients where symptoms do develop, LAM seems to behave in a similar way to those patients with sporadic LAM [49].

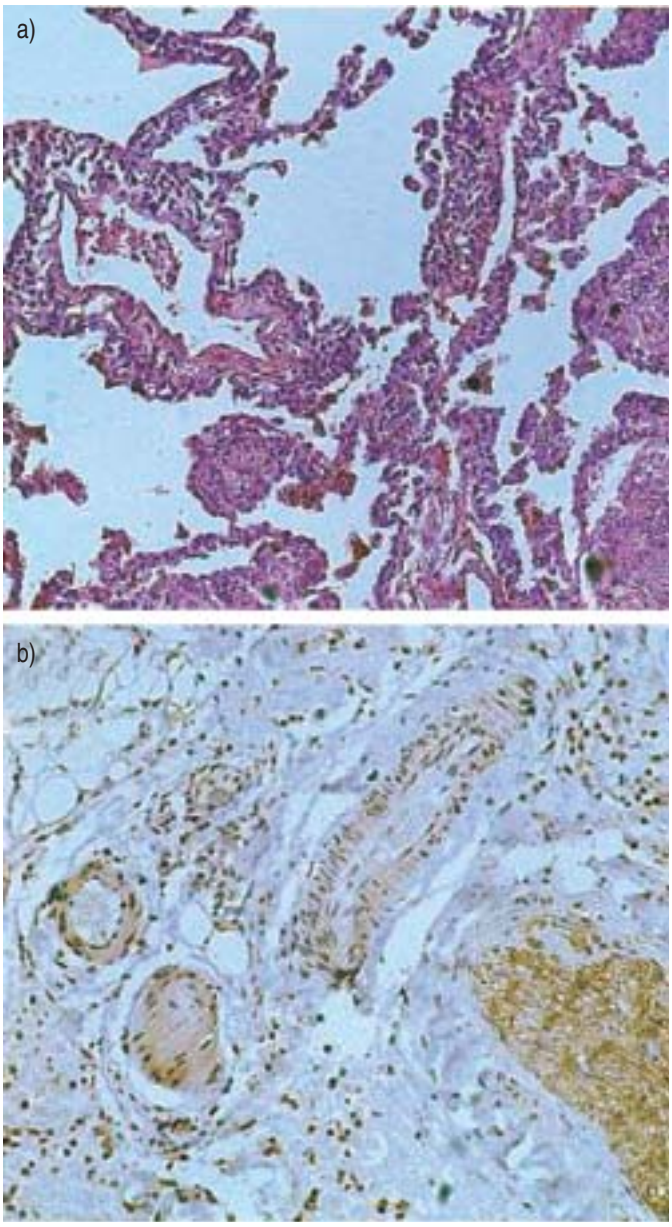

FIGURE 4. a) Histological appearance of lymphangioleiomyomatosis (LAM) showing nodular accumulation of LAM cells. b) Angiomyolipoma showing proliferating smooth muscle cells, fat and blood vessels. The smooth muscle elements are of the same phenotype as LAM cells.

ADVANCES IN CELL BIOLOGY AND GENETICS

For some years, it had been postulated that LAM and tuberous sclerosis were related due to the increased prevalence of LAM in patients with tuberous sclerosis. Tuberous sclerosis is an autosomal dominant disease characterised by a germline mutation in one of two genes, TSC1 and TSC2 [52]. Tuberous sclerosis-related hamartomas develop when loss of the second allelle results in complete loss of the protein product [52]. In sporadic LAM, somatic mutations have been found in LAM

