ERS TASK FORCE

European Respiratory Society Guidelines for the diagnosis and management of lymphangioleiomyomatosis (LAM)

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Introduction

Lymphangioleiomyomatosis (LAM) is an orphan lung disease, which occurs sporadically or in association with the genetic disease tuberous sclerosis complex (TSC)[1, 2]. Sporadic LAM is rare, affecting approximately 1:400,000 adult women; whereas in TSC, LAM occurs in 30-40% of adult women[3, 4] and exceptionally in men and children[5, 6].

Although some are asymptomatic, patients with LAM usually develop progressive dyspnoea, recurrent pneumothorax, chylous collections and occasionally haemoptysis[1]. Extrapulmonary complications of LAM include lymphadenopathy and cystic masses of the axial lymphatics termed lymphangioleiomyomas which may result in abdominal and pelvic lymphatic obstruction[7]. LAM is often associated with angiomyolipoma, a benign tumour generally occurring in the kidneys[8], and an increased frequency of meningioma[9]. LAM is highly variable in terms of clinical features and rate of progression: this together with an absence of clear prognostic factors results in patients being given conflicting information about their prognosis.

Diagnosis is made by tissue biopsy and/or a combination of history and computed tomography (CT) scanning. Tissue biopsy is generally from the lung, especially when surgical procedures for the treatment of pneumothorax are required but occasionally lymph nodes or lymphangioleiomyomas are sampled. Pathological diagnosis is reliant on characteristic LAM cell morphology and positive immunoreactivity to smooth muscle actin and HMB-45 antibodies. Increasingly high resolution CT scanning (HRCT) is used to diagnose LAM without resorting to lung biopsy; however a number of conditions with multiple pulmonary cysts can mimic LAM and the reliability of this approach has not been studied.

As LAM is rare, there have been no controlled trials of its management which varies from centre to centre. Supportive treatment includes management of airflow obstruction and hypoxaemia with

bronchodilators and oxygen respectively, specific treatment for surgical or pleural complications including pneumo- and chylothorax, and interventional treatment of renal lesions[10, 11]. As LAM is a disease of women and is thought to be accelerated by oestrogen: oophorectomy, tamoxifen, progesterone and gonadotropin-releasing hormone (GnRH) analogues have been used although there is no evidence that any are effective. More recently the finding of abnormalities in the TSC1/2 genes resulting in constitutive activation of the kinase mammalian target of rapamycin (mTOR)[12, 13] has led to trials of mTOR inhibitors including sirolimus in patients with LAM and angiomyolipoma[14, 15].

The purpose of the LAM Task Force was to produce evidence based, consensus guidelines for the diagnosis, assessment, and treatment of patients with LAM.

METHODS

The two Chairmen (S. Johnson and J.F. Cordier) designed the objectives of the LAM Taskforce, submitted the project to the *European Respiratory Society* for sponsorship, contacted recognised specialists with competence in LAM to participate in the Core and Consultant panels, and organised the process of elaborating guidelines through face to face meetings and electronic communication.

The working party was composed of three panels. The *Core panel* had overall responsibility for the guidelines and developing the project. The *Consultant panel* advised on specialist aspects of the guidelines including lung transplantation, pathology, and tuberous sclerosis. The *Review panel* reviewed the documents and comprised all members of the Core and consultant panels plus international experts in LAM, interstitial lung diseases, and representatives of European Thoracic

Societies.

The process of guideline development was as follows: 1) question formulation, 2) evidence collection and synthesis *(Core and Consultant panels),* 3) grading of recommendation strength using the 2004 American College of Chest Physicians health and science policy grading system[16] *(Core and Consultant panels),* 4) circulation of documents and first version of the guidelines *(Core and Consultant panels),* 5) first formal review with scoring of agreement and proposals for modifications using Likert scale statistics and definitions[17] *(Core, Consultant and Review panels),* 6) integration of proposals *(Core panel),* 7) second formal review with re-assessment of agreement *(Core, Consultant and Review panels),* and 8) final revision *(Core panel).* Final recommendations are scored by 1) strength of recommendation: (grade) from A (strongest) to D (weakest) and I (inconclusive), 2) quality of evidence (quality) 3), magnitude of benefit, and 4) strength of expert consensus. Further details are contained in appendix 1.

DESCRIPTION OF DISEASE

Respiratory manifestations

Symptoms In most cases of LAM respiratory manifestations dominate the clinical picture. Dyspnoea is the most common symptom occurring in almost all patients and is the presenting feature in 42% of cases (Table 1). In many cases dyspnoea is associated with wheeze and cough and may be caused by replacement of the lung parenchyma by cysts, by airflow obstruction, and by the presence of pneumothorax or chylous pleural effusions. Cough is generally dry in the early stages of LAM although patients with more advanced disease may produce sputum and have recurrent infections. A small number of patients have intermittent, mild, haemoptysis and others cough sticky white secretions, which probably represent chyloptysis. Pneumothorax appears the most common mode of presentation and is bilateral in up to 4% of patients[18]. Pneumothorax is

more common during pregnancy[10] and pneumothorax during pregnancy should raise the possibility of LAM.

	At presentation	**During course of disease**
Pneumothorax	43 (256)	65 (213)
Dyspnoea	42 (256)	87 (164)
Cough	20 (221)	51 (164)
Haemoptysis	14 (138)	22 (164)
Phlegm		27 (230)
Chyloptysis		7 (230)
Chylothorax	12 (256)	28 (213)

Table 1. Summary of symptom prevalence expressed as percentage (n) from 10 surveys [3, 7, 8, 10, 19-24].

Physical findings There are generally no positive physical findings in patients with early disease unless pneumothorax or chylous effusion is the presenting problem. In those with more advanced disease, signs of lung hyperinflation, wheezing and cyanosis may be present. Signs of TSC (appendix 2) may be present in those with TSC-LAM.

Physiological tests Patients with LAM develop airflow obstruction and impaired gas transfer with preserved lung volumes. Early studies featured patient cohorts who had more advanced disease and the majority of these patients had abnormal spirometry and gas transfer[20, 25]. More recent studies using national cohorts have included more patients with mild or early disease (table 2). In two such studies, TLCO was within the normal range in 18% of 80 patients whereas FEV_1 was normal in 42% of 45 patients[3, 8]. Lung function, particularly TLCO and FEV_1 have been correlated with histological[26] and CT grading of disease severity[27] and used to assess disease progression in large series of patients. Patients with LAM have limitation of their exercise performance. Cardiopulmonary exercise testing has shown that maximal oxygen uptake during exercise (VO_2max) correlated well with TLCO, extent of disease on CT[28] and was more sensitive at detecting early disease than standard lung function[28].

Series	Number in series	FEV_1	FVC	TLC	RV	TLCO
Lazor[29]	31	72	85	97	119	55
Ryu[24]	218	70	87	96	103	67
Taveira DaSilva[30]	275	75	87	94	104	73
Johnson[10]	47	65	82	98		62

Table 2. Baseline lung function in recent series of LAM (% predicted values).

Radiological findings The chest radiograph may be normal in early disease although in the majority of cases cysts, bullae, reticulonodular shadows and hyperinflation are present with pneumothorax and pleural effusion also seen (table 3). Multiple, round, thin-walled, well-defined air-filled cysts with preserved or increased lung volume are seen in all patients with LAM examined by HRCT (figure 1a).

	At presentation	During course of disease
Chest X-ray		
Normal	5 (147)	0 (32)
Reticulonodular change	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)
HRCT		
Cysts	100 (104)	100 (35)
Ground glass opacity	29 (104)	
Nodules	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)

Table 3. Frequency of radiological findings in LAM expressed as percentage (n).Adapted from references [3, 8, 20, 25]

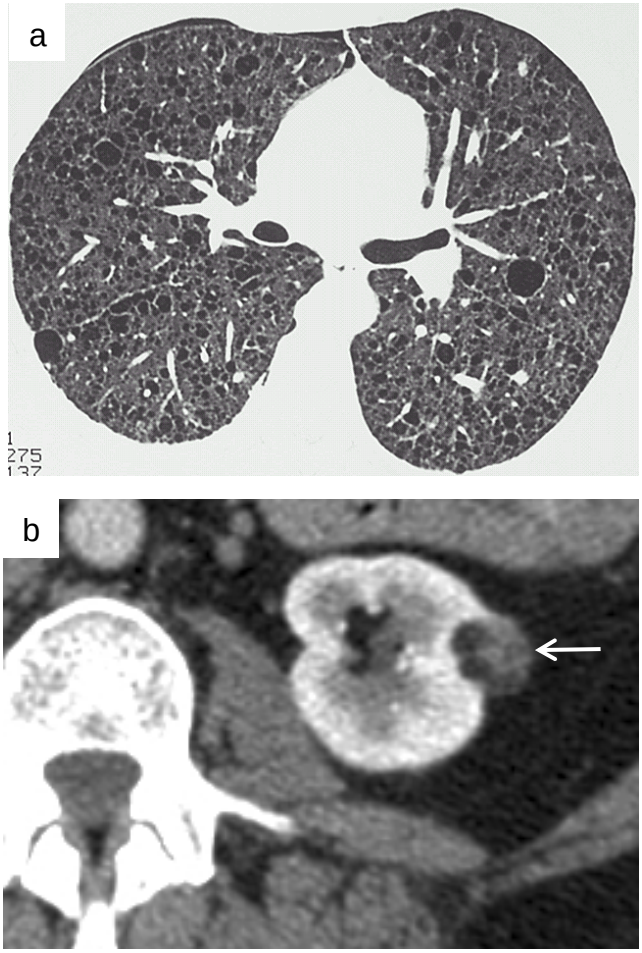

Figure 1.

(a) HRCT scan showing typical changes in a patient with moderate LAM. (b) CT of an asymptomatic renal angiomyolipoma showing characteristic heterogeneous lesion in the left kidney (arrow). Further lung, renal and abdominal CT images are shown in supplementary figure 2.

Lymphatic manifestations

The axial lymphatics of the thorax, retroperitoneum, abdomen, and pelvis may become thickened, dilated and in some cases occluded by LAM cells[19, 31]. This results in lymphadenopathy in 40% of patients[7] and enlarged cystic lymphatic collections termed lymphangioleiomyomas in 21% of patients[7, 32]. Symptoms are rare in patients with abdomino-pelvic lymphadenopathy. 45% of those with lymphangioleiomyomas develop symptoms including palpable masses, abdominal discomfort, bloating, leg oedema, paresthaesia and local pressure symptoms, particularly where pelvic masses compress the bladder[32, 33]. Rupture of lymphangioleiomyoma has been occasionally reported, leading to chylous ascites in 10%[34],

chyluria, abdominal discomfort, distension and bloating. Chylous pericardial effusions have been occasionally described although are rarely clinically significant. In addition approximately 7% of patients develop chyloptysis, presumably due to occlusion of lung parenchymal lymphatics[24]. Chyluria, occurring by a similar mechanism in the bladder has also been observed[35].

Renal manifestations

Angiomyolipomas are benign tumours consisting of smooth muscle (LAM) cells, blood vessels and fat (figure 1b). Angiomyolipomas occur in up to 50% of patients with sporadic LAM, 69-80% of patients with TSC[36-39] and almost all patients with TSC-LAM[40]. The majority of angiomyolipomas are less than 1.5 cm but in some patients, especially those with TSC, angiomyolipomas may enlarge and multiple tumours can occur in both kidneys[41]. Tumours greater than 4 cm, particularly those with aneurysmal vessels are prone to bleeding, presenting as haematuria and haemoperitoneum. During the course of the disease further angiomyolipomas may develop or enlarge. TSC is associated with other renal lesions including renal cysts and polycystic kidney disease that may result in chronic renal failure[22, 38, 39, 42-46].

Meningioma

Both sporadic and TSC-LAM are associated with an increased risk of meningioma. Meningioma has been reported in case reports[47-49] and in a study of 250 patients was detected by screening in 9 patients (3.6%), three of whom were symptomatic[9, 50].

TSC-LAM

The recent observations that 26-39% of adult women with TSC have lung cysts consistent with LAM[2, 51, 52] but less than 3% have symptoms of LAM[53] suggests that a large number of

women with TSC have a mild form of the disease which may progress only slowly or not at all. Consistent with this, those with sporadic LAM in the National Heart Lung and Blood Institute (NHLBI) registry, had more cysts and worse lung function than those with TSC-LAM[24, 54]. However, this observation is prone to ascertainment bias, with TSC patients more likely to be diagnosed with LAM than the general population. Although TSC-LAM can be asymptomatic it may be as severe as the sporadic form in some cases. It is important to consider TSC in those with LAM. TSC has a highly variable phenotype with only one third of patients having the classical triad of epilepsy, learning difficulties, and facial angiofibromas. Those who do not have epilepsy or learning difficulties may have mild cutaneous features of TSC which can be overlooked. In many cases a history of childhood epilepsy, renal disease, skin problems, learning difficulties or a family history of these problems may be found although 2/3 of cases of TSC arise as spontaneous mutations where no family history is present. Diagnostic criteria for TSC are found in appendix 2[55].

Pathology

The lung parenchyma is progressively replaced by a combination of cysts and a nodular proliferation of immature smooth muscle and perivascular epithelioid cells, called LAM cells[56-58] (figure 2). LAM cell proliferations are usually found around lymphatic vessels, beneath the pleura, and the alveolar septa. LAM nodules are heterogeneous proliferations of spindle and epithelioid LAM cells associated with proliferation of lymphatics[59]. LAM cells, particularly epithelioid cells, express pre-melanocyte proteins which can be detected immunohistochemically by the antibody HMB-45. This combination of melanocytic and smooth muscle origin is consistent with the perivascular epithelioid cell origin for LAM cells[60, 61]. Sporadic and TSC-LAM is morphologically indistinguishable. LAM cells frequently infiltrate the axial lymphatics

and the thoracic duct can also be involved. Rarely other organs such as the serosa of the uterus or fallopian tubes can be involved.

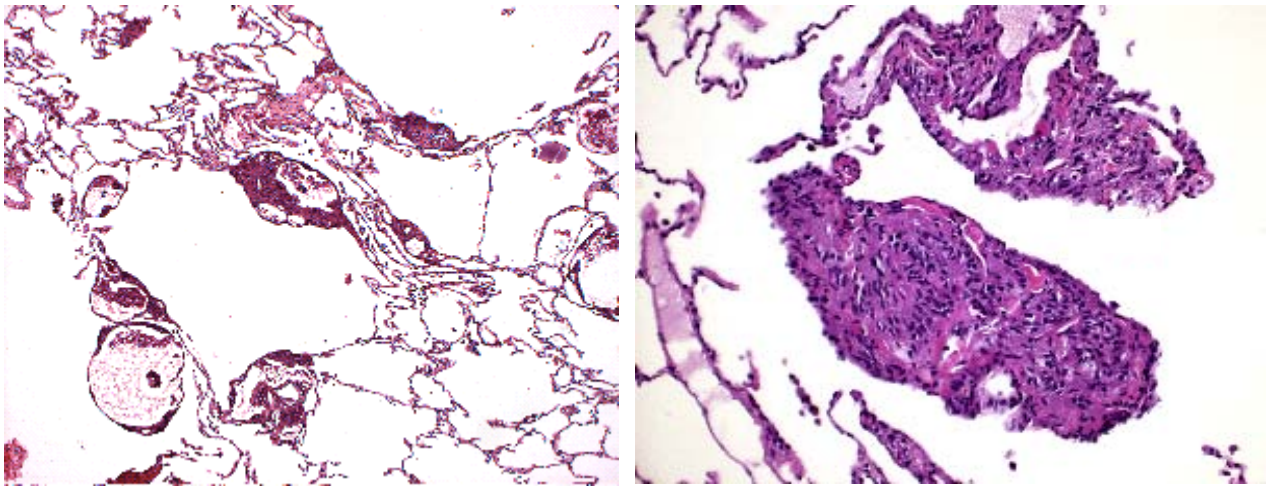

Figure 2.
Lung biopsies showing proliferating nodules of LAM cells at low (left) and high (right) power stained with haematoxylin and eosin. Further pathological images are shown in supplementary figure 3.