cells in the lungs, lymph nodes and angiomyolipomas, predominantly for TSC2 [16, 53] and a lesser extent TSC1 [54], suggesting that the disease generally develops due to somatic mutations in TSC2. In tuberous sclerosis, TSC1- and TSC2-related disease have a slightly different phenotype [55] with LAM, and larger and more frequent angiomyolipomas that are more commonly associated with TSC2 mutations [3]. The protein products of TSC1 and 2 (termed hamartin and tuberin, respectively) form a cytoplasmic complex in normal cells and function to inhibit the protein mammalian target of rapamycin (mTOR) *via* the guanosine triphosphatase rheb [17, 56]. mTOR is activated as a result of growth factor signalling through phospho-inositide 3-OH kinase and AKT, resulting in downstream activation of the ribosomal protein P70S6 kinase and ribosomal S6 [56], leading to increased protein synthesis and cellular proliferation. Cells with loss of either hamartin or tuberin have constitutive activation of mTOR and P70S6 kinase, which can be inhibited in cell and animal models by rapamycin [57], thus suggesting that rapamycin and similar drugs may be potential therapies for LAM and tuberous sclerosis. Clinical trials of rapamycin in LAM and tuberous sclerosis are currently underway.

TREATMENT

Pulmonary complications

The initial approach to pneumothorax in LAM is the same as other lung diseases; however, when a second pneumothorax or a persisting air leak occurs, a thoracic surgeon should be involved early on in the management. A review of pneumothorax in LAM has shown that medical treatment is associated with a recurrence rate of two thirds [6]. Even following surgical treatment, pneumothorax may recur, and loculated pneumothorax on the treated side can result in chest pain and a gurgling sensation within the chest. Treatment of pneumothorax in patients likely to require lung transplantation should avoid radical pleural procedures if possible, especially if bilateral pneumothorax has occurred. However, improvements in transplant technique have made pleural surgery a minor contraindication to lung transplantation and, in general, the patient should have the appropriate procedure performed for their symptoms at the time.

Chylothorax may contribute to symptomatic dyspnoea in LAM and 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 is aimed at obliterating the pleural space to prevent lymphatic accumulation or ligation of the thoracic duct. The natural history of chylous collections is variable; while some will have small persisting effusions that require no treatment, for moderate or large effusions associated with dyspnoea, treatment is required. In most cases, simple aspiration or chest tube drainage results in re-accumulation in a short time. Patients with persisting effusions after aspiration have been successfully treated by pleurodesis, pleurectomy and, in some cases, thoracic duct ligation. Early experience with thoracic duct ligation was poor; however, this now appears to be a relatively safe procedure in patients with LAM.

Reduction in lymphatic formation by strictly lowering dietary fat or substitution of fat by medium-chain triglycerides, which are absorbed from the intestine and carried in blood rather than the lymphatics, is difficult for patients to adhere to and has generally not been very successful. Some reports have suggested that progesterone may be useful in patients with chylous collections [14]. However, most of these patients have also had pleural interventions and this finding is difficult to evaluate.

In the absence of effective treatments for LAM, dyspnoea resulting from progressive lung disease rather than pleural complications is difficult to treat. Twenty-five to 30% of patients, particularly those with more severe airflow obstruction, may have some improvement in FEV1 following β_2-agonist inhalation. There is some evidence that lung function declines more quickly in patients with LAM who take oestrogen [58, 59] and, therefore, patients should be encouraged to stop smoking, avoid hormone replacement therapy and the combined oral contraceptive pill. Other measures for severe lung disease, including pulmonary rehabilitation, oxygen where appropriate, prophylactic pneumococcal and influenza vaccinations, are important.

Hormone therapy

As LAM generally presents in pre-menopausal females and may be exacerbated by exogenous oestrogen, various anti-oestrogen strategies have been used in the treatment of LAM ever since SILVERSTEIN *et al*. [60] reported the use of ovarian ablation in 1974. In 1980, MCCARTY *et al*. [61] reported the first successful use of progesterone in a single patient and, currently, progesterone is the most commonly used hormone treatment for LAM.

A number of case reports and small series have suggested that progesterone may be helpful in some patients. There have been no controlled trials of progesterone (nor any other treatment) in LAM. Two retrospective studies have tried to assess the efficacy of progesterone, one showing 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 in those treated with progesterone compared with untreated patients [1]. These effects were small and there was a wide variation in rates of decline in FEV1. Furthermore, the effect did not appear to extend beyond 3 yrs. Another larger study showed no difference in rate of decline in patients treated with progesterone compared with untreated patients, although these patients had slightly better lung function than those in the previous study [62].