At a molecular level LAM cells are characterised by dysregulation of the mTOR pathway as the result of mutations in the TSC1/2 genes[12, 62, 63]. This leads to a complex cell phenotype capable of increased growth, metastatic behaviour, and the expression of hormone receptors, proteases, and growth factors including vascular endothelial growth factor (VEGF)[64]. This is discussed further in appendix 3.

PROPOSED DEFINITIONS AND DIAGNOSTIC WORKUP FOR LAM

Diagnostic criteria

No studies have been performed which examine the diagnostic accuracy of strategies which do not include lung biopsy (the gold standard for diagnosis in most studies). The diagnostic criteria result from approaches used by large series, registries[3, 24, 25, 30, 65] and expert opinion.

DEFINITE LAM

1. Characteristic[a] or compatible[a] lung HRCT

   and

   lung biopsy fitting the pathological criteria for LAM[a]

   OR

2. Characteristic[a] lung HRCT and any of the following:

   - angiomyolipoma (kidney)[b]
   - thoracic or abdominal chylous effusion[c]
   - lymphangioleiomyoma[d] or lymph-node involved by LAM[d]
   - definite or probable TSC[e]

PROBABLE LAM

1. Characteristic[a] HRCT and compatible clinical history[f]

   OR

2. Compatible[a] HRCT and any of the following:

   - angiomyolipoma (kidney)[b]
   - thoracic or abdominal chylous effusion[c]

POSSIBLE LAM

Characteristic[a] or compatible[a] HRCT

FOOTNOTES

a. as defined below
b. diagnosed by characteristic CT features and/or on pathological examination
c. based on visual and/or biochemical characteristics of the effusion
d. based on pathological examination
e. see appendix 2
f. compatible clinical features include pneumothorax (especially multiple and/or bilateral) and/or altered lung function tests as in LAM

REMARKS

1. LAM is considered associated with TSC (TSC-LAM) when definite or probable TSC is present. Otherwise LAM is considered sporadic.
2. The diagnosis of LAM defined above is only for female patients. LAM is most exceptional in males without TSC (definite or probable) and exceptional in males with TSC. In these, diagnosis requires characteristic or compatible HRCT and typical pathological features on lung biopsy.
3. The diagnosis of LAM requires exclusion of the alternative causes of cystic lung disease (section 5.3). A complete diagnostic work-up for these alternative causes of cystic lung disease is necessary in patients with probable and especially possible LAM.

   Agreement on diagnostic criteria (Consensus) very good

Pathologic criteria for diagnosis

Two lesions characterize LAM: cysts and a multifocal nodular proliferation of immature smooth muscle and perivascular epithelioid cells (LAM cells)[56-58]. Both lesions are found together in variable percentages and the findings may be inconspicuous in early disease. Epithelioid and immature looking smooth muscle cells form the nodular lesions characteristic of LAM. A few cells, but also aggregates of more than 20 cells can form the nodules. While perivascular epithelioid cell and spindle cells are present in LAM, intermediate forms with a combined muscular and epithelioid phenotype can be encountered. Thus it seems appropriate to consider them as a morpho-phenotypical modulation of the same cell, probably arising from a common precursor[66, 67]. Sporadic and TSC-associated LAM are morphologically and phenotypically indistinguishable.

The sensitivity and specificity of the pathologic changes seen in LAM have not been determined.

As a consequence the correct diagnosis mainly relies on the experience of the pathologist. Where a typical proliferation of immature smooth muscle cells and epithelioid cells outside the normal muscular structures occur, associated with cyst formation, routine haematoxylin and eosin staining in combination with adequate clinical and radiological information is sufficient to make the diagnosis in most cases. Immunohistochemistry for smooth muscle actin, desmin, and HMB45 is an important adjunct to diagnosis. Smooth muscle actin will stain all muscular cells, desmin will stain the more mature smooth muscle cells. Epithelioid LAM cells and some immature spindle cells are generally positive for HMB45[8, 61, 67, 68]. Although HMB45 is a highly sensitive marker in LAM only 17-67% of LAM cells are positive and in early disease where only a few scattered cells are present this may be overlooked unless there is a strong clinical suspicion of LAM. HMB45 is particularly useful in samples obtained by transbronchial biopsy[61]. In rare cases, HMB45 staining is absent but the characteristic lesions are present and the diagnosis of LAM can still be made[8, 61]. In such cases a correlation with clinical and high-resolution CT scan is essential to increase the confidence level of diagnosis. In about half of the cases oestrogen and/or progesterone receptor can be detected by immunohistochemistry[69, 70].

Differential diagnosis in lung biopsy tissue

Muscle cell proliferations can occur in emphysema[71], some variants of pulmonary hypertension, hypertrophic bronchitis / bronchiolitis, and some interstitial pneumonias[72] especially idiopathic pulmonary fibrosis. Metastasis of endometrial stromal sarcoma of the uterus can mimic LAM[73]. In these cases the smooth muscle cells are HMB45 negative. Metastasis of malignant melanoma, peripheral nerve sheath tumours of Schwann or perivascular epithelioid cell origin, benign metastasizing leiomyoma and metastatic leiomyosarcoma can stain positively with HMB45 but have a different morphologic appearance.

Extra-pulmonary involvement

If lymph nodes are involved a lymph node biopsy from the retroperitoneum or mediastinum may be diagnostic. Where lymphatics alone are sampled the presence of characteristic immature smooth muscle component must be convincing to make a diagnosis of LAM. Primary lymphatic disorders may mimic LAM (and present with chylothorax) including pulmonary lymphangiomatosis, Gorham-Stout syndrome, and lymphangioleiomyoma of the thoracic duct[74, 75].

The diagnosis of angiomyolipoma can be made by imaging in the correct context; the histologic diagnosis of angiomyolipoma is made by the mixture of proliferating small and medium sized blood vessels, perivascular epithelioid cells and fat cells and can often be made on frozen section. Renal cell carcinoma has been considered a feature of kidney pathology in TSC although some cases have been recognised recently as a carcinoma-like variant of angiomyolipoma.

Recommendations / pathologic criteria and procedures for diagnosis of LAM

1. Pathological samples from patients with suspected LAM (or any diffuse parenchymal lung disease) should be examined by a pathologist experienced in LAM.
2. LAM should be considered when there is a variable predominance of cysts, multifocal, nodular proliferating immature smooth muscle and perivascular epithelioid cells.
3. Immunohistochemistry for α-smooth muscle actin and HMB45 should be performed especially where morphologic features do not allow a secure diagnosis to be made. Oestrogen and progesterone receptor may be an adjunct to diagnosis.

   (Grade) expert opinion / A (Quality) expert opinion (Benefit) substantial (Consensus) very good

Radiologic criteria for diagnosis

Characteristic features of pulmonary LAM on HRCT

The appearance, size, and contour of lung cysts vary considerably with cysts typically ranging from 2-5 mm in diameter but occasionally as large as 30 mm[76, 77]. The cysts may decrease in size in expiratory images, indicating a communication with the airways[78]. Cysts are distributed evenly throughout the lungs, are usually round and generally surrounded by normal lung parenchyma. Cyst wall thickness ranges from barely perceptible to 2 mm thick in most series[77, 79] but has been described as measuring up to 4 mm[76]. In some cases reticulation or ground-glass attenuation may be seen. Small nodules are occasionally present[80], most commonly multifocal micronodular pneumocyte hyperplasia in patients with TSC (which may occur with or without LAM)[2]. Ill-defined areas of increased attenuation may result from complications such as haemorrhage or oedema. Sometimes ground-glass attenuation is related to proliferation of smooth cells in the alveolar walls. Rarely, centrilobular micronodules corresponding to smooth muscle cells around the bronchioles are observed. Uni or bilateral pneumothorax and chylous pleural effusions can be seen. Mediastinal or hilar adenopathy may be present.

Differential diagnoses of LAM by HRCT scanning

The main differential diagnosis is Langerhans cell histiocytosis (LCH). Nodules, cavitating nodules, and thick-walled cysts are common findings in early LCH but are very unusual in LAM[81]. A cystic pattern predominates in later phases[82]. Unlike LAM, in LCH the cysts are irregular with bizarre shapes and have a predilection for the upper lung zones and spare the bases[83]. In emphysema, commonly seen affecting the upper lobes in smokers, HRCT shows areas of low attenuation with or without visible walls, but more often the cystic areas have no perceptible wall. The Birt-Hogg-Dubé syndrome (BHDS) is a rare autosomal dominantly

inherited genodermatosis without gender predominance with features somewhat reminiscent of TSC including lung cysts and pneumothorax, cutaneous fibrofolliculomas, and kidney tumours. The BHDS is associated with germline mutations of the folliculin gene. Multiple lung cysts are present in about 90% and pneumothorax occurs in about 24% of patients; patients with a history of pneumothorax have multiple lung cysts (with a median age at first pneumothorax of 38 years)[84]. Familial isolated primary spontaneous pneumothorax with pulmonary cysts (without skin and renal disease) is also associated with germline mutations in folliculin[85, 86].

Cystic spaces can be seen in a small proportion of patients with hypersensitivity pneumonitis[87], and in up to 60-80% of patients with lymphocytic interstitial pneumonia[88]. Occasionally, cystic lung changes have been observed in amyloidosis[89], non-amyloid immunoglobulin light chain deposition disease[90], Marfan's syndrome[91], cystic pulmonary metastases of sarcoma[73] and multiple cystic mesenchymal hamartoma[92].

CT protocol for the diagnosis of LAM

HRCT is the recommended imaging technique for the diagnosis, assessment, and follow-up of diffuse infiltrative lung disease including LAM[93]. Images are obtained during end inspiration with the patient in the supine position, without intravenous contrast. A thin collimation, high spatial reconstruction algorithm must be used to acquire high-quality HRCT scans. The acquisition may be performed with sequential scanning (images with 1mm collimation at 1-cm intervals) or low dose spiral multi-detector CT.

Recommendations

1. Patients with suspected LAM should have a pulmonary HRCT scan using a thin collimation, high spatial reconstruction algorithm.

2. The acquisition may be performed with sequential scanning (images with 1mm collimation at 1-cm intervals) or low dose spiral HRCT. **(Grade) expert opinion / A (Quality) expert opinion (Benefit) substantial (Consensus) very good**

Remarks

HRCT features *characteristic* of LAM are multiple thin-walled round well-defined air-filled cysts with preserved or increased lung volume with no other significant pulmonary involvement. In particular, there should be no interstitial lung disease with the exception of possible features of multifocal micronodular pneumocyte hyperplasia in patients with TSC.

HRCT features *compatible* with pulmonary LAM are only few multiple (> 2 and ≤ 10) thin-walled round well-defined air-filled cysts (less than 30 mm) with preserved or increased lung volume with no other significant pulmonary involvement, in particular, there should be no interstitial lung disease with the exception of possible features of multifocal micronodular pneumocyte hyperplasia in patients with TSC.

Radiology in abdominal LAM

Once a diagnosis of LAM is made or suspected, abdominal CT scanning can be used to detect angiomyolipomas, lymphangioleiomyomas or lymphadenopathy to support the diagnosis of LAM, to plan the management of angiomyolipomas, and to follow the evolution of the lesions. In a large series of abdominopelvic imaging findings in 80 patients with LAM abnormalities were found in up to 2/3 of patients[7]. Both ultrasound and CT are used to detect renal angiomyolipomas. CT is more sensitive and specific and can detect tumours less than 1 cm in diameter[7]. Magnetic resonance imaging (MRI) with and without fat suppression techniques

may be adequate for diagnosis of fat-containing tumours when iodinated contrast is contraindicated[94].

Criteria for radiologic diagnosis of kidney angiomyolipomas

Ultrasound A hyper-echoic appearance at ultrasound is suggestive but not diagnostic of angiomyolipoma[94].

CT Angiomyolipomas usually manifest as a tumour with fat attenuation in the renal cortex. Intratumoral fat with negative attenuation values is virtually pathognomonic of angiomyolipoma. In LAM the mean size is <1.5 cm[7]. Fat is not detectable in 5% of angiomyolipomas overall although an absence of fat is more common in patients with LAM[7]. If fat is not detected, close follow-up of these lesions with US or unenhanced CT is recommended. In case of rapid growth, an image-guided biopsy may be considered.

MRI Fat containing tumours have high signal intensity on T1-weighted images that is similar to that of subcutaneous and retroperitoneal fat and demonstrated saturation of signal on fat-saturation images.

Recommendations for abdominal CT scanning in LAM

1. All patients with LAM or suspected LAM should have an abdomino-pelvic CT at diagnosis or during workup to identify angiomyolipomas and other abdominal lesions.
2. The abdomen should be scanned contiguously with 3mm collimation or less, before and after the intravenous administration of non-ionic contrast.
3. Since a proven therapeutic intervention is not currently available for lymphangioleiomyomas, screening of asymptomatic patients for lymphangioleiomyomas during the course of the disease should not be performed.
4. Patients with abdominal symptoms should be evaluated for the presence of

lymphadenopathy or lymphangioleiomyomas by CT scanning.

(Grade) C (Quality) low (Benefit) intermediate (Consensus) very good

Screening for meningioma in patients with sporadic LAM

Patients with LAM have an increased risk of meningioma. As meningiomas express progesterone receptors and their growth may be promoted by progesterone; these lesions should be identified especially in patients receiving progesterone. Brain imaging is also useful in the workup of possible TSC in patients with LAM.

Recommendations

1. Brain MRI as a baseline evaluation may be useful for comparison during follow up and should be performed in the presence of symptoms compatible with meningioma. **(Grade) C (Quality) low (Benefit) intermediate (Consensus) very good**
2. Brain MRI for screening meningioma should be performed in women with LAM receiving progestative drugs or planned to receive such treatment. **(Grade) expert opinion / B (Quality) expert opinion (Benefit) intermediate (Consensus) very good**

Work-up for TSC in patients with LAM

Patients presenting with apparent sporadic LAM may have TSC. As TSC has a highly variable phenotype and 2/3 of cases arise as spontaneous mutations the diagnosis can be overlooked. Data on the prevalence of TSC in patients presenting with LAM is limited as many of the earlier series did not formally examine their patients for TSC and many excluded patients with TSC LAM from their analysis[4].

The diagnosis of TSC has important implications for patients and their families. Thorough evaluation of patients with TSC is recommended to avoid complications of specific lesions such

as sub-ependymal giant cell astrocytoma[37], and renal morbidity from haemorrhage, carcinoma and renal failure[95-98]. In addition the diagnosis of TSC has significant implications for genetic counselling in women contemplating pregnancy. Diagnosis of TSC may require the input of more than one specialist. Diagnostic criteria for TSC and recommendations for assessment of patients are provided in appendix 2[55] .

Conclusion

Patients diagnosed with LAM may have TSC and making this diagnosis has important implications for patients and their families. Patients should undergo a full history and physical examination to exclude TSC. Where doubt exists the patient should be referred to a clinical geneticist for further evaluation.

Recommendations

1. Patients presenting with LAM should have a thorough history and family history taken concerning the manifestations of TSC. Physical examination should include the skin, retina and nervous systems by a physician familiar with the manifestations of TSC. **(Grade) B (Quality) low (Benefit) substantial (Consensus) very good**
2. Patients with LAM and bilateral angiomyolipomas and other patients where doubt remains should be referred to a clinical geneticist for full evaluation. **(Grade) D (Quality) low (Benefit) substantial (Consensus) very good**
3. Routine genetic analysis of patients with sporadic LAM is not of benefit and should not be performed. **(Grade) D (Quality) low (Benefit) negative (Consensus) very good**

Lung function testing

To be informative, lung function tests need to be reproducible, abnormal in disease, and

deteriorate with disease progression. TLCO and FEV_1, have been correlated with histological[26] and CT grading[27] in large series of patients with LAM. Most longitudinal studies of lung function in LAM have examined change in FEV_1 and TLCO over time[4, 29, 30]. Mean rate of decline in FEV_1 and TLCO vary between 69-118 ml/yr and 0.69-0.9 ml/min/mmHg respectively[4, 29, 30]. All studies showed a large range in rate of decline between individual patients. Various studies have used these data in addition to pathology and imaging in an attempt to predict rate of decline in individuals. Total lung capacity and residual volume measured by body plethysmography have not been studied in detail; however as irreversible airflow obstruction and lung cysts are often present this may provide further information.

Conclusion

FEV_1 and TLCO correlate with CT and histological abnormalities in LAM, and change over time as the disease progresses. TLCO is abnormal in more patients than FEV_1 and may be a more sensitive indicator of early disease. Cardiopulmonary exercise testing may provide additional information especially in patients with milder disease but is more difficult to obtain and perform in a reproducible manner. The rate of decline in FEV_1 and TLCO varies between individuals and it remains difficult to predict the clinical course in individuals and hence how often to repeat lung function. Most physicians initially perform standard lung function tests every 3-6 months. In patients with stable disease; after a period of observation this may be increased to yearly intervals.

Recommendations

1. Spirometry, bronchodilator testing, and TLCO should be performed in the initial evaluation of patients with LAM (including TSC-LAM). **(Grade) B (Quality) low (Benefit) substantial (Consensus) very good**
2. FEV_1 and TLCO should be performed to assess disease progression and response to

treatment. **(Grade) B (Quality) low (Benefit) substantial (Consensus) very good**

3. Lung function tests should be repeated every 3 - 6 months in patients with progressive disease and every 6 - 12 months in those with more stable disease as determined by a period of observation of one year. **(Grade) C (Quality) low (Benefit) intermediate (Consensus) very good**

Arterial blood gas measurement

Arterial hypoxaemia is common in LAM[20, 25]. In the NIH registry of 214 patients mean PaO_2 was 10.85 kPa and mean $PaCO_2$ 4.5 kPa[24]. This study included a large number of patients with early disease. Hypercapnia is rare at presentation and uncommon during the course of the disease[3, 99] being seen in 3 of 25 patients directly before lung transplant[100].

Conclusion

Blood gases do not provide useful information above that obtained by oximetry in the assessment of patients with mild to moderate disease. However they provide useful baseline data and in advanced disease may be useful to define the indication for oxygen therapy in patients, especially for transplant evaluation and to exclude hypercapnia.

Recommendations

1. Blood gases may be performed at initial evaluation of patients with LAM to obtain a baseline value, and in the assessment of patients with severe disease including before transplant referral. **(Grade) expert opinion / A (Quality) expert opinion (Benefit) substantial (Consensus) very good**
2. Blood gases should be performed to assess the indication for oxygen therapy in patients with advanced disease. **(Grade) expert opinion / A (Quality) expert opinion (Benefit) substantial (Consensus) very good**

Cardiopulmonary exercise testing and six minute walk test (6MWT)

Patients with LAM have limitation of their exercise performance. Impaired performance and reduced maximal oxygen consumption (VO_2 max) on cardiopulmonary exercise testing may occur before abnormalities are detected in standard lung function tests[28]. Although the six minute walk test (6MWT) is commonly used to assess patients with LAM no specific studies have examined its use in this context. As in other lung diseases the 6MWT is likely to provide evidence of disability and its decrease might reflect disease progression[101].

Conclusion

Exercise performance and VO_2 max are impaired in patients with LAM. As in other lung diseases, the 6MWT is likely to be helpful in evaluating exercise performance in patients with LAM.

Recommendations

1. Cardiopulmonary exercise testing may be performed to provide additional information over standard lung function tests in symptomatic patients. **(Grade) C (Quality) low (Benefit) small / weak (Consensus) very good**
2. The 6MWT may be performed in the evaluation of disability in LAM, disease progression, and response to treatment in symptomatic patients **(Grade) expert opinion / B (Quality) expert opinion (Benefit) intermediate (Consensus) very good**

Screening for pulmonary hypertension

Despite being well documented in other diffuse parenchymal lung diseases, pulmonary hypertension has not been reported frequently in cohorts of patients with LAM. In a systematic study of echocardiography in 120 patients with LAM only eight had pulmonary hypertension at

rest although exercise induced pulmonary hypertension was observed in 56. In most cases this was associated with exercise induced desaturation[28]. No data are available on the efficacy of treatment of pulmonary hypertension in LAM.

Recommendations

1. Screening for pulmonary hypertension is not recommended in patients with non-severe LAM. **(Grade) I (Quality) low (Benefit) conflicting (Consensus) very good**
2. Estimation of pulmonary artery pressure by echocardiography may be performed in patients with severe disease and those requiring long-term oxygen therapy. It should be performed in those considered for lung transplantation. **(Grade) C (Quality) low (Benefit) intermediate (Consensus) very good**

SCREENING FOR LAM IN AT RISK GROUPS

The estimated numbers of patients with LAM based on prevalence in registries and the long delay between the first symptom and diagnosis in many patients suggest that in many patients LAM is either not detected for many years or patients are wrongly diagnosed with another disease. Although no treatment has been proven to affect the clinical course of LAM, patients with LAM may benefit from several low risk interventions including education on the symptoms of pneumothorax, avoidance of oestrogen containing treatments, prophylactic vaccination against influenza and pneumococcus, smoking cessation measures and monitoring to detect progression at an earlier stage, possibly allowing patients to participate in clinical studies or use symptomatic treatments earlier in their disease course.

Is CT indicated in women with apparently spontaneous pneumothorax?

Guidelines developed for the management of spontaneous pneumothorax do not recommend the

routine use of chest CT imaging for patients with a first-time pneumothorax. CT may be indicated to evaluate the presence of suspected pulmonary disorders not detectable on standard radiographs. The rate of recurrence for secondary pneumothorax is about 40-50% (about 30% in primary pneumothorax). The rate of recurrence of pneumothorax in LAM is about 75%. The estimated prevalence of LAM in women with recurrent spontaneous pneumothorax based on the relative frequencies of these conditions is between 0.07 and 1.4%.

Conclusion

The low prevalence of LAM does not justify chest CT for diagnosing LAM at first pneumothorax. It may be justified at the second pneumothorax, and should be done at the third (and more) pneumothorax, especially in non smoking women, and if symptoms (e.g. dyspnoea) are present before the pneumothorax.

Recommendations

1. Chest CT for patients with a first-time pneumothorax should not be performed routinely. **(Grade) I (Quality) low (Benefit) conflicting (Consensus) good**
2. Chest CT may be indicated to evaluate the presence of LAM that is suspected clinically but is not apparent on standard radiographs. **(Grade) C (Quality) low (Benefit) small / weak (Consensus) good**
3. The panel did not achieve consensus regarding the utility of chest CT scans for evaluating patients with recurrent pneumothoraces, persistent air leaks, or planned surgical interventions. **(Grade) I (Quality) low (Benefit) conflicting (Consensus) none**

Should women with TSC undergo screening for LAM by high resolution CT scan?

Prevalence of TSC in LAM

Symptomatic LAM in TSC (TSC-LAM) is more prevalent than in the general population. In the largest retrospective survey of the prevalence of LAM in TSC, 388 patients seen at a tertiary referral centre for TSC over a 43 year period were evaluated. Nine (2.3%) were found to have symptomatic LAM[53]. Recently three studies systematically examined the prevalence of TSC-LAM by using HRCT to screen both symptomatic and asymptomatic patients with TSC for cystic lung disease. These studies found that 26 - 39% of patients had lung cysts consistent with LAM[2, 51, 52].

Conclusion

There is a high prevalence of LAM in women with TSC. The significance of this observation is unknown as most of these women have no symptoms of lung disease and the natural history of LAM detected by screening in TSC is not known. However detection of LAM in otherwise asymptomatic patients may allow earlier recognition and treatment of symptoms if they occur. In addition it may be helpful for women with LAM to avoid oestrogen containing medication and receive additional pre-pregnancy counselling. The high prevalence of LAM in TSC suggests that women with TSC should be examined for LAM. As clinical examination, chest radiography and lung function tests may all be normal in the presence of LAM. HRCT is the investigation of choice.

Recommendations

1. Women with TSC should undergo screening for LAM by HRCT of the thorax at the age of 18 and if negative again at the age of 30-40 years. **(Grade) C (Quality) low (Benefit) intermediate (Consensus) very good**
2. HRCT should be repeated if persistent respiratory symptoms develop. **(Grade) C (Quality) low (Benefit) intermediate (Consensus) very good**
3. Women with TSC should undergo HRCT of the thorax in the presence of otherwise

unexplained respiratory symptoms. **(Grade) B (Quality) low (Benefit) small / weak (Consensus) very good**

Should men with TSC be screened for LAM by HRCT?

TSC has no sex predilection; however TSC-LAM occurs almost exclusively in women. There are only a few case reports describing LAM in men with TSC[5, 102]. Screening of 10 men with TSC using HRCT did not reveal any cases of LAM[52]. It is likely that LAM is rare in men with TSC. Screening is unlikely to detect significant numbers of cases. In addition the potential benefit of diagnosing early asymptomatic disease would be less likely to benefit men due to a lower likelihood of being exposed to oestrogen.

Conclusion

LAM can occur in men with TSC but is very rare. As men are less likely to be exposed to oestrogen containing treatments early diagnosis of LAM is less likely to be of benefit to patients.

Recommendations

1. Men with TSC and otherwise unexplained respiratory symptoms should be investigated as dictated by their symptoms; this may include HRCT scanning. **(Grade) C (Quality) low (Benefit) intermediate (Consensus) very good**
2. Men without respiratory symptoms should not be screened for LAM with HRCT **(Grade) D (Quality) low (Benefit) negative (Consensus) very good**

Is screening for LAM needed in women with sporadic angiomyolipoma?

Screening for LAM may be needed in women with angiomyolipoma and no pulmonary symptoms or manifestations of LAM if the prevalence of LAM in this population is high. Surprisingly, in the published series of angiomyolipoma, sporadic LAM has been reported in

only 1 patient[103], whereas the prevalence of angiomyolipomas in LAM is 40-50 % of patients when screened by CT[7]. The prevalence of angiomyolipomas in TSC is about 80%[38, 104, 105]. Of these, bilateral angiomyolipomas occur in 86% of cases of TSC and angiomyolipoma and in only 12% of patients with sporadic angiomyolipoma. TSC patients have larger tumours and more frequent haemorrhage than those with sporadic angiomyolipoma[103, 106-109]. Case series suggest the lower and upper limits of prevalence of LAM in TSC are 10 and 39% respectively, the lower and upper limits prevalence of LAM in women with angiomyolipoma are respectively 1.8 and 7.1%. As TSC is present in 63.7% of bilateral angiomyolipomas, the lower and upper limits of prevalence of LAM in patients with bilateral angiomyolipomas are 6.4 and 24.8% respectively.

Recommendations

1. In patients with unilateral angiomyolipomas, no clinical features of TSC and no pulmonary symptoms, screening for LAM by HRCT may be performed.
2. In patients with bilateral angiomyolipoma screening for TSC should be performed, with further LAM screening if TSC is present. **(Grade) B (Quality) low (Benefit) small / weak (Consensus) very good**

PROGNOSIS

Estimation of prognosis

The clinical course of LAM is highly variable with some patients developing progressive airflow obstruction whilst others remain stable for many years. In addition to worsening airflow obstruction, patients may have intermittent pneumothorax and in some cases chylous collections. Patients with sporadic LAM generally develop progressive airflow obstruction. Two national

studies have shown that FEV_1 declines at around 120 ml/yr on average (approximately four times the normal rate), although the variation about this mean value was large in both studies[3, 4]. In a large study from a tertiary centre decline in FEV_1 was slower at 70 ml/year however this study included relatively few patients with severe disease[30]. This clinical variation means it is difficult to accurately assess the prognosis of an individual patient at the onset of disease. Studying a cohort of patients, it has been shown that at 10 yrs from the onset of symptoms, 55% of patients are more breathless than their peers or have to stop when walking at their own pace on the flat, and 10% are housebound due to dyspnoea[65].

To date, all analyses of survival in LAM have been based on retrospective case series, with the potential bias of missing older and more severe cases. In the two oldest series with cases diagnosed before 1973 the 10 yr survival was respectively 24 and 30%[19, 110]. In the three most recent series with cases diagnosed from 1973 to 2003, the 10-yr survival was 79, 71 and 91%[3, 57, 65]. The most likely causes of the apparent improvement in survival are earlier diagnosis, especially since CT became available, a better knowledge of the disease and increased clinical awareness, as reflected by an increasing number of publications and diagnosed cases[3, 111]. The main therapeutic interventions, which could also have contributed to a true increase in survival in LAM are lung transplantation and possibly long-term oxygen therapy.

A number of studies have attempted to predict the rate of disease progression from pathological, physiological, imaging and clinical data: these studies are discussed below. For the purpose of estimation of prognosis at diagnosis, a predictor is defined as an explanatory variable measured at diagnosis. Prognosis is defined as a variable indicating disease severity measured after initial evaluation.

Histological factors

Relationships between histological features of pulmonary LAM at diagnosis and survival have

been analysed in two retrospective studies. Although using different scoring systems, both studies evaluated the relative proportions of abnormal lung tissue, cystic destruction and LAM cell invasion. In both cases, a greater proportion of abnormal lung and cystic change were correlated with shorter survival. The percentage of hemosiderosis was found to predict survival in one study but not in a second. The extent of LAM cell proliferation did not predict survival. [25, 57].

Clinical factors

Relationships between clinical features at diagnosis and either survival or decline in lung function have been evaluated in three retrospective studies. In one, lower FEV_1/FVC and higher total lung capacity (TLC) at diagnosis was associated with shorter survival[25]. In another, a positive response to β-agonists correlated with more rapid decline in FEV_1[26]. The third, found that lower initial TLCO and KCO, predicted more rapid FEV_1 decline[29]. None of these factors has been evaluated prospectively.

TSC-associated and sporadic LAM

Data from retrospective studies suggest that for a similar age at diagnosis, pulmonary involvement appears less severe in TSC-LAM than in sporadic-LAM[24, 111]. However no at risk population for sporadic LAM has been screened in the same way as for TSC-LAM. It is not therefore possible to determine if this apparent difference is due to a number of undiagnosed patients with asymptomatic sporadic LAM. Cross sectional data suggest that progression of lung disease occurs in TSC-LAM, but whether disease activity and rate of progression differ between TSC-LAM and S-LAM is currently unknown. Longitudinal studies are needed to address this issue.

Conclusions

Some histological and lung function variables have been found to be predictive of either survival

or more rapid deterioration of lung function at diagnosis. However, these predictors have not been validated prospectively. Moreover, some of these variables reflect more advanced disease at the time of diagnosis, and thus a greater probability of death. They do not necessarily provide information about disease activity and rate of progression and should not, on their own, influence clinical decisions at the present time. TLCO and FEV_1 are likely to be the best current indicators of disease progression and survival. Patients with TSC-LAM may have a more indolent course than those with sporadic LAM but more studies are required to address this issue.