In the absence of good evidence, the routine use of progesterone or other hormonal strategies is not recommended in LAM and the approach to treatment varies between different authorities. It is the current author's practice to use medroxyprogesterone (400 mg·month^{-1} *i.m.*) in patients who have rapidly progressing symptoms or declining lung function. Common side-effects of progesterone include bloating, fluid retention and nausea, and these may be severe enough to stop the drug. Concerns have been raised that progesterone treatment may be associated with the increased incidence of meningiomas in LAM; subsequently, cerebral magnetic resonance imaging (MRI) scans before and during progesterone treatment have been recommended [63], but are not currently routine practice in most centres. Oopherectomy is no longer

generally performed for LAM, and gonadotrophin-releasing hormone agonists can produce the same reduction in oestrogen levels as ovarian ablation; however, evidence for their use is restricted to case reports [64, 65]. Tamoxifen, a partial agonist of the oestrogen receptor, has been used with mixed success [13, 66, 67]; 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 [68] and, since then, >100 patients with LAM have undergone lung transplantation with single-lung transplant, the most commonly performed procedure. Transplantation may be considered in patients with progressive disease and severe disability (FEV_1 <30% predicted) and those dependent on oxygen. Survival following transplant is similar to other lung diseases at 76, 56 and 51% at 1, 3 and 5 yrs, respectively [69]. Early post-transplant deaths are due to acute lung injury, haemorrhage and sepsis, with later deaths predominantly due to obliterative bronchiolitis and sepsis [69]. Haemorrhage due to adhesions, either due to LAM alone or following previous pleural surgery, was the main intra-operative complication, which has resulted in repeat thoracotomy but no deaths [29]. Specific complications related to LAM are native lung pneumothorax following single lung transplant and post-operative chylothorax [29]. Recurrence of LAM in the graft has been reported in several patients, although this did not compromise graft function [70, 71]. This is now recognised to be due to the ''metastatic'' spread of LAM cells to the graft from residual LAM tissue [72].

Treatment of angiomyolipomas

Although most patients do not have symptoms from renal angiomyolipomas, these tumours may bleed, which can result in life-threatening haemorrhage. Patients with LAM should be screened for angiomyolipoma at diagnosis by CT or MRI scanning. In general, those with tumours <4 cm in diameter are at a lower risk of progression [25, 73–75] and can be followed-up by ultrasound at 1–2-yr intervals. Those with larger tumours should have ultrasound more frequently, possibly at 6-monthly intervals [25]. Some would advocate prophylactic intervention for large tumours, although most would only treat symptomatic patients. In patients with symptoms from enlarging or bleeding angiomyolipomas, treatments should attempt to conserve renal tissue wherever possible, especially where patients have multiple or bilateral tumours. The treatment of choice would be either selective embolisation or nephron-sparing surgery. Embolisation can be performed without a general anaesthetic, even in patients who are actively bleeding, and has been shown to be an effective treatment in case series followed over several years [75, 76]. Nephron-sparing surgery is also an option but will require general anaesthetic [74]. The choice between the two modalities will be dependent upon local expertise and technical considerations of the individual tumours. The most important aspect of management is to avoid a large haemorrhage being treated by emergency nephrectomy and compromising renal function in patients who may develop or have further angiomyolipomas.

It is not known if hormonal treatment is effective for angiomyolipoma, although the tumours generally have receptors for oestrogen and progesterone [77] and should behave in a similar way to pulmonary LAM cells.

Pregnancy

Patients with LAM may develop more complications of the disease during pregnancy, particularly pneumothorax and chylous pleural effusions. A significant number of patients with LAM will develop their initial symptoms during pregnancy [2, 6]. There are no useful data on whether pregnancy affects the progression of lung disease, as well as rates of pneumothorax and pleural effusion. In addition, patients with angiomyolipoma may have an increased risk of bleeding from these lesions [78–80] and, in some cases, an increased rate of growth during pregnancy [81]. However, a significant number of patients with LAM have had an uncomplicated pregnancy and this choice should belong to the patients. Nevertheless, an increased risk of complications should be discussed prior to conception to allow an informed decision to be made and to alert the patient that new symptoms may be due to LAM.