Recommendations

1. Lung biopsy does not provide prognostic information and should not be performed for this purpose alone. **(Grade) D (Quality) low (Benefit) negative (Consensus) very good**
2. Disease progression may be evaluated by repeating lung function tests at 3-6 monthly intervals during the first year following diagnosis then at 3-12 monthly intervals depending on the severity and progression of the disease. **(Grade) C (Quality) low (Benefit) small / weak (Consensus) very good**

Follow up of patients with TSC-LAM with no pulmonary symptoms

Sporadic LAM is generally a progressive disease characterised by deteriorating lung function[4, 30]. In patients with TSC-LAM and progressive disease regular follow up and serial lung function is recommended to detect and intervene early where the clinical picture changes. No prospective studies have analysed the rate of decline of lung function in patients with TSC-LAM, particularly when LAM has been identified in patients with no symptoms. At the current time there are no treatments which have been shown to reduce the rate of decline of lung function in LAM. However as in any patient with LAM, a baseline evaluation with spirometry and measurement of TLCO is recommended at diagnosis.

Conclusions

In patients with TSC-LAM and minimal symptoms the risk of progressive decline in lung function appears to be lower than in those with sporadic LAM. As no therapy is effective for early disease the benefit of regular follow up and lung function measurement are not clear.

Recommendations

1. Regular follow up by a respiratory specialist or serial lung function studies may not be required for patients with TSC-LAM with normal lung function after initial evaluation and who have been stable after a period of observation of one year. Follow up respiratory evaluation and lung function should be performed if respiratory symptoms develop. **(Grade) expert opinion / C (Quality) expert opinion (Benefit) small / weak (Consensus) very good**
2. Other health professionals involved in the care of patients with TSC and patients themselves should be informed that patients experiencing respiratory symptoms should be seen by a respiratory specialist. This may be in an information document given to patients and general physicians. **(Grade) expert opinion / C (Quality) expert opinion (Benefit) small / weak (Consensus) very good**

MANAGEMENT

General advice and interventions

In common with other pulmonary diseases, patients with LAM should be encouraged to maintain a normal weight and refrain from smoking. The diagnosis of an orphan disease and its consequences often leave patients with a feeling of isolation. Patients groups can help with these issues and other practical matters.

Advice for patients on pneumothorax

LAM is associated with an increased risk of pneumothorax. About 40% of women with LAM have a pneumothorax at presentation and 66% of patients have a pneumothorax during the course of the disease. LAM is associated with an increased risk of recurrence of pneumothorax after a first episode. The estimated rate of recurrence of pneumothorax in LAM is approximately 75%.

Recommendation

1. Patients with both sporadic and TSC-LAM including those with no or minimal symptoms must be warned of the risk of pneumothorax and told to seek urgent medical attention in the event of symptoms of pneumothorax. **(Grade) A (Quality) fair (Benefit) substantial (Consensus) very good**

Advice for patients and management of pregnancy

There are a number of reports of women presenting with LAM during pregnancy, usually with a pneumothorax and occasionally chylous pleural effusion[112-116]. There are also reports of an increased risk of pneumothorax during pregnancy[10]. As a result of these initial case reports a recent survey has shown that 30% of women with LAM are worried about the effect of pregnancy on the disease and 25% have been told by a physician to avoid pregnancy[117]. Despite this, two thirds of women with LAM have been pregnant either before or during their disease[24]. There is no evidence that pregnancy increases the risk of developing LAM in patients with TSC[118]. Patients with TSC-LAM have the additional issue that their baby has a 50% risk of inheriting TSC. There are a number of case reports documenting the rupture of angiomyolipoma during pregnancy, although the data are limited to case reports and the relative

risk in pregnancy is not established[119-122].

Conclusion

It is likely that pregnancy in LAM is associated with an increased risk of pneumothorax and chylothorax, which can on occasion require surgery. It is not clear if pregnancy accelerates the decline in lung function. Although no clear evidence exists it is likely that patients with poor baseline lung function are less likely to tolerate a pneumothorax or chylous effusion if they were to occur during pregnancy than those with good pre-pregnancy lung function. Although infrequent there may be an increased risk of bleeding from angiomyolipoma during pregnancy.

Recommendations

1. To become pregnant is the patients' decision. However all patients, including those with few or no symptoms, should be informed that there is a greater risk of pneumothorax and chylous effusion during pregnancy. Those with recurrent pneumothorax or effusion outside pregnancy and those with poor baseline lung function are at greater risk during pregnancy. **(Grade) expert opinion / B (Quality) expert opinion (Benefit) intermediate (Consensus) very good**
2. Women with LAM who are pregnant should receive information, ideally pre-pregnancy or as soon after conception as feasible to warn of the risk of pneumothorax, effusion and bleeding from angiomyolipoma. **(Grade) expert opinion / B (Quality) expert opinion (Benefit) intermediate (Consensus) very good**
3. Patients with tuberous sclerosis should further receive genetic counselling prior to conception. **(Grade) A (Quality) good (Benefit) substantial (Consensus) very good**
4. Patients should be monitored during pregnancy by both a pulmonary physician and an obstetrician informed about LAM. **(Grade) expert opinion / B (Quality) expert opinion (Benefit) intermediate (Consensus) very good**

5. It may be appropriate to discourage patients with severe disease from becoming pregnant, this counsel being given on an individual basis **(Grade) expert opinion / B (Quality) expert opinion (Benefit) intermediate (Consensus) very good**

Avoidance of oestrogen including the contraceptive pill and hormone replacement

Although no clear evidence links oestrogen to more rapid progression of LAM the supposition that LAM is oestrogen dependent comes from several observations. Firstly, sporadic LAM is (almost) exclusively a disease of women[1, 59]. In TSC-LAM the overwhelming majority of patients are women[2, 51, 52] with only a very small number of case reports in men[5, 102]. A number of case reports describe complications of LAM during administration of exogenous oestrogens[123-125]. In perhaps the most relevant study to this question use of the oral contraceptive pill in women with LAM is associated with an earlier onset of symptoms[126]. Further, two retrospective studies have shown a reduced rate of decline in lung function in post-menopausal, compared with pre-menopausal women although this was statistically significant in only the larger study[4, 30]. In addition, in a study of UK patients with LAM five of 57 presented after the menopause, of whom four had been taking oestrogen containing hormone replacement therapies up to presentation.

Conclusions

Exogenous oestrogens may promote the progression of pulmonary LAM in at least some cases.

Recommendation

1. Women with LAM should avoid oestrogen containing treatments including the combined oral contraceptive pill and hormone replacement therapy. **(Grade) C (Quality) low (Benefit) intermediate (Consensus) very good**

Information for patients concerning air travel

The high frequency of pneumothorax in LAM and reports of pneumothorax occurring in flight has resulted in women with LAM being advised not to travel by air. In a recent survey of 454 flights by 276 patients the risk of pneumothorax during flight was 2% and in half of these patients symptoms had begun before travel. Other problems included hypoxaemia and dizziness[127]. Although the patients in the study were slightly less dyspnoeic than patients who never flew this difference was not significant and the numbers of patients who had had a pneumothorax previously was similar to all patients with LAM[127].

Conclusions

Patients with sporadic and TSC-LAM with well preserved lung function do not need to take specific precautions or avoid air travel. They should be advised not to board a flight if they have new respiratory symptoms. Those with advanced disease should be evaluated for the need for oxygen during flight to prevent hypoxemia and as they are less likely to tolerate pneumothorax.

Recommendations

1. Patients with sporadic or TSC-LAM and minimal symptoms should not be discouraged from air travel. They should be warned that they should not travel if new respiratory symptoms have not been evaluated. **(Grade) C (Quality) low (Benefit) intermediate (Consensus) very good**
2. Patients with advanced disease should be evaluated for the need for oxygen during flight and should not travel if new respiratory symptoms have not been evaluated. Those for whom an untreated pneumothorax may have serious consequences should consider alternatives to air travel. **(Grade) C (Quality) low (Benefit) intermediate (Consensus) very good**
3. Patients with a known untreated pneumothorax, or a pneumothorax treated within the

previous month, should not travel by air **(Grade) B (Quality) low (Benefit) substantial (Consensus) very good**

Pulmonary rehabilitation

Pulmonary rehabilitation is aimed at reducing functional impairment and disability of patients with chronic lung disease[128]. There have been no specific studies examining the impact of pulmonary rehabilitation in LAM; evidence supporting pulmonary rehabilitation in LAM may be extrapolated from other diseases including COPD. The British Thoracic Society statement on pulmonary rehabilitation states: *'Although most patients will have COPD, the benefits of rehabilitation may apply to all patients with dyspnoea from respiratory disease. The introduction of rehabilitation becomes appropriate when patients become aware of their disability. Rehabilitation should be considered at all stages of disease progression when symptoms are present and not at a predetermined level of impairment. This would usually be MRC dyspnoea grade 3 (walk slower than people of the same age on the level or have to stop when walking at own pace on the level) or above'[128].*

Conclusion

Pulmonary rehabilitation is indicated in patients with LAM who are limited by dyspnoea.

Recommendation

1. Pulmonary rehabilitation may be offered to patients with LAM who are limited by dyspnoea. **(Grade) expert opinion / B (Quality) expert opinion (Benefit) intermediate (Consensus) very good**

Influenza and pneumococcal vaccination

Although the effect of prophylactic vaccination in patients with LAM has not been tested, by

analogy with COPD, it may be proposed to patients with LAM and impaired lung function[129].

Recommendation

1. Influenza and pneumococcal vaccination should be offered to patients with LAM. **((Grade) expert opinion / B (Quality) expert opinion (Benefit) intermediate (Consensus) very good**

Assessment and management of osteoporosis

One study of 211 patients has evaluated bone mineral density (BMD) in LAM[130]. Decreased BMD was found in 70% of patients, and correlated with increasing severity of lung disease, age menopause, and oophorectomy. Progesterone treatment was not associated with an effect on BMD but bisphosphonate-treated patients had lower rates of decline in lumbar spine BMD and T-scores than untreated patients.

Conclusions

In view of the rapid deterioration in BMD observed after lung transplantation, early initiation of therapy for osteoporosis in LAM patients with severe lung disease and osteopenia at any bone site is recommended. In addition to pharmacologic therapy, weight-bearing exercise and strength training should be encouraged because of the growing evidence that exercise improves bone density.

Recommendations

1. Patients with LAM, especially post-menopausal, should undergo periodic evaluation of BMD. **(Grade) B (Quality) low (Benefit) substantial (Consensus) very good**
2. Those with osteoporosis should be treated as other patients with osteoporosis. **(Grade) B (Quality) low (Benefit) substantial (Consensus) very good**
3. In view of the rapid deterioration in BMD observed after lung transplantation, aggressive

therapy for osteoporosis should be initiated early in LAM patients with severe lung disease and osteopenia at any bone site. In addition to pharmacologic therapy, weight-bearing exercise and strength training should be encouraged because of the growing evidence that exercise improves bone density. **(Grade) B (Quality) low (Benefit) substantial (Consensus) very good**

Drug therapy

Inhaled bronchodilators

Patients with LAM are often treated with inhaled bronchodilators because these provide a symptomatic improvement. 20-24% of patients meet standard criteria for bronchodilator responsiveness[8, 26]. There have been no studies of the efficacy of inhaled corticosteroids in LAM although some patients have been treated with these drugs, generally in combination with β-agonists. Airway inflammation in the form of bronchiolitis is observed in LAM and could be a potential target of inhaled corticosteroids although no association between bronchiolar inflammation and bronchodilator reversibility has been observed[26]. As asthma is common in the general population it is probable that some patients with LAM will also have asthma.

Conclusion

Patients with LAM are frequently prescribed and continue to take inhaled bronchodilators. One quarter of patients respond to inhaled bronchodilators according to standard objective criteria and more may obtain some clinical benefit. Patients who respond to bronchodilators tend to have airflow obstruction and have a greater rate of decline in FEV_1. Although bronchiolar inflammation is seen in some patients the efficacy of inhaled corticosteroids in LAM has not

been assessed.

Recommendation

1. Inhaled bronchodilators should be trialled in patients with airflow obstruction and continued if a response is observed. **(Grade) B (Quality) low (Benefit) substantial (Consensus) very good**

Hormone therapy - Progesterone

Progesterone treatment was initially described for LAM in 1985[131] and has been the most commonly used hormone treatment for LAM. Progesterone was being used by 55% of patients on the NHLBI LAM registry[24]. There have been no randomised controlled trials or prospective studies of progesterone for LAM. Several studies have compared progesterone treated patients with untreated patients. In one study progesterone treated patients had a lower rate of decline in TLCO and a trend towards a lower rate of decline in FEV_1 than non-treated patients. However this effect was not sustained after two years[4]. Moreover, the patients in the progesterone treated group had lower baseline FEV_1 and TLCO than the untreated patients[4]. In a larger study where age and initial lung function were allowed for in a more complex statistical model, the rate of decline in FEV_1 was more rapid in progesterone treated, than in untreated patients. Intramuscular progesterone was associated with a slower decline than oral progesterone although none of these differences was significant[30]. Other smaller studies showed no difference in progesterone treated patients than controls[11] and in a further retrospective study looking at dyspnoea as an outcome rather than lung function, progesterone treated patients had faster progression of dyspnoea than untreated patients[65].

Conclusions

There are no randomised placebo controlled trials of progesterone in LAM. There are a limited

amount of data from case series and case reports suggesting it to be effective at least in the short term in some patients. However drawing conclusions from case reports is prone to bias as positive outcomes are more likely to be reported than harmful or ineffective treatments. Attempts to formally examine the effect of progesterone are also limited by selection bias since more rapidly declining patients are treated with progesterone. Such studies have shown either no effect or worsening of lung function or dyspnoea in the progesterone treated patients and in one case a non-sustained reduction in rate of decline in TLCO.

Recommendations

1. Oral or intramuscular progesterone should not be used routinely in patients with LAM. (**Grade) I (Quality) low (Benefit) conflicting (Consensus) very good**
2. In patients with rapid decline in lung function or symptoms, intramuscular progesterone may be trialled. **(Grade) C (Quality) low (Benefit) small / weak (Consensus) very good**
3. If used, progesterone may be given for 12 months with clinical evaluation and lung function at 3 monthly intervals. If lung function and symptoms continue to decline at the same rate on progesterone treatment after one year, progesterone should be withdrawn. **(Grade) expert opinion / C (Quality) expert opinion (Benefit) small / weak (Consensus) very good**

Hormone therapy - other anti-oestrogen interventions

Various anti-oestrogen strategies have been used to treat LAM. Treatments other than progesterone have largely been used as second line treatment or in combination with progesterone and cannot be formally analysed. Case reports have described the use of oophorectomy[132-136], tamoxifen[137-140] and GnRH agonists[141-143] all with varying outcomes. These reports are difficult to evaluate as the patients are a heterogeneous group with

different rates of disease progression and periods of decline and stabilisation. In addition, many of the interventions have been used in combination with other treatments, at a range of doses and durations. Finally, as previously stated, case reports are much more likely to report favourable rather than unfavourable outcomes leading to bias. In an attempt to avoid case reporting bias the following data comprises only the effect of these interventions in unselected patients from registries: seven received oophorectomy alone, two stabilised, one improved; tamoxifen stabilised disease in five of fourteen patients but has exacerbated LAM in another report[3, 20, 25, 144]. A significant number of these patients received combinations of treatment although no combinations appeared especially effective. One recent open label study that examined 11 patients treated with the GnRH agonist triptorelin found that no patients improved and the drug was associated with a reduction in bone mineral density[145].

Conclusion

No confident data exist on the efficacy of oophorectomy, GnRH agonists or anti-oestrogens in LAM. A small number of reports suggest oophorectomy and tamoxifen may be associated with stabilisation of the disease. Due to the morbidity associated with surgical oophorectomy and a lack of clear evidence of benefit, oophorectomy cannot be recommended for LAM alone. Similar oestrogen levels as obtained after oophorectomy may be obtained with GnRH agonists although there is no evidence for their benefit in LAM.

Recommendation

1. Hormone treatments other than progesterone should not be used in patients with LAM. **(Grade) I (Quality) low (Benefit) conflicting (Consensus) very good**

mTOR inhibitors

Inherited mutations of the TSC-1 or TSC-2 genes cause TSC while acquired (somatic) mutations

of either gene are associated with sporadic LAM. Mutations of TSC-1 and TSC-2 are associated with activation of the mTOR pathway. The mTOR inhibitors sirolimus and everolimus block mTOR signalling by mTOR complex 1 and reduce mTOR-mediated proliferation and growth of LAM cells in vitro.

One prospective, uncontrolled, open-label, phase II clinical trial has shown that sirolimus reduced mean angiomyolipoma volume at 12 months by 53 +/- 27% of the baseline value ($p<0.001$) in patients with TSC or sporadic LAM. Of the 25 patients enrolled, 6 had TSC-LAM and 5 sporadic-LAM. During sirolimus therapy, the mean forced expiratory volume in one second (FEV_1) increased by 118 +/- 330 ml ($p=0.06$) and there were significant improvements in FVC and residual volume. Improvements in angiomyolipoma volume and pulmonary function were reduced in the year following treatment but not back to baseline values[14]. Interim analysis of another prospective, multicenter, phase-II open-label clinical trial in patients with TSC (7 patients) or sporadic-LAM (6 patients) showed a similar reduction in angiomyolipoma volume after 12-month therapy with sirolimus[15]. No clear improvement in lung function was observed. In both studies adverse events were common and included frequent aphthous ulcers, diarrhoea and upper respiratory infections.

As sirolimus impairs wound healing and has been associated with an increased risk of bronchial anastomotic leakage after transplantation[146] it is standard practice to withhold sirolimus prior to surgery and transplant procedures.

Conclusions

There are currently no reports from randomised placebo controlled trials of mTOR inhibitors in LAM. Two prospective open-label clinical trials suggest that sirolimus reduces angiomyolipoma volume. However, the effect on bleeding from angiomyolipomas has not been evaluated. Further, the relative risk/benefit of treatment has not been compared to that of other established treatments

of angiomyolipoma (i.e. catheter embolisation, conservative surgery). The effect of mTOR inhibitors on pulmonary function is unclear and their use is associated with frequent adverse events. mTOR inhibitors may be a future therapeutic option in patients with LAM and further studies are required.

Recommendations

1. Sirolimus should not be prescribed routinely outside clinical trials for pulmonary LAM. Patients with LAM should be encouraged to participate in clinical trials whenever possible. **(Grade) C (Quality) low (Benefit) small / weak (Consensus) very good**
2. In renal angiomyolipoma mTOR inhibitors should not be used as first-line therapy. Sirolimus may be considered on an individual basis in patients with symptomatic angiomyolipoma or LAM-related masses not amenable to embolisation or conservative surgery in experienced centres. **(Grade) C (Quality) low (Benefit) small / weak (Consensus) very good**
3. In the current context of scientific uncertainty but possible treatment benefit; sirolimus may be considered on an individual basis in patients with rapid decline in lung function or symptoms, after careful evaluation of risk/benefit ratio in an experienced centre. When sirolimus is used, the effect of therapy should be carefully monitored for tolerance and effect on lung function at 3 monthly intervals. Sirolimus should be stopped once patients are listed for active lung transplantation. **(Grade) C (Quality) low (Benefit) small / weak (Consensus) very good**

Complications and co-morbidities

Management of pneumothorax

Pneumothorax is common in LAM. Forty percent of patients present with this complication and it occurs in two thirds of patients at some point in their disease. There is a recurrence rate of around 75% of patients after first pneumothorax[10, 18]. The largest retrospective study has shown that on average patients have 3.5 pneumothoraces resulting in hospital admissions for 29 days[18]. In one study conservative treatment of pneumothorax by any of observation, aspiration, chest tube, or pleurodesis via chest tube, was associated with recurrence in two thirds of patients. Any surgical treatment including video assisted thorascopic (VATS) pleurodesis, pleural abrasion, pleurectomy, or open procedure was associated with a much lower recurrence rate[10]. In a larger series of 676 pneumothoraces in LAM, 17% were observed without intervention, 83% had either simple aspiration, chest tube or chest tube plus pleurodesis. Twenty-eight percent went on to have a surgical intervention, either mechanical pleurodesis, bullectomy or pleurectomy. In this study recurrence was again common after conservative treatment (66%) but was reduced by more than half by chemical (27%) or surgical (32%) pleurodesis ($p<0.01$). In both studies patients frequently needed more than one intervention for pneumothorax.

Pleural surgery and lung transplantation

Intra-pleural procedures causing a partially or completely fused pleural space and extensive pleural adhesions was previously considered a contraindication to lung transplantation. As experience with transplantation increased, previous intra-pleural procedures or thoracic surgery have become a relative, rather than absolute, contraindication to transplantation. However pleural surgery causing extensive adhesions increases the complexity of the operative dissection, pleural-related peri-operative bleeding and operation time[18, 100, 147, 148]. In patients with LAM and previous pleural surgery, there is an increased likelihood of re-operation for haemorrhage and bleeding related death [100, 148, 149].

Conclusions

Pneumothorax occurs in the majority of patients, results in significant hospital stays, and is frequently recurrent. Conservative treatments are associated with higher rates of recurrence than pleurodesis via chest tube or appropriate surgical interventions. Lung transplantation is feasible in patients with previous thoracic surgery or pleural procedures, although associated with increased technical difficulty in some cases and an increased risk or perioperative bleeding.

Recommendations.

1 Pneumothorax in LAM should ideally be managed jointly by a chest physician and thoracic surgeon. **(Grade) C (Quality) low (Benefit) intermediate (Consensus) very good**

2 A chemical pleurodesis may be performed at first pneumothorax. Patients who do not respond to initial therapy including pleurodesis, should undergo an appropriate surgical procedure according to their clinical condition and local expertise. **(Grade) C (Quality) low (Benefit) intermediate (Consensus) very good**

3 Patients with second pneumothorax should have an appropriate surgical procedure according to their clinical condition and local expertise. **(Grade) C (Quality) low (Benefit) intermediate (Consensus) very good**

4 When transplantation is considered patients with a history of pleurodesis or pleurectomy should be referred to transplantation centres with experience of LAM to anticipate possible pleural complications. **(Grade) C (Quality) low (Benefit) intermediate (Consensus) very good**

5 A history of pleurodesis or pleurectomy should not be considered a contraindication to lung transplantation in patients with LAM. However, patients should be informed of an increased risk of perioperative pleural bleeding **(Grade) C (Quality) low (Benefit)**

intermediate (Consensus) very good

Management of chylothorax

Chylothorax in LAM may have little impact on the patients symptoms, or cause marked dyspnoea. Various case reports and short series have reported on a range of procedures for the management of chylothorax occurring in the context of LAM. Some efficacy and clinical benefit have been reported anecdotally using various procedures, including thoracic duct ligation, thoracocentesis and talc pleurodesis[11, 20, 139, 150-155]. In the largest series to address this issue, chylothorax was seen in eight of 79 patients with LAM at a tertiary centre. Six had unilateral and two bilateral effusions. The size of the chylothorax varied and in some cases did not enlarge over time. Management ranged from thoracocentesis only, to thoracotomy with thoracic duct ligation and parietal pleurectomy. When needed, pleurodesis by instillation of sclerosing agents or parietal pleurectomy appeared to be effective in controlling chylothorax[152]. The use of pleuro-peritoneal shunts has also been reported in a small number of cases[155]. The use of fat free diet (with or without oral supplementation of medium-sized triglycerides) or fat free total parenteral nutrition has been used in anecdotal reports to minimize the volume of chyle formation[156]. In a similar manner to pneumothorax, pleural intervention for chylothorax may increase the risk of perioperative bleeding at lung transplantation.

Conclusion

Management of chylothorax in patients with LAM should be appropriate to the size and clinical impact of the effusion in individual patients. These interventions will also depend upon co-morbid factors and local expertise. In a small number of cases pleurodesis with or without thoracic duct ligation has been effective in treating symptomatic chylothorax. For small, stable effusions observation or thoracocentesis may be sufficient.

Recommendations

1. Patients with chylothorax may be placed on a fat free diet, with supplementation with mid-chain triglycerides. **(Grade) expert opinion / C (Quality) expert opinion (Benefit) small / weak (Consensus) very good**
2. For treatment of symptomatic chylous pleural effusions the decision to intervene and technique used should be performed on an individual basis, based on clinical evaluation including amount of chyle collected, recurrence of chylothorax, respiratory condition of the patient and consideration of future lung transplantation. **(Grade) expert opinion / B (Quality) expert opinion (Benefit) intermediate (Consensus) very good**

Treatment and follow up of angiomyolipoma

As angiomyolipomas are benign, nephrectomy is not required for their removal. During the course of the disease angiomyolipomas may enlarge and/or further tumours may develop. TSC is associated with other renal lesions including simple cysts and polycystic kidney disease. Renal failure occurs requiring dialysis in 0.1-1% of patients with TSC[22, 38, 39, 42-46]. Therefore preservation of functioning renal tissue is important to avoid the need for renal replacement therapy: optimal treatment of angiomyolipoma should comprise a nephron sparing approach. Currently used approaches are selective embolisation and nephron sparing surgery. Embolisation of the renal arteries has been used in both prophylactic treatment of tumours to prevent bleeding and for emergency treatment of bleeding tumours. Small case series of embolisation for angiomyolipoma show the procedure is safe and reduces tumour volume by 24-56%. The procedure has been used in elective cases[157, 158] and to treat acute renal haemorrhage[159] including during pregnancy[121]. Renal function is generally preserved and although re-bleeding may occur it is infrequent[108, 158-161]. In one study of 30 angiomyolipomas treated by

embolisation there was a 30% incidence of recurrent symptoms or increase in size (>2cm) requiring further embolisation over a mean follow up of 51 months. Recurrence was more common in patients with TSC[162]. In another series of 21 patients followed for up to 21 years tumour recurrence was infrequent[36]. Complications of embolisation include failure to occlude the blood supply and tumour liquefaction occasionally requiring drainage. Additionally, post-embolisation syndrome characterised by flank pain and fever occurs in up to 80% of those treated and may be reduced by corticosteroid treatment[163].

Nephron sparing surgery for angiomyolipoma in both elective situations and when actively bleeding has been described in a number of case reports and two case series. In one series nephron sparing surgery of 28 angiomyolipomas was performed either to prevent bleeding in large tumours (16%), to treat bleeding tumours (20%), or for diagnostic uncertainty (64%). After a mean follow up of 55 months there had been no local recurrences and no change from pre-operative serum creatinine levels although two patients developed ureteric fistula[164]. In a second retrospective study 23 patients with larger, predominantly symptomatic tumours underwent surgery without significant complications[165].

Conclusions

Although clinical experience is based entirely on data from case series, both embolisation and nephron sparing surgery have been performed safely to reduce tumour volume in angiomyolipoma without compromising renal function. However there is no agreement as to when renal angiomyolipoma may need intervention other than during, or after, an episode of haemorrhage. Embolisation has the advantage of being less invasive and not requiring general anaesthesia but it may need to be repeated and can result in post embolisation syndrome. Embolisation can also be performed for active bleeding including during pregnancy[166]. Although, for these reasons, embolisation may be favoured over surgery in patients with bleeding

angiomyolipoma, there are no trials comparing the two strategies. The decision as to which option is taken may depend upon technical factors associated with the tumour, whether the patient can tolerate general anaesthesia and local expertise. In elective cases where bleeding is not present, nephron sparing surgery may be preferred when a malignant lesion is suspected after imaging. Surgery with intra-operative frozen section biopsy may be considered with the option to perform conservative or radical surgery as appropriate; however the risk of a false diagnosis of carcinoma must be borne in mind[167]. Where possible, these decisions are best made electively after screening for angiomyolipoma or in response to symptoms rather than in the setting of an acute haemorrhage. Early detection of angiomyolipoma is therefore important in patients with LAM.

Recommendations

1. Patients should be advised to seek urgent medical attention in the presence of symptoms of bleeding angiomyolipoma. **(Grade) B (Quality) low (Benefit) substantial (Consensus) very good**
2. Embolisation should be first-line treatment for bleeding angiomyolipoma. Nephron sparing surgery is also acceptable dependent upon local expertise. **(Grade) expert opinion / B (Quality) expert opinion (Benefit) substantial (Consensus) very good**
3. Embolisation should be performed as first line therapy of angiomyolipoma in elective cases, with nephron sparing surgery indicated where a malignant lesion cannot be excluded. Technical factors associated with the tumour blood supply and local expertise should also be taken into account. **(Grade) C (Quality) low (Benefit) intermediate (Consensus) very good**

When is treatment of angiomyolipoma indicated in asymptomatic patients?

The natural history of angiomyolipoma in LAM and TSC has mainly been reported in two series

comprising a total of 58 patients[107, 168]. Indicators of the risk of bleeding are tumour size[36, 107] and the presence of aneurysms[168]. Aneurysm formation appears to be related to tumour size and larger aneurysms confer a higher probability of rupture. Aneurysms are not well visualised by CT and renal angiography is required although this is not routinely performed. Tumour size was larger than 4 cm and aneurysms were 5 mm or larger in all hemorrhagic lesions[168]. Patients with TSC and angiomyolipomas had a higher incidence of bilateral renal involvement, larger tumours that were more likely to grow and more frequently required surgery[107]. In addition, angiomyolipomas almost exclusively composed of fat are less likely to bleed, whereas those with rapid growth are more likely to bleed. Patients with larger tumours contemplating pregnancy or undergoing lung transplantation may also have increased bleeding risk.

Conclusions

The risk of bleeding of angiomyolipoma is linked to tumour size and is clinically appreciable in tumours 4 cm in diameter or larger and where aneurysms 5 mm or larger are present.

Recommendations

1 Asymptomatic renal angiomyolipoma under 4 cm should not be treated, but should be followed by yearly ultrasound unless symptoms occur. Where ultrasound measurements are unreliable due to technical factors, CT or MRI should be performed. **(Grade) B (Quality) low (Benefit) substantial (Consensus) very good**

2 Renal angiomyolipomas greater than 4 cm or with renal aneurysms greater than 5 mm in diameter are at an increased risk of bleeding, and should be followed by ultrasound imaging twice yearly to evaluate growth. Treatment by embolisation or nephron sparing surgery should be considered. **(Grade) expert opinion / A (Quality) expert opinion (Benefit) substantial (Consensus) very good**

Lung transplantation for LAM

LAM accounts for 1.1% of lung transplant recipients in the International Registry of Heart and Lung transplantation[169]. Overall survival varies according to the cohort described, although there have been no significant differences in early or late mortality, length of intensive care unit or hospital stay or overall survival in LAM patients compared to patients transplanted for other indications[100, 148, 170, 171]. In a recent survey the actuarial survival of lung transplantation for LAM was 86% at 1 year, 76% at 3 years, and 65% at 5-years[171].

Referral criteria for lung transplantation

Due to the small number of patients treated, coupled with the variable rates of fall in lung function in LAM mean firm recommendations are difficult to make. As discussed, factors predicting the rate of decline have not been studied prospectively[3, 25, 26, 57, 100, 149]. As a result transplant decisions are generally made after serial observation of clinical and physiological parameters. In a recent survey of patients undergoing transplantation for LAM, most had severe airway obstruction and were transplanted with a mean FEV_1 of around 25% and DLCO of 27% predicted. About 15% had a combined restrictive-obstructive pattern. In the published series of transplanted patients with LAM, differences in mortality and morbidity between younger and older women were not examined and there is no evidence that the age at transplantation affects the postoperative outcome. The oldest patient reported was 65 years[171]. The upper age limit is dependent on the transplantation policy of the country.