Air travel

Patients with LAM are often advised not to fly due to the risk of pneumothorax. Although it is difficult to provide firm guidelines on this issue, the risk may be overstated. In a survey of several hundred patients with LAM in the USA, one in 20 had experienced a problem when flying, not all due to pneumothorax (data from the LAM Foundation). Patients with an existing pneumothorax should not fly and those with new symptoms compatible with a pneumothorax should have a chest radiograph before flying. The increased risk of pneumothorax during flight is probably small for most patients and whether the risk is acceptable or not depends on the patient's lung function, those with little reserve being less able to tolerate a pneumothorax. The risk is probably greater in those with previous pneumothorax and reduced after pleural surgery.

CURRENT ISSUES

Although significant progress has been made in the supportive care of patients and the molecular biology of LAM, there is still no evidence from placebo-controlled trials on how these patients should be treated. The use of rapamycin to correct the cellular abnormality produced by loss of function of TSC1/2 is an exciting development. The results of initial trials of rapamycin assessing its safety and efficacy in LAM and tuberous sclerosis-related angiomyolipoma are eagerly awaited, and it is hoped that, if the outcome of such trials is favourable, a suitable collaboration can be formed to perform placebo-controlled trials of rapamycin on the rate of progression of the lung disease. The role of progesterone or the selective oestrogen antagonists in LAM and how these may compare or work synergistically with rapamycin and its analogues is still not known. An explanation of why some patients decline rapidly and others remain stable for many years is also needed. It is likely that genetic variation in modifier genes in related pathways is responsible for this clinical variation. One study has suggested polymorphisms in the MMP-9 gene may affect the severity of the lung disease in

LAM [82]. Identification of such gene polymorphisms may allow prediction of which patients are likely to decline rapidly and target more aggressive treatment toward them. The discovery that the LAM cells in the lungs and lymph nodes contain the same gene mutations has suggested that they metastasise from one to other sites [16, 72].

In conclusion, understanding the cell type of origin and the signalling methods used to target lymphangioleiomyomatosis cells to the lungs, lymphatics and kidneys may bring future treatment strategies. Clearly, careful clinical and molecular studies of lymphangioleiomyomatosis are still needed to improve treatment and outcome in this disease.

REFERENCES

1 Johnson SR, Tattersfield AE. Decline in lung function in lymphangioleiomyomatosis: relation to menopause and progesterone treatment. *Am J Respir Crit Care Med* 1999; 160: 628–633.

2 Urban T, Lazor R, Lacronique J, *et al.* Pulmonary lymphangioleiomyomatosis. A study of 69 patients. Groupe d'Etudes et de Recherche sur les Maladies ''Orphelines'' Pulmonaires (GERM''O''P). *Medicine (Baltimore)* 1999; 78: 321–337.

3 Franz DN, Brody A, Meyer C, *et al.* Mutational and radiographic analysis of pulmonary disease consistent with lymphangioleiomyomatosis and micronodular pneumocyte hyperplasia in women with tuberous sclerosis. *Am J Respir Crit Care Med* 2001; 164: 661–668.

4 Moss J, Avila NA, Barnes PM, *et al.* Prevalence and clinical characteristics of lymphangioleiomyomatosis (LAM) in patients with tuberous sclerosis complex. *Am J Respir Crit Care Med* 2001; 164: 669–671.

5 Costello LC, Hartman TE, Ryu JH. High frequency of pulmonary lymphangioleiomyomatosis in women with tuberous sclerosis complex. *Mayo Clin Proc* 2000; 75: 591–594.

6 Johnson SR, Tattersfield AE. Clinical experience of lymphangioleiomyomatosis in the UK. *Thorax* 2000; 55: 1052–1057.

7 Aubry MC, Myers JL, Ryu JH, *et al.* Pulmonary lymphangioleiomyomatosis in a man. *Am J Respir Crit Care Med* 2000; 162: 749–752.

8 Lutembacher R. Dysembryomes metatypiques des reins. Carcinose sublimiare aigue du poumon avec emphyseme generalise et double pneumothorax [Atypical kidney dysembryoma. Acute submiliary lung carcinomatosis with generalised emphysema and double pneumothorax]. *Ann Med* 1918; 5: 435.