Conclusions

Until better prognostic indicators are found to predict the clinical course of LAM, patients should be considered for lung transplantation when they reach NYHA functional class III or IV with

severe impairment in lung function and exercise capacity (VO_2 max <50% predicted, hypoxaemia at rest). The upper age limit for transplantation in patients with LAM will depend upon the patients' wishes, co-morbidities and local access to transplantation. However transplantation above 65 years may only exceptionally be considered.

Recommendation

1. Patients should be considered for lung transplantation when they reach NYHA functional class III or IV with hypoxemia at rest, severe impairment in lung function and exercise capacity (VO_2 max<50% predicted). **(Grade) A (Quality) fair (Benefit) substantial (Consensus) very good**

Which type of transplantation is indicated in LAM ?

Single, bilateral lung and more rarely, heart-lung transplantation have been performed successfully for LAM. In the International Society of Heart and Lung Transplantation registry report (2006), 54 single and 88 bilateral lung transplants had been performed for LAM with the type of procedure depending on the surgical team and the country[171, 172]. The type of transplant did not affect survival in the largest patient cohort[171]. Bilateral lung transplant has been favoured over single lung transplant for LAM due to LAM-related complications in the native lung after single lung transplant including recurrent pneumothorax, over inflation leading to compression of the graft[100, 171, 173] and the theoretical risk of recurrence of host origin to spread from the remaining native lung[148, 171, 173]. In addition, lung function was better in double lung transplant recipients[100, 111],[173] although no differences were found in subjective measures of function between single and double lung recipients[111]. Living donor lobar lung transplantation has been applied to patients with various end-stage lung diseases, with only a small number of case reports in LAM[174].

Conclusions

No significant difference in survival with single and bilateral lung transplant has been seen, although bilateral lung transplant is associated with better post transplant lung function and probably a reduction in LAM related complications.

Recommendations

1. The choice of single lung transplant or bilateral lung transplant in LAM should be determined by surgical technical factors and organ availability. **(Grade) B (Quality) fair (Benefit) intermediate (Consensus) very good**

Special considerations related to lung transplantation for patients with TSC

Patients with TSC have received successful lung transplantation for severe LAM. From two recent series nearly 10% of the transplanted patients had TSC-LAM[173, 175]. Although no TSC specific problems have been identified, no systematic studies examining the outcome of transplantation in this group of patients have been performed. Clearly patients with TSC-LAM are likely to have more co-morbidities than those with sporadic LAM. Almost all patients with TSC-LAM have co-existent angiomyolipoma, which may be bilateral, and many have epilepsy or learning difficulties. The impact of these processes and their treatment require careful pre-transplant evaluation.

Recommendations.

1. Patients with TSC in the context of LAM should not be precluded from lung transplantation by TSC alone. Some patients may have TSC related medical or cognitive problems which preclude transplantation. **(Grade) B (Quality) low (Benefit) substantial (Consensus) very good**
2. TSC-LAM patients should have careful multi-disciplinary assessment when being

evaluated for lung transplantation. **(Grade) B (Quality) low (Benefit) substantial (Consensus) very good**

Does the presence of an angiomyolipoma affect lung transplant suitability ?

Angiomyolipoma in patients with sporadic LAM are generally small, have a low rate of growth and do not affect renal function. In those with TSC-LAM, angiomyolipoma are almost always present, and are more likely to be large, bilateral and multiple[40]. Detection of renal angiomyolipoma in LAM is important preoperatively, as the risk of bleeding associated with a large angiomyolipoma is well established. In two recent series, renal angiomyolipoma were detected in 35-38% of LAM patients during pre-transplant assessment[149, 173]. In one series 4/13 patients had complications related to renal angiomyolipoma, including retroperitoneal haemorrhage (requiring nephrectomy in 2), renal colic and renal failure. There was no difference in the incidence of post-transplant renal insufficiency in those with angiomyolipoma over those transplanted without angiomyolipoma. The major risk factor for renal impairment in all series was the use of calcineurin inhibitors[149, 173].

Recommendation

1. Angiomyolipoma may not be a contra-indication to lung transplantation but may affect transplant suitability, surgery and postoperative follow up. **(Grade) B (Quality) low (Benefit) substantial (Consensus) very good**
2. The presence of renal angiomyolipoma should be sought in the preoperative assessment, and those at risk of bleeding should be treated prior to transplantation. **(Grade) B (Quality) low (Benefit) substantial (Consensus) very good**

Should the possibility of recurrent LAM in the graft be investigated post transplant?

LAM can recur in the allograft of both single and bilateral lung transplant. However, this is a rare

event and generally asymptomatic. Recurrent LAM has been identified at post mortem examination or in biopsies performed for other purposes. Recurrent LAM does not seem to affect survival post transplantation[100, 148, 171, 176-178].

Recommendation

1. Routine investigation for recurrent LAM post transplantation with biopsy should not be performed. **(Grade) D (Quality) low (Benefit) negative (Consensus) very good**

Post transplant immunosuppression regimen for LAM

There have been no studies of post transplant regimens for patients with LAM. The same immunosuppressive regimen has been given as for other indications[148, 170, 173, 179]. In one study 50% of patients received induction therapy followed by maintenance immunosuppression consisting of conventional triple therapy (calcineurin inhibitor / metabolite antagonist / prednisolone). None received an mTOR inhibitor. The morbidity resulting from long-term immunosuppression was similar for LAM and non-LAM recipients[148].

Recommendation

1. Post-transplant regimen for patients with LAM should be the same as for other indications. **(Grade) C (Quality) low (Benefit) intermediate (Consensus) very good**

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REFERENCES

1. Johnson S. Rare diseases. 1. Lymphangioleiomyomatosis: clinical features, management and basic mechanisms. *Thorax* 1999: 54(3): 254-264.
2. Franz DN, Brody A, Meyer C, Leonard J, Chuck G, Dabora S, Sethuraman G, Colby TV, Kwiatkowski DJ, McCormack FX. 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(4): 661-668.
3. Urban T, Lazor R, Lacronique J, Murris M, Labrune S, Valeyre D, Cordier JF. 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(5): 321-337.
4. Johnson SR, Tattersfield AE. Decline in lung function in lymphangioleiomyomatosis: relation to menopause and progesterone treatment. *Am J Respir Crit Care Med* 1999: 160(2): 628-633.
5. Aubry MC, Myers JL, Ryu JH, Henske EP, Logginidou H, Jalal SM, Tazelaar HD. Pulmonary lymphangioleiomyomatosis in a man. *Am J Respir Crit Care Med* 2000: 162(2 Pt 1): 749-752.
6. Schiavina M, Di Scioscio V, Contini P, Cavazza A, Fabiani A, Barberis M, Bini A, Altimari A, Cooke RM, Grigioni WF, D'Errico-Grigioni A. Pulmonary Lymphangioleiomyomatosis in a Karyotypically Normal Man Without Tuberous Sclerosis Complex. *Am J Respir Crit Care Med* 2007: 200610-201408CR.
7. Avila NA, Kelly JA, Chu SC, Dwyer AJ, Moss J. Lymphangioleiomyomatosis: abdominopelvic CT and US findings. *Radiology* 2000: 216(1): 147-153.
8. Chu SC, Horiba K, Usuki J, Avila NA, Chen CC, Travis WD, Ferrans VJ, Moss J. Comprehensive evaluation of 35 patients with lymphangioleiomyomatosis. *Chest* 1999: 115(4): 1041-1052.
9. Moss J, DeCastro R, Patronas NJ, Taveira-DaSilva A. Meningiomas in Lymphangioleiomyomatosis. *JAMA* 2001: 286(15): 1879-1881.
10. Johnson SR, Tattersfield AE. Clinical experience of lymphangioleiomyomatosis in the UK. *Thorax* 2000: 55(12): 1052-1057.
11. Ryu JH, Doerr CH, Fisher SD, Olson EJ, Sahn SA. Chylothorax in Lymphangioleiomyomatosis. *Chest* 2003: 123(2): 623-627.
12. Goncharova EA, Goncharov DA, Eszterhas A, Hunter DS, Glassberg MK, Yeung RS, Walker CL, Noonan D, Kwiatkowski DJ, Chou MM, Panettieri RA, Jr., Krymskaya VP. 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(34): 30958-30967.
13. Kenerson H, Folpe AL, Takayama TK, Yeung RS. Activation of the mTOR pathway in sporadic angiomyolipomas and other perivascular epithelioid cell neoplasms. *Human Pathology* 2007: 38: 1361-1371.
14. Bissler JJ, McCormack FX, Young LR, Elwing JM, Chuck G, Leonard JM, Schmithorst VJ, Laor T, Brody AS, Bean J, Salisbury S, Franz DN. Sirolimus for Angiomyolipoma in Tuberous Sclerosis Complex or Lymphangioleiomyomatosis. *N Engl J Med* 2008: 358(2): 140-151.

15. Davies DM, Johnson SR, Tattersfield AE, Kingswood JC, Cox JA, McCartney DL, Doyle T, Elmslie F, Saggar A, de Vries PJ, Sampson JR. Sirolimus Therapy in Tuberous Sclerosis or Sporadic Lymphangioleiomyomatosis. *N Engl J Med* 2008: 358(2): 200-203.
16. McCrory DC, Lewis SZ. Methodology and Grading for Pulmonary Hypertension Evidence Review and Guideline Development. *Chest* 2004: 126(1_suppl): 11S-13.
17. Baumann MH, Strange C, Heffner JE, Light R, Kirby TJ, Klein J, Luketich JD, Panacek EA, Sahn SA. Management of Spontaneous Pneumothorax : An American College of Chest Physicians Delphi Consensus Statement. *Chest* 2001: 119(2): 590-602.
18. Almoosa KF, Ryu JH, Mendez J, Huggins JT, Young LR, Sullivan EJ, Maurer J, McCormack FX, Sahn SA. Management of Pneumothorax in Lymphangioleiomyomatosis: Effects on Recurrence and Lung Transplantation Complications. *Chest* 2006: 129(5): 1274-1281.
19. Corrin B, Liebow AA, Friedman PJ. Pulmonary lymphangioleiomyomatosis. *American Journal of Pathology* 1975: 79: 348-382.
20. Taylor JR, Ryu J, Colby TV, Raffin TA. Lymphangioleiomyomatosis. Clinical course in 32 patients. *N Engl J Med* 1990: 323(18): 1254-1260.
21. Kitaichi M, Izumi T. Lymphangioleiomyomatosis. *Curr Opin Pulm Med* 1995: 1(5): 417-424.
22. 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(6 Pt 1): 2138-2143.
23. Maziak DE, Kesten S, Rappaport DC, Maurer J. Extrathoracic angiomyolipomas in lymphangioleiomyomatosis. *Eur Respir J* 1996: 9(3): 402-405.
24. Ryu JH, Moss J, Beck GJ, Lee J-C, Brown KK, Chapman JT, Finlay GA, Olson EJ, Ruoss SJ, Maurer JR, Raffin TA, Peavy HH, McCarthy K, Taveira-DaSilva A, McCormack FX, Avila NA, DeCastro RM, Jacobs SS, Stylianou M, Fanburg BL, for the NHLBI LAM Registry Group. The NHLBI Lymphangioleiomyomatosis Registry: Characteristics of 230 Patients at Enrollment. *Am J Respir Crit Care Med* 2006: 173(1): 105-111.
25. 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(2 Pt 1): 527-533.
26. Taveira-DaSilva AM, Hedin C, Stylianou MP, Travis WD, Matsui K, Ferrans VJ, Moss J. Reversible Airflow Obstruction, Proliferation of Abnormal Smooth Muscle Cells, and Impairment of Gas Exchange as Predictors of Outcome in Lymphangioleiomyomatosis. *Am J Respir Crit Care Med* 2001: 164(6): 1072-1076.
27. Avila NA, Chen CC, Chu SC, Wu M, Jones EC, Neumann RD, Moss J. Pulmonary lymphangioleiomyomatosis: correlation of ventilation-perfusion scintigraphy, chest radiography, and CT with pulmonary function tests. *Radiology* 2000: 214(2): 441-446.
28. Taveira-DaSilva AM, Stylianou MP, Hedin CJ, Kristof AS, Avila NA, Rabel A, Travis WD, Moss J. Maximal Oxygen Uptake and Severity of Disease in Lymphangioleiomyomatosis. *Am J Respir Crit Care Med* 2003: 168(12): 1427-1431.
29. Lazor R, Valeyre D, Lacronique J, Wallaert B, Urban T, Cordier JF. Low initial KCO predicts rapid FEV1 decline in pulmonary lymphangioleiomyomatosis. *Respir Med* 2004: 98(6): 536-541.
30. 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(6): 1867-1874.

31. Matsui K, Tatsuguchi A, Valencia J, Yu Z, Bechtle J, Beasley MB, Avila N, Travis WD, Moss J, Ferrans VJ. Extrapulmonary lymphangioleiomyomatosis (LAM): clinicopathologic features in 22 cases. *Hum Pathol* 2000: 31(10): 1242-1248.
32. Avila NA, Bechtle J, Dwyer AJ, Ferrans VJ, Moss J. Lymphangioleiomyomatosis: CT of Diurnal Variation of Lymphangioleiomyomas. *Radiology* 2001: 221(2): 415-421.
33. Matsui K, Tatsuguchi A, Valencia J, Yu Z, Bechtle J, Beasley MB, Avila N, Travis WD, Moss J, Ferrans VJ. Extrapulmonary lymphangioleiomyomatosis (LAM): clinicopathologic features in 22 cases. [Review] [21 refs]. *Human Pathology* 2000: 31(10): 1242-1248.
34. Peh WC, Law S, Fok M, Ngan H. Case report: lymphangiomyomatosis with spontaneous peritoneal rupture. *Br J Radiol* 1994: 67(798): 605-608.
35. Gray S, Carrington C, Cornog J. Lymphangiomyomatosis: report of a case with ureteral involvement and chyluria. *Cancer* 1975: 35: 490-498.
36. van Baal JG, Smits NJ, Keeman JN, Lindhout D, Verhoef S. The evolution of renal angiomyolipomas in patients with tuberous sclerosis.[comment]. *Journal of Urology* 1994: 152(1): 35-38.
37. Roach ES, DiMario FJ, Kandt RS, Northrup H. Tuberous Sclerosis Consensus Conference: recommendations for diagnostic evaluation. National Tuberous Sclerosis Association. *Journal of Child Neurology* 1999: 14(6): 401-407.
38. Ewalt DH, Sheffield E, Sparagana SP, Delgado MR, Roach ES. Renal lesion growth in children with tuberous sclerosis complex. *Journal of Urology* 1998: 160(1): 141-145.
39. O'Callaghan FJ, Noakes MJ, Martyn CN, Osborne JP. An epidemiological study of renal pathology in tuberous sclerosis complex. *BJU International* 2004: 94(6): 853-857.
40. Rakowski SK, Winterkorn EB, Paul E, Steele DJ, Halpern EF, Thiele EA. Renal manifestations of tuberous sclerosis complex: Incidence, prognosis, and predictive factors. *Kidney International* 2006: 70(10): 1777-1782.
41. Lemaitre L, Robert Y, Dubrulle F, Claudon M, Duhamel A, Danjou P, Mazeman E. Renal angiomyolipoma: growth followed up with CT and/or US. *Radiology* 1995: 197(3): 598-602.
42. Clarke A, Hancock E, Kingswood C, Osborne JP. End-stage renal failure in adults with the tuberous sclerosis complex. *Nephrology, Dialysis, Transplantation* 1999: 14(4): 988-991.
43. Schillinger F, Montagnac R. Chronic renal failure and its treatment in tuberous sclerosis. *Nephrology, Dialysis, Transplantation* 1996: 11(3): 481-485.
44. Kida Y, Yamaguchi K, Suzuki H, Kanda E, Ando M, Ohashi K, Funata N, Saito H. Tuberous sclerosis, associated with renal cell carcinoma and angiomyolipoma, in a patient who developed endstage renal failure after nephrectomy. *Clinical & Experimental Nephrology* 2005: 9(2): 179-182.
45. Sampson JR, Maheshwar MM, Aspinwall R, Thompson P, Cheadle JP, Ravine D, Roy S, Haan E, Bernstein J, Harris PC. Renal cystic disease in tuberous sclerosis: role of the polycystic kidney disease 1 gene. *American Journal of Human Genetics* 1997: 61(4): 843-851.
46. Torres VE, Zincke H, King BK, Bjornsson J. Renal manifestations of tuberous sclerosis complex. *Contributions to Nephrology* 1997: 122: 64-75.
47. Cagnano M, Benharroch D, Geffen DB. Pulmonary lymphangioleiomyomatosis. Report of a case with associated multiple soft-tissue tumors. *Arch Pathol Lab Med* 1991: 115(12): 1257-1259.