9 von Stossel E. Uber muskulare Cirrhose der Lunge [Muscular cirrhosis of the lungs]. *Beitr Klin Tuberk* 1937; 90: 432–442.

10 Cornog JL Jr, Enterline HT. Lymphangiomyoma, a benign lesion of chyliferous lymphatics synonymous with lymphangiopericytoma. *Cancer* 1966; 19: 1909–1930.

11 Corrin B, Liebow AA, Friedman PJ. Pulmonary lymphangioleiomyomatosis. *Am J Pathol* 1975; 79: 348–382.

12 Chu SC, Horiba K, Usuki J, *et al.* Comprehensive evaluation of 35 patients with lymphangioleiomyomatosis. *Chest* 1999; 115: 1041–1052.

13 Taylor JR, Ryu J, Colby TV, Raffin TA. Lymphangioleiomyomatosis. Clinical course in 32 patients. *N Engl J Med* 1990; 323: 1254–1260.

14 Kitaichi M, Nishimura K, Itoh H, Izumi T. Pulmonary lymphangioleiomyomatosis: a report of 46 patients including a clinicopathologic study of prognostic factors. *Am J Respir Crit Care Med* 1995; 151: 527–533.

15 Wahedna I, Cooper S, Williams J, Paterson IC, Britton JR, Tattersfield AE. Relation of pulmonary lymphangio-leiomyomatosis to use of the oral contraceptive pill and fertility in the UK: a national case control study. *Thorax* 1994; 49: 910–914.

16 Carsillo T, Astrinidis A, Henske EP. Mutations in the tuberous sclerosis complex gene TSC2 are a cause of sporadic pulmonary lymphangioleiomyomatosis. *Proc Natl Acad Sci USA* 2000; 97: 6085–6090.

17 Goncharova EA, Goncharov DA, Eszterhas A, *et al.* Tuberin regulates p70 S6 kinase activation and ribosomal protein S6 phosphorylation. A role for the TSC2 tumor suppressor gene in pulmonary lymphangioleiomyomatosis (LAM). *J Biol Chem* 2002; 277: 30958–30967.

18 Ryu JH, Doerr CH, Fisher SD, Olson EJ, Sahn SA. Chylothorax in lymphangioleiomyomatosis. *Chest* 2003; 123: 623–627.

19 Matsui K, Tatsuguchi A, Valencia J, *et al.* Extrapulmonary lymphangioleiomyomatosis (LAM): clinicopathologic features in 22 cases. *Hum Pathol* 2000; 31: 1242–1248.

20 Avila NA, Kelly JA, Chu SC, Dwyer AJ, Moss J. Lymphangioleiomyomatosis: abdominopelvic CT and US findings. *Radiology* 2000; 216: 147–153.

21 Bernstein SM, Newell JD Jr, Adamczyk D, Mortenson RL, King TE Jr, Lynch DA. How common are renal angiomyolipomas in patients with pulmonary lymphangiomyomatosis? *Am J Respir Crit Care Med* 1995; 152: 2138–2143.

22 Maziak DE, Kesten S, Rappaport DC, Maurer J. Extrathoracic angiomyolipomas in lymphangioleiomyomatosis. *Eur Respir J* 1996; 9: 402–405.

23 Avila NA, Bechtle J, Dwyer AJ, Ferrans VJ, Moss J. Lymphangioleiomyomatosis: CT of diurnal variation of lymphangioleiomyomas. *Radiology* 2001; 221: 415–421.

24 Lemaitre L, Robert Y, Dubrulle F, *et al.* Renal angiomyolipoma: growth followed up with CT and/or US. *Radiology* 1995; 197: 598–602.

25 Steiner MS, Goldman SM, Fishman EK, Marshall FF. The natural history of renal angiomyolipoma. *J Urol* 1993; 150: 1782–1786.

26 L'Hostis H, Deminiere C, Ferriere JM, Coindre JM. Renal angiomyolipoma: a clinicopathologic, immunohistochemical, and follow-up study of 46 cases. *Am J Surg Pathol* 1999; 23: 1011–1020.

27 Ernst JC, Sohaey R, Cary JM. Pelvic lymphangioleiomyomatosis. Atypical precursor to pulmonary disease. *Chest* 1994; 106: 1267–1269.

28 Roach ES, DiMario FJ, Kandt RS, Northrup H. Tuberous Sclerosis Consensus Conference: recommendations for diagnostic evaluation. National Tuberous Sclerosis Association. *J Child Neurol* 1999; 14: 401–407.

29 Boehler A, Speich R, Russi EW, Weder W. Lung transplantation for lymphangioleiomyomatosis. *N Engl J Med* 1996; 335: 1275–1280.

30 Berger JL, Shaff MI. Pulmonary lymphangioleiomyomatosis. *J Comput Assist Tomogr* 1981; 5: 565–567.
31 Tanaka H, Imada A, Morikawa T, *et al.* Diagnosis of pulmonary lymphangioleiomyomatosis by HMB45 in surgically treated spontaneous pneumothorax. *Eur Respir J* 1995; 8: 1879–1882.
32 Bonetti F, Chiodera PL, Pea M, *et al.* Transbronchial biopsy in lymphangiomyomatosis of the lung. HMB45 for diagnosis. *Am J Surg Pathol* 1993; 17: 1092–1102.
33 Avila NA, Chen CC, Chu SC, *et al.* Pulmonary lymphangioleiomyomatosis: correlation of ventilation-perfusion scintigraphy, chest radiography, and CT with pulmonary function tests. *Radiology* 2000; 214: 441–446.
34 Mahadeva R, Stewart S, Wallwork J. Metastatic endometrial stromal sarcoma masquerading as pulmonary lymphangioleiomyomatosis. *J Clin Pathol* 1999; 52: 147–148.
35 Matsumoto Y, Horiba K, Usuki J, Chu SC, Ferrans VJ, Moss J. Markers of cell proliferation and expression of melanosomal antigen in lymphangioleiomyomatosis. *Am J Respir Cell Mol Biol* 1999; 21: 327–336.
36 Matsui K, Takeda K, Yu ZX, *et al.* Downregulation of estrogen and progesterone receptors in the abnormal smooth muscle cells in pulmonary lymphangioleiomyomatosis following therapy. An immunohistochemical study. *Am J Respir Crit Care Med* 2000; 161: 1002–1009.
37 Banner AS. Hormone receptors in lymphangioleiomyomatosis. *Chest* 1984; 85: 3–4.
38 Hayashi T, Fleming MV, Stetler-Stevenson WG, *et al.* Immunohistochemical study of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) in pulmonary lymphangioleiomyomatosis (LAM). *Hum Pathol* 1997; 28: 1071–1078.
39 Matsui K, Takeda K, Yu ZX, Travis WD, Moss J, Ferrans VJ. Role for activation of matrix metalloproteinases in the pathogenesis of pulmonary lymphangioleiomyomatosis. *Arch Pathol Lab Med* 2000; 124: 267–275.
40 Matsui K, Riemenschneider KW, Hilbert SL, *et al.* Hyperplasia of type II pneumocytes in pulmonary lymphangioleiomyomatosis. *Arch Pathol Lab Med* 2000; 124: 1642–1648.
41 Pea M, Bonetti F, Zamboni G, *et al.* Melanocyte-marker-HMB-45 is regularly expressed in angiomyolipoma of the kidney. *Pathology* 1991; 23: 185–188.
42 Bonetti F, Pea M, Martignoni G, *et al.* PEC and sugar. *Am J Surg Pathol* 1992; 16: 307–308.
43 Flieder DB, Travis WD. Clear cell ''sugar'' tumor of the lung: association with lymphangioleiomyomatosis and multifocal micronodular pneumocyte hyperplasia in a patient with tuberous sclerosis. *Am J Surg Pathol* 1997; 21: 1242–1247.
44 Saxena A, Alport EC, Custead S, Skinnider LF. Molecular analysis of clonality of sporadic angiomyolipoma. *J Pathol* 1999; 189: 79–84.