48. Cottin V, Vukusic S, Jouanneau E, Lazor R, Cordier J-F. Should patients with lymphangioleiomyomatosis undergo screening for meningioma? *Eur Respir J* 2004: 24(5): 888-889.
49. Pozzati E, Zucchelli M, Schiavina M, Contini P, Foschini M. Rapid growth and regression of intracranial meningiomas in lymphangioleiomyomatosis:case report. . *Surg Neurol* 2007: 68: 671-674.
50. Franz DN, Moss J, DeCastro R, Taveira-DaSilva A, Patronas NJ. Meningiomas in Women With Lymphangioleiomyomatosis. *JAMA %R 101001/jama287111397* 2002: 287(11): 1397-1398.
51. Costello LC, Hartman TE, Ryu JH. High frequency of pulmonary lymphangioleiomyomatosis in women with tuberous sclerosis complex. *Mayo Clin Proc* 2000: 75(6): 591-594.
52. Moss J, Avila NA, Barnes PM, Litzenberger RA, Bechtle J, Brooks PG, Hedin CJ, Hunsberger S, Kristof AS. Prevalence and clinical characteristics of lymphangioleiomyomatosis (LAM) in patients with tuberous sclerosis complex. *Am J Respir Crit Care Med* 2001: 164(4): 669-671.
53. Castro M, Shepherd CW, Gomez MR, Lie JT, Ryu JH. Pulmonary tuberous sclerosis. *Chest* 1995: 107(1): 189-195.
54. Avila NA, Dwyer AJ, Rabel A, Moss J. Sporadic Lymphangioleiomyomatosis and Tuberous Sclerosis Complex with Lymphangioleiomyomatosis: Comparison of CT Features. *Radiology* 2006: 2421051767.
55. Roach ES, Sparagana SP. Diagnosis of tuberous sclerosis complex. *J Child Neurol* 2004: 19: 643-649.
56. Carrington CB, Cugell DW, Gaensler EA, Marks A, Redding RA, Schaaf JT, Tomasian A. Lymphangioleiomyomatosis. Physiologic-pathologic-radiologic correlations. *Am Rev Respir Dis* 1977: 116(6): 977-995.
57. Matsui K, Beasley MB, Nelson WK, Barnes PM, Bechtle J, Falk R, Ferrans VJ, Moss J, Travis WD. Prognostic significance of pulmonary lymphangioleiomyomatosis histologic score. *Am J Surg Pathol* 2001: 25(4): 479-484.
58. Corrin B, Liebow A, Friedman P. Pulmonary lymphangiomyomatosis. A review. *Am J Pathol* 1975: 79: 348-382.
59. Sullivan EJ. Lymphangioleiomyomatosis: a review. *Chest* 1998: 114(6): 1689-1703.
60. Pea M, Bonetti F, Zamboni G, Martignoni G, Riva M, Colombari R, Mombello A, Bonzanini M, Scarpa A, Ghimenton C, Donati LF. Melanocyte-marker-HMB-45 is regularly expressed in angiomyolipoma of the kidney. *Pathology* 1991: 23(3): 185-188.
61. Bonetti F, Chiodera PL, Pea M, Martignoni G, Bosi F, Zamboni G, Mariuzzi GM. Transbronchial biopsy in lymphangiomyomatosis of the lung. HMB45 for diagnosis. *Am J Surg Pathol* 1993: 17(11): 1092-1102.
62. 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 U S A* 2000: 97(11): 6085-6090.
63. Sato T, Seyama K, Fujii H, Maruyama H, Setoguchi Y, Iwakami S, Fukuchi Y, Hino O. Mutation analysis of the TSC1 and TSC2 genes in Japanese patients with pulmonary lymphangioleiomyomatosis. *Journal of Human Genetics* 2002: 47(1): 20-28.
64. Seyama K, Kumasaka T, Souma S, Sato T, Kurihara M, Mitani K, Tominaga S, Fukuchi Y. Vascular Endothelial Growth Factor-D Is Increased in Serum of Patients with Lymphangioleiomyomatosis. *Lymphatic Research and Biology* 2006: 4(3): 143-152.

65. Johnson SR, Whale CI, Hubbard RB, Lewis SA, Tattersfield AE. Survival and disease progression in UK patients with lymphangioleiomyomatosis. *Thorax* 2004: 59(9): 800-803.
66. Krymskaya VP. Smooth muscle like cells in pulmonary lymphangioleiomyomatosis. *Proc Am Thorac Soc* 2008: 5(1): 119-126.
67. Zhe X, Schuger L. Combined smooth muscle and melanocytic differentiation in lymphangioleiomyomatosis. *J Histochem Cytochem* 2004: 52(12): 1537-1542.
68. 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(3): 327-336.
69. Matsui K, Takeda K, Yu ZX, Valencia J, Travis WD, Moss J, Ferrans VJ. 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(3 Pt 1): 1002-1009.
70. Glassberg MK, Elliot SJ, Fritz J, Catanuto P, Potier M, Donahue R, Stetler-Stevenson W, Karl M. Activation of the Estrogen Receptor contributes to the Progression of Pulmonary Lymphangioleiomyomatosis via MMP-induced Cell Invasiveness. *J Clin Endocrinol Metab* 2008.
71. Glasser SW, Detmer EA, Ikegami M, Na CL, Stahlman MT, Whitsett JA. Pneumonitis and emphysema in sp-C gene targeted mice. *J Biol Chem* 2003: 278(16): 14291-14298.
72. Flaherty KR, Travis WD, Colby TV, Toews GB, Kazerooni EA, Gross BH, Jain A, Strawderman RL, Flint A, Lynch JP, Martinez FJ. Histopathologic variability in usual and nonspecific interstitial pneumonias. *Am J Respir Crit Care Med* 2001: 164(9): 1722-1727.
73. Itoh T, Mochizuki M, Kumazaki S, Ishihara T, Fukayama M. Cystic pulmonary metastases of endometrial stromal sarcoma of the uterus, mimicking lymphangiomyomatosis: a case report with immunohistochemistry of HMB45. *Pathol Int* 1997: 47(10): 725-729.
74. Tazelaar HD, Kerr D, Yousem SA, Saldana MJ, Langston C, Colby TV. Diffuse pulmonary lymphangiomatosis. *Hum Pathol* 1993: 24(12): 1313-1322.
75. Moller G, Priemel M, Amling M, Werner M, Kuhlmey AS, Delling G. The Gorham-Stout syndrome (Gorham's massive osteolysis). A report of six cases with histopathological findings. *J Bone Joint Surg Br* 1999: 81(3): 501-506.
76. Lenoir S, Grenier P, Brauner MW, Frija J, Remy-Jardin M, Revel D, Cordier JF. Pulmonary lymphangiomyomatosis and tuberous sclerosis: comparison of radiographic and thin-section CT findings. *Radiology* 1990: 175(2): 329-334.
77. Muller NL, Chiles C, Kullnig P. Pulmonary lymphangiomyomatosis: correlation of CT with radiographic and functional findings. *Radiology* 1990: 175(2): 335-339.
78. Worthy SA, Brown MJ, Muller NL. Technical report: Cystic air spaces in the lung: change in size on expiratory high-resolution CT in 23 patients. *Clin Radiol* 1998: 53(7): 515-519.
79. Abbott GF, Rosado-de-Christenson ML, Frazier AA, Franks TJ, Pugatch RD, Galvin JR. From the Archives of the AFIP: Lymphangioleiomyomatosis: Radiologic-Pathologic Correlation. *Radiographics* 2005: 25(3): 803-828.
80. Kirchner J, Stein A, Viel K, Dietrich CF, Thalhammer A, Schneider M, Jacobi V. Pulmonary lymphangioleiomyomatosis: high-resolution CT findings. *Eur Radiol* 1999: 9(1): 49-54.
81. Keyzer C, Bankier AA, Remmelinck M, Gevenois PA. Pulmonary lymphangiomyomatosis mimicking Langerhans cell histiocytosis. *J Thorac Imaging* 2001: 16(3): 185-187.
82. Brauner MW, Grenier P, Tijani K, Battesti JP, Valeyre D. Pulmonary Langerhans cell histiocytosis: evolution of lesions on CT scans. *Radiology* 1997: 204(2): 497-502.

83. Abbott GF, Rosado-de-Christenson ML, Frazier AA, Franks TJ, Pugatch RD, Galvin JR. From the archives of the AFIP: lymphangioleiomyomatosis: radiologic-pathologic correlation. *Radiographics* 2005: 25(3): 803-828.
84. Toro JR, Pautler SE, Stewart L, Glenn GM, Weinreich M, Toure O, Wei M-H, Schmidt LS, Davis L, Zbar B, Choyke P, Steinberg SM, Nguyen DM, Linehan WM. Lung Cysts, Spontaneous Pneumothorax, and Genetic Associations in 89 Families with Birt-Hogg-Dube Syndrome. *Am J Respir Crit Care Med* 2007: 175(10): 1044-1053.
85. Graham RB, Nolasco M, Peterlin B, Garcia CK. Nonsense Mutations in Folliculin Presenting as Isolated Familial Spontaneous Pneumothorax in Adults. *Am J Respir Crit Care Med* 2005: 172(1): 39-44.
86. Painter J, Tapanainenb H, Somer M, Tukiainen P, Aittomäki K. A 4-bp Deletion in the Birt-Hogg-Dubé Gene (FLCN) Causes Dominantly Inherited Spontaneous Pneumothorax. *The American Journal of Human Genetics* 2005: 76(3): 522-527.
87. Franquet T, Lee KS, Muller NL. Thin-section CT findings in 32 immunocompromised patients with cytomegalovirus pneumonia who do not have AIDS. *AJR Am J Roentgenol* 2003: 181(4): 1059-1063.
88. Johkoh T, Muller NL, Colby TV, Ichikado K, Taniguchi H, Kondoh Y, Fujimoto K, Kinoshita M, Arakawa H, Yamada H, Suga M, Ando M, Koyama M, Nakamura H. Nonspecific Interstitial Pneumonia: Correlation between Thin-Section CT Findings and Pathologic Subgroups in 55 Patients. *Radiology %R 101148/radiol2251011555* 2002: 225(1): 199-204.
89. Ohdama S, Akagawa S, Matsubara O, Yoshizawa Y. Primary diffuse alveolar septal amyloidosis with multiple cysts and calcification. *Eur Respir J* 1996: 9(7): 1569-1571.
90. Colombat M, Stern M, Groussard O, Droz D, Brauner M, Valeyre D, Mal H, Taille C, Monnet I, Fournier M, Herson S, Danel C. Pulmonary Cystic Disorder Related to Light Chain Deposition Disease. *Am J Respir Crit Care Med* 2006: 173(7): 777-780.
91. Sharma BK, Talukdar B, Kapoor R. Cystic lung in Marfan's syndrome. *Thorax* 1989: 44(11): 978-979.
92. Chadwick SL, Corrin B, Hansell DM, Geddes DM. Fatal haemorrhage from mesenchymal cystic hamartoma of the lung. *Eur Respir J* 1995: 8(12): 2182-2184.
93. Zompatori M, Poletti V, Battista G, Schiavina M, Fadda E, Tetta C. Diffuse cystic lung disease in the adult patient. *Radiol Med (Torino)* 2000: 99(1-2): 12-21.
94. Helenon O, Merran S, Paraf F, Melki P, Correas JM, Chretien Y, Moreau JF. Unusual fat-containing tumors of the kidney: a diagnostic dilemma. *Radiographics* 1997: 17(1): 129-144.
95. Shepherd CW, Gomez MR, Lie JT, Crowson CS. Causes of death in patients with tuberous sclerosis. *Mayo Clinic proceedings* 1991: 66: 792-796.
96. Bissler J, Kingswood J. Renal angiomyolipomata. *Kidney International* 2004: 66(3): 924-934.
97. Bjornsson J, Short MP, Kwiatkowski DJ, Henske EP. Tuberous sclerosis-associated renal cell carcinoma. Clinical, pathological, and genetic features. *American Journal of Pathology* 1996: 149(4): 1201-1208.
98. Clarke A, Webb D, Osborne JP. Re: Early presentation of tuberous sclerosis as bilateral renal cysts. *Journal of Urology* 1995: 153(1): 161.
99. Burger CD, Hyatt RE, Staats BA. Pulmonary mechanics in lymphangioleiomyomatosis. *Am Rev Respir Dis* 1991: 143(5 Pt 1): 1030-1033.

100. Boehler A, Speich R, Russi EW, Weder W. Lung transplantation for lymphangioleiomyomatosis. *N Engl J Med* 1996: 335(17): 1275-1280.
101. ATS Statement: Guidelines for the Six-Minute Walk Test. *Am J Respir Crit Care Med* 2002: 166(1): 111-117.
102. Kim NR, Chung MP, Park CK, Lee KS, Han J. Pulmonary lymphangioleiomyomatosis and multiple hepatic angiomyolipomas in a man. *Pathology International* 2003: 53(4): 231-235.
103. L'Hostis H, Deminiere C, Ferriere JM, Coindre JM. Renal angiomyolipoma: a clinicopathologic, immunohistochemical, and follow-up study of 46 cases. *American Journal of Surgical Pathology* 1999: 23(9): 1011-1020.
104. Casper KA, Donnelly LF, Chen B, Bissler JJ. Tuberous sclerosis complex: renal imaging findings. *Radiology* 2002: 225(2): 451-456.
105. Weiner DM, Ewalt DH, Roach ES, Hensle TW. The tuberous sclerosis complex: a comprehensive review. *Journal of the American College of Surgeons* 1998: 187(5): 548-561.
106. Nelson CP, Sanda MG. Contemporary diagnosis and management of renal angiomyolipoma. *Journal of Urology* 2002: 168(4 Pt 1): 1315-1325.
107. Steiner MS, Goldman SM, Fishman EK, Marshall FF. The natural history of renal angiomyolipoma. *Journal of Urology* 1993: 150(6): 1782-1786.
108. Kennelly MJ, Grossman HB, Cho KJ. Outcome analysis of 42 cases of renal angiomyolipoma.[comment]. *Journal of Urology* 1994: 152(6 Pt 1): 1988-1991.
109. Dickinson M, Ruckle H, Beaghler M, Hadley HR. Renal angiomyolipoma: optimal treatment based on size and symptoms. *Clinical Nephrology* 1998: 49(5): 281-286.
110. Silverstein EF, Ellis K, Wolff M, Jaretzki A, 3rd. Pulmonary lymphangiomyomatosis. *American Journal of Roentgenology, Radium Therapy & Nuclear Medicine* 1974: 120(4): 832-850.
111. Cohen MM, Pollock-BarZiv S, Johnson SR. Emerging clinical picture of lymphangioleiomyomatosis. *Thorax* 2005: 60(10): 875-879.
112. Fujimoto M, Ohara N, Sasaki H, Funakoshi T, Morita H, Deguchi M, Maruo T. Pregnancy complicated with pulmonary lymphangioleiomyomatosis: case report. *Clinical & Experimental Obstetrics & Gynecology* 2005: 32(3): 199-200.
113. Brunelli A, Catalini G, Fianchini A. Pregnancy exacerbating unsuspected mediastinal lymphangioleiomyomatosis and chylothorax. *Int J Gynaecol Obstet* 1996: 52(3): 289-290.
114. McLoughlin L, Thomas G, Hasan K. Pregnancy and lymphangioleiomyomatosis: anaesthetic management. *International Journal of Obstetric Anesthesia* 2003: 12(1): 40-44.
115. Yockey CC, Riepe RE, Ryan K. Pulmonary lymphangioleiomyomatosis complicated by pregnancy. *Kans Med* 1986: 87(10): 277-278, 293.
116. Warren SE, Lee D, Martin V, Messink W. Pulmonary lymphangiomyomatosis causing bilateral pneumothorax during pregnancy. *Annals of Thoracic Surgery* 1000: 55(4): 998-1000.
117. Cohen M, Freyer A, Johnson S. Pregnancy experiences among women with lymphangioleiomyomatosis. *Respiratory Medicine* 2008: In press.
118. Mitchell AL, Parisi MA, Sybert VP. Effects of pregnancy on the renal and pulmonary manifestations in women with tuberous sclerosis complex. *Genetics in Medicine* 2003: 5(3): 154-160.
119. Raft J, Lalot JM, Meistelman C, Longrois D. [Renal angiomyolipoma rupture during pregnancy]. [French]. *Gynecologie, Obstetrique & Fertilite* 2006: 34(10): 917-919.