45 Karbowniczek M, Yu J, Henske EP. Renal angiomyolipomas from patients with sporadic lymphangiomyomatosis contain both neoplastic and non-neoplastic vascular structures. *Am J Pathol* 2003; 162: 491–500.
46 Guinee D, Singh R, Azumi N, *et al.* Multifocal micronodular pneumocyte hyperplasia: a distinctive pulmonary manifestation of tuberous sclerosis. *Mod Pathol* 1995; 8: 902–906.
47 Lazor R, Lauque D, Deleval P, Lacronique J, Urban T, Cordier JF. Predictors of rapid decline of FEV1 in 50 cases of pulmonary lymphangioleiomyomatosis followed for >1 year. *Am J Respir Crit Care Med* 2000; 161: A15.
48 Johnson SR, Whale CI, Hubbard RB, Lewis SA, Tattersfield AE. Survival and disease progression in UK patients with lymphangioleiomyomatosis. *Thorax* 2004; 59: 800–803.
49 Hancock E, Tomkins S, Sampson J, Osborne J. Lymphangioleiomyomatosis and tuberous sclerosis. *Respir Med* 2002; 96: 7–13.
50 Castro M, Shepherd CW, Gomez MR, Lie JT, Ryu JH. Pulmonary tuberous sclerosis. *Chest* 1995; 107: 189–195.
51 McCormack F, Brody A, Meyer C, *et al.* Pulmonary cysts consistent with lymphangioleiomyomatosis are common in women with tuberous sclerosis: genetic and radiographic analysis. *Chest* 2002; 121: Suppl. 3, 61S.
52 Sepp T, Yates JR, Green AJ. Loss of heterozygosity in tuberous sclerosis hamartomas. *J Med Genet* 1996; 33: 962–964.
53 Astrinidis A, Khare L, Carsillo T, *et al.* Mutational analysis of the tuberous sclerosis gene TSC2 in patients with pulmonary lymphangioleiomyomatosis. *J Med Genet* 2000; 37: 55–57.
54 Sato T, Seyama K, Fujii H, *et al.* Mutation analysis of the TSC1 and TSC2 genes in Japanese patients with pulmonary lymphangioleiomyomatosis. *J Hum Genet* 2002; 47: 20–28.
55 Dabora SL, Jozwiak S, Franz DN, *et al.* Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. *Am J Hum Genet* 2001; 68: 64–80.
56 McManus EJ, Alessi DR. TSC1-TSC2: a complex tale of PKB-mediated S6K regulation. *Nat Cell Biol* 2002; 4: E214–E216.
57 Kenerson HL, Aicher LD, True LD, Yeung RS. Activated mammalian target of rapamycin pathway in the pathogenesis of tuberous sclerosis complex renal tumors. *Cancer Res* 2002; 62: 5645–5650.
58 Shen A, Iseman MD, Waldron JA, King TE. Exacerbation of pulmonary lymphangioleiomyomatosis by exogenous estrogens. *Chest* 1987; 91: 782–785.
59 Yano S. Exacerbation of pulmonary lymphangioleiomyomatosis by exogenous oestrogen used for infertility treatment. *Thorax* 2002; 57: 1085–1086.
60 Silverstein EF, Ellis K, Wolff M, Jaretzki A 3rd. Pulmonary lymphangiomyomatosis. *Am J Roentgenol Radium Ther Nucl Med* 1974; 120: 832–850.
61 McCarty KS, Mossler JA, McLelland R, Sieker HO. Pulmonary lymphangiomyomatosis responsive to progesterone. *N Engl J Med* 1980; 303: 1461–1465.
62 Taveira-DaSilva AM, Stylianou MP, Hedin CJ, Hathaway O, Moss J. Decline in lung function in patients with lymphangioleiomyomatosis treated with or without progesterone. *Chest* 2004; 126: 1867–1874.
63 Moss J, DeCastro R, Patronas NJ, Taveira-DaSilva A. Meningiomas in lymphangioleiomyomatosis. *JAMA* 2001; 286: 1879–1881.
64 Desurmont S, Bauters C, Copin MC, Dewailly D, Tonnel AB, Wallaert B. [Treatment of pulmonary lymphangioleiomyomatosis using a GnRH agonist]. *Rev Mal Respir* 1996; 13: 300–304.

65 Rossi GA, Balbi B, Oddera S, Lantero S, Ravazzoni C. Response to treatment with an analog of the luteinizing-hormone-releasing hormone in a patient with pulmonary lymphangioleiomyomatosis. *Am Rev Respir Dis* 1991; 143: 174–176.

66 Tomasian A, Greenberg MS, Rumerman H. Tamoxifen for lymphangioleiomyomatosis. *N Engl J Med* 1982; 306: 745–746.

67 Eliasson AH, Phillips YY, Tenholder MF. Treatment of lymphangioleiomyomatosis. A meta-analysis. *Chest* 1989; 96: 1352–1355.

68 Wellens F, Estenne M, de Francquen P, Goldstein J, Leclerc JL, Primo G. Combined heart-lung transplantation for terminal pulmonary lymphangioleiomyomatosis. *J Thorac Cardiovasc Surg* 1985; 89: 872–876.

69 Trulock EP. Lung transplantation: special considerations and outcome in LAM. *In*: Moss J, ed. LAM and Other Diseases Characterised by Smooth Muscle Proliferation. New York, Marcel Dekker, 1999; pp. 65–78.

70 Bittmann I, Dose TB, Muller C, Dienemann H, Vogelmeier C, Lohrs U. Lymphangioleiomyomatosis: recurrence after single lung transplantation. *Hum Pathol* 1997; 28: 1420–1423.

71 Nine JS, Yousem SA, Paradis IL, Keenan R, Griffith BP. Lymphangioleiomyomatosis: recurrence after lung transplantation. *J Heart Lung Transplant* 1994; 13: 714–719.

72 Karbowniczek M, Astrinidis A, Balsara BR, *et al.* Recurrent lymphangiomyomatosis after transplantation: genetic analyses reveal a metastatic mechanism. *Am J Respir Crit Care Med* 2003; 167: 976–982.

73 Yamakado K, Tanaka N, Nakagawa T, Kobayashi S, Yanagawa M, Takeda K. Renal angiomyolipoma: relationships between tumor size, aneurysm formation, and rupture. *Radiology* 2002; 225: 78–82.

74 Yip SK, Tan PH, Cheng WS, Li MK, Foo KT. Surgical management of angiomyolipoma: nephron-sparing surgery for symptomatic tumour. *Scand J Urol Nephrol* 2000; 34: 32–35.

75 Kennelly MJ, Grossman HB, Cho KJ. Outcome analysis of 42 cases of renal angiomyolipoma. *J Urol* 1994; 152: 1988–1991.

76 Desai S, Hejmadi R, Krishnamurthy S, Chinoy RF. Renal angiomyolipoma. A clinicopathologic, immunohistochemical, and follow-up study of 46 cases. *Am J Surg Pathol* 2001; 25: 972–973.

77 Logginidou H, Ao X, Russo I, Henske EP. Frequent estrogen and progesterone receptor immunoreactivity in renal angiomyolipomas from women with pulmonary lymphangioleiomyomatosis. *Chest* 2000; 117: 25–30.

78 Mascarenhas R, McLaughlin P. Haemorrhage from angiomyolipoma of kidney during pregnancy--a diagnostic dilemma. *Ir Med J* 2001; 94: 83–84.

79 Shah J, Jones J, Miller MA, Patel U, Anson KM. Selective embolization of bleeding renal angiomyolipoma in pregnancy. *J R Soc Med* 1999; 92: 414–415.

80 Oka D, Mizutani S, Takao T, Inoue H, Nishimura K, Miyoshi S. [Spontaneous rupture of a renal angiomyolipoma in pregnancy: a case report]. *Hinyokika Kiyo – Acta Urologica Japonica* 1999; 45: 423–425.

81 McLoughlin L, Thomas G, Hasan K. Pregnancy and lymphangioleiomyomatosis: anaesthetic management. *Int J Obstet Anesth* 2003; 12: 40–44.

82 Glasgow CG, Steagall WK, Rabel AC, *et al.* Disease severity in lymphangioleiomyomatosis is correlated with an MMP9 promoter polymorphism. *Am J Respir Crit Care Med* 2003; 167: A954.