120. Storm DW, Mowad JJ. Conservative management of a bleeding renal angiomyolipoma in pregnancy. *Obstetrics & Gynecology* 2006: 107(2 Pt 2): 490-492.
121. Morales JP, Georganas M, Khan MS, Dasgupta P, Reidy JF. Embolization of a bleeding renal angiomyolipoma in pregnancy: case report and review. [Review] [21 refs]. *Cardiovascular & Interventional Radiology* 2005: 28(2): 265-268.
122. Mascarenhas R, McLaughlin P. Haemorrhage from angiomyolipoma of kidney during pregnancy--a diagnostic dilemma. *Irish Medical Journal* 2001: 94(3): 83-84.
123. Yano S. Exacerbation of pulmonary lymphangioleiomyomatosis by exogenous oestrogen used for infertility treatment. *Thorax* 2002: 57(12): 1085-1086.
124. Shen A, Iseman MD, Waldron JA, King TE. Exacerbation of pulmonary lymphangioleiomyomatosis by exogenous estrogens. *Chest* 1987: 91(5): 782-785.
125. Wilson AM, Slack HL, Soosay SA, Taylor T, Carey FA, Grove A, Brown PH, Winter JH. Lymphangioleiomyomatosis. A series of three case reports illustrating the link with high oestrogen states. *Scottish Medical Journal* 2001: 46(5): 150-152.
126. Oberstein EM, Fleming LE, Gomez-Marin O, Glassberg MK. Pulmonary lymphangioleiomyomatosis (LAM): examining oral contraceptive pills and the onset of disease. *Journal of Women's Health* 2003: 12(1): 81-85.
127. Pollock-BarZiv S, Cohen MM, Downey GP, Johnson SR, Sullivan E, McCormack FX. Air travel in women with lymphangioleiomyomatosis. *Thorax* 2007: 62(2): 176-180.
128. Rehabilitation BTSSoCs-coP. BTS Statement on Pulmonary Rehabilitation. *Thorax* 2001: 56: 827-834.
129. Managing stable COPD. *Thorax* 2004: 59: i39-130.
130. Taveira-DaSilva AM, Stylianou MP, Hedin CJ, Hathaway O, Moss J. Bone Mineral Density in Lymphangioleiomyomatosis. *Am J Respir Crit Care Med* 2005: 171(1): 61-67.
131. McCarty KS, Mossler JA, McLelland R, Sieker HO. Pulmonary lymphangiomyomatosis responsive to progesterone. *N Engl J Med* 1980: 303: 1461-1465.
132. Adamson D, Heinrichs WL, Raybin DM, Raffin TA. Successful treatment of pulmonary lymphangiomyomatosis with oophorectomy and progesterone. *American Review of Respiratory Disease* 1985: 132(4): 916-921.
133. Anker N, Francis D, Viskum K. [2 cases of lymphangioleiomyomatosis treated by hormonal manipulation]. *Ugeskr Laeger* 1993: 155(30): 2354-2356.
134. Banner AS, Carrington CB, Emory WB, Kittle F, Leonard G, Ringus J, Taylor P, Addington WW. Efficacy of oophorectomy in lymphangioleiomyomatosis and benign metastasizing leiomyoma. *N Engl J Med* 1981: 305(4): 204-209.
135. Itoi K, Kuwabara M, Okubo K, Matsuoka K. [A case of pulmonary lymphangiomyomatosis treated with bilateral oophorectomy and methyl-progesterone-acetate]. *Nihon Kyobu Shikkan Gakkai Zasshi* 1993: 31(9): 1146-1150.
136. Kanbe A, Hajiro K, Adachi Y, Honda K, Suzuki T, Yamamoto T. Lymphangiomyomatosis associated with chylous ascites and high serum CA-125 levels: a case report. *Japanese Journal of Medicine* 1987: 26(2): 237-242.
137. Brock ET, Votto JJ. Lymphangioleiomyomatosis: treatment with hormonal manipulation. *N Y State J Med* 1986: 86(10): 533-536.
138. Klein M, Krieger O, Ruckser R, Rosen A, Waldner R, Preis P, Beck A. Treatment of lymphangioleiomyomatosis by ovariectomy, interferon alpha 2b and tamoxifen--a case report. *Arch Gynecol Obstet* 1992: 252(2): 99-102.
139. Svendsen TL, Viskum K, Hansborg N, Thorpe SM, Nielsen NC. Pulmonary lymphangioleiomyomatosis: a case of progesterone receptor positive

lymphangioleiomyomatosis treated with medroxyprogesterone, oophorectomy and tamoxifen. *Br J Dis Chest* 1984: 78(3): 264-271.
140. Tomasian A, Greenberg MS, Rumerman H. Tamoxifen for lymphangioleiomyomatosis. *N Engl J Med* 1982: 306(12): 745-746.
141. de la Fuente J, Paramo C, Roman F, Perez R, Masa C, de Letona JM. Lymphangioleiomyomatosis: unsuccessful treatment with luteinizing-hormone-releasing hormone analogues. *Eur J Med* 1993: 2(6): 377-378.
142. 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(3): 300-304.
143. 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(1): 174-176.
144. Oh YM, Mo EK, Jang SH, Yoo CG, Kim YW, Seo JW, Han SK, Im JG, Shim YS. Pulmonary lymphangioleiomyomatosis in Korea. *Thorax* 1999: 54(7): 618-621.
145. Harari S, Cassandro R, Chiodini J, Taveira-DaSilva AM, Moss J. Effect of a Gonadotrophin-Releasing Hormone Analogue on Lung Function in Lymphangioleiomyomatosis. *Chest* 2008: 133(2): 448-454.
146. King-Biggs MB, Dunitz JM, Park SJ, Kay Savik S, Hertz MI. Airway anastomotic dehiscence associated with use of sirolimus immediately after lung transplantation. *Transplantation* 2003: 75(9): 1437-1443.
147. Detterbeck FC, Egan TM, Mill MR. Lung Transplantation After Previous Thoracic Surgical Procedures. *Ann Thorac Surg* 1995: 60(1): 139-143.
148. Pechet TT, Meyers BF, Guthrie TJ, Battafarano RJ, Trulock EP, Cooper JD, Patterson GA. Lung transplantation for lymphangioleiomyomatosis. *The Journal of Heart and Lung Transplantation* 2004: 23(3): 301-308.
149. Collins J, Muller NL, Kazerooni EA, McAdams HP, Leung AN, Love RB. Lung transplantation for lymphangioleiomyomatosis: role of imaging in the assessment of complications related to the underlying disease. *Radiology* 1999: 210(2): 325-332.
150. Morimoto N, Hirasaki S, Kamei T, Horiike A, Miyatake H, Ogita Y, Nakano H. Pulmonary lymphangiomyomatosis (LAM) developing chylothorax. *Intern Med* 2000: 39(9): 738-741.
151. Christodoulou M, Ris H-B, Pezzetta E. Video-assisted right supradiaphragmatic thoracic duct ligation for non-traumatic recurrent chylothorax. *Eur J Cardiothorac Surg* 2006: 29(5): 810-814.
152. Avila NA, Dwyer AJ, Rabel A, DeCastro RM, Moss J. CT of pleural abnormalities in lymphangioleiomyomatosis and comparison of pleural findings after different types of pleurodesis. *AJR American Journal of Roentgenology* 2006: 186(4): 1007-1012.
153. Druelle S, Aubry P, Levi-Valensi P. [Pulmonary lymphangiomyomatosis: a 3-year follow-up of medroxyprogesterone acetate therapy. Apropos of a case]. *Rev Pneumol Clin* 1995: 51(5): 284-287.
154. Zanella A, Toppan P, Nitti D, Lise M. Pulmonary lymphangioleiomyomatosis: a case report in postmenopausal woman treated with pleurodesis and progesterone (medroxyprogesterone acetate). *Tumori* 1996: 82(1): 96-98.
155. Wójcik P, Otto T, Jagiełło R, Komarow I, Zaremba J, Drygalska-Pozorańska A, Chudański M. Use of pleuro-peritoneal shunt in the treatment of chronic chylothorax. *Pneumonol Alergol Pol* 1998: 66: 473-479.

156. Calvo E, Amarillas L, Mateos MA, Orradre JL, Gilsanz G, Alvarez-Sala JL, Espinos D. Lymphangioleiomyomatosis, chylous ascites, and diet. *Dig Dis Sci* 1996: 41(3): 591-593.
157. Hamlin JA, Smith DC, Taylor FC, McKinney JM, Ruckle HC, Hadley HR. Renal angiomyolipomas: long-term follow-up of embolization for acute hemorrhage. *Canadian Association of Radiologists Journal* 1997: 48(3): 191-198.
158. Williams JM, Racadio JM, Johnson ND, Donnelly LF, Bissler JJ. Embolization of renal angiomyolipomata in patients with tuberous sclerosis complex. *American Journal of Kidney Diseases* 2006: 47(1): 95-102.
159. Igarashi A, Masuyama T, Watanabe K, Higaki Y, Kuramoto N, Suzuki K, Yoshida H. Long-term result of the transcatheter arterial embolization for ruptured renal angiomyolipoma. *Nippon Hinyokika Gakkai Zasshi - Japanese Journal of Urology* 2002: 93(6): 702-706.
160. Mourikis D, Chatziioannou A, Antoniou A, Kehagias D, Gikas D, Vlahos L. Selective arterial embolization in the management of symptomatic renal angiomyolipomas. *European Journal of Radiology* 1999: 32(3): 153-159.
161. Rimon U, Duvdevani M, Garniek A, Golan G, Bensaid P, Ramon J, Morag B. Ethanol and polyvinyl alcohol mixture for transcatheter embolization of renal angiomyolipoma. *American Journal of Roentgenology* 2006: 187(3): 762-768.
162. Kothary N, Soulen MC, Clark TW, Wein AJ, Shlansky-Goldberg RD, Crino PB, Stavropoulos SW. Renal angiomyolipoma: long-term results after arterial embolization.[see comment]. *Journal of Vascular & Interventional Radiology* 2005: 16(1): 45-50.
163. Bissler J, Racadio J, Donnelly L, Johnson N. Reduction of postembolization syndrome after ablation of renal angiomyolipoma. *American Journal of Kidney Diseases* 2002: 39(5): 966-971.
164. Heidenreich A, Hegele A, Varga Z, von Knobloch R, Hofmann R. Nephron-sparing surgery for renal angiomyolipoma. *European Urology* 2002: 41(3): 267-273.
165. Yip SK, Tan PH, Cheng WS, Li MK, Foo KT. Surgical management of angiomyolipoma: nephron-sparing surgery for symptomatic tumour. *Scandinavian Journal of Urology & Nephrology* 2000: 34(1): 32-35.
166. Ramon J, Rimon U, Garniek A, Golan G, Bensaid P, Kitrey ND, Nadu A, Dotan ZA. Renal Angiomyolipoma: Long-term Results Following Selective Arterial Embolization. *Eur Urol* 2008.
167. Bender B, Yunis E. The pathology of tuberous sclerosis. *Pathol Annu* 1982: 17: 339-382.
168. 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(1): 78-82.
169. Trulock EP. Lung transplantation: special considerations and outcome in LAM. *In:* Moss J, ed. LAM and other Diseases Characterised by Smooth Muscle Proliferation. Marcel Dekker, New York, 1999; pp. 65-78.
170. Pigula FA, Griffith BP, Zenati MA, Dauber JH, Yousem SA, Keenan RJ. Lung transplantation for respiratory failure resulting from systemic disease. *Ann Thorac Surg* 1997: 64(6): 1630-1634.
171. Kpodonu J, Massad MG, Chaer RA, Caines A, Evans A, Snow NJ, Geha AS. The US Experience with Lung Transplantation for Pulmonary Lymphangioleiomyomatosis. *The Journal of Heart and Lung Transplantation* 2005: 24(9): 1247-1253.

172. Boehler A. Lung transplantation for cystic lung diseases: lymphangioleiomyomatosis, histiocytosis x, and sarcoidosis. *Seminars in Respiratory & Critical Care Medicine* 2001: 22(5): 509-516.
173. Reynaud-Gaubert M, Mornex JF, Mal H, Treilhaud M, Dromer C, Quetant S, Leroy-Ladurie F, Guillemain R, Philit F, Dauriat G, Grenet D, Stern M. Lung transplantation for lymphangioleiomyomatosis: the French experience. *Transplantation* 2008: 86(4): 515-520.
174. Chen F, Fukuse T, Hasegawa S, T. B, Hanaoka N, Kawashima M, Sakai H, Komeda M, Wada H. Living-donor lobar lung transplantation for pulmonary and abdominopelvic lymphangioleiomyomatosis. *Thorac Cardiovasc Surg* 2005: 53: 125-127.
175. Benden C, Rea F, Behr J, Corris PA, Reynaud-Gaubert M, Stern M, Speich R, A. B. Lung transplantation for lymphangioleiomyomatosis: the European experience. *J Heart Lung Transplant* 2008.
176. Nine JS, Yousem SA, Paradis IL, Keenan R, Griffith BP. Lymphangioleiomyomatosis: recurrence after lung transplantation. *J Heart Lung Transplant* 1994: 13(4): 714-719.
177. Bittmann I, Rolf B, Amann G, Lohrs U. Recurrence of lymphangioleiomyomatosis after single lung transplantation: New insights into pathogenesis. *Human Pathology* 2003: 34(1): 95-98.
178. Karbowniczek M, Astrinidis A, Balsara BR, Testa JR, Lium JH, Colby TV, McCormack FX, Henske EP. Recurrent Lymphangiomyomatosis after Transplantation: Genetic Analyses Reveal a Metastatic Mechanism. *Am J Respir Crit Care Med* 2003: 167(7): 976-982.
179. Benden C, Boehler A, Faro A. Pediatric lung transplantation: Literature review. *Pediatric Transplantation* 2008: 12(3): 266-273.