REVIEW ARTICLE

Pulmonary Lymphangioleiomyomatosis*

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Lymphangioleiomyomatosis (LAM) is a rare lung disease of unknown etiology that primarily affects women of childbearing age. Clinically, it manifests as progressive dyspnea, hemoptysis, pneumothorax and chylous pleural effusion resulting from abnormal smooth muscle proliferation in the lung parenchyma, lymph nodes, small airways and blood vessels. Recent cytogenetic studies have disclosed mutations of the tuberous sclerosis complex (TSC)-2 gene in cells of renal angiomyolipoma and in abdominal lymph nodes, pointing to hamartomatous lesions as a possible etiology. Chest radiography may appear normal or yield reticulonodular infiltrates and signs of hyperinflation. In high-resolution computed tomography scans, multiple thin-walled cysts can be seen throughout the lung parenchyma. Abdominal imaging by either ultrasound or computed tomography may show renal angiomyolipomas and retroperitoneal lymph node enlargement. Meningiomas may be seen concomitantly, requiring that testing for TSC be performed. Physiologically, LAM is characterized by progressive airflow obstruction, air trapping and gas-transfer impairment. Estrogenic suppression with either oophorectomy, deposit progestogens, tamoxifen and gonadotropin-releasing hormone analogs, is still the primary treatment. In addition to this therapy, lung transplants have increased patient median survival rates by more than ten years.

Key words: **Lymphangiomyomatosis/etiology. Lung neoplasms.**

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Submitted: 25/06/2003. Accepted, after revision: 15/09/2003

***Abbreviations used in this paper*:**

LAM	**– Lymphangioleiomyomatosis**
TPR	**– Total pulmonary resistance**
CO	**– Carbon monoxide**
DLCO	**– Diffusion capacity for carbon monoxide**
TS	**– Tuberous sclerosis**
TSC	**– Tuberous sclerosis complex**
GnRH	**– Gonadotropin-releasing hormone**
COPD	**– Chronic obstructive pulmonary disease**
ACE	**– Angiotensin-converting enzyme**
HRT	**– Hormone replacement therapy**
PCNA	**– Proliferating cell nuclear antigen**
MMP	**– Matrix metalloproteinase**
MT1-MMP	**– Membrane-type 1 matrix metalloproteinase**
HMB-45	**– Anti-melanoma monoclonal antibody**
α-SMA	**– α-smooth muscle actin**
FEV_1	**– Forced expiratory volume in one second**
CNS	**– Central nervous system**
FSH	**– Follicle stimulating hormone**
LH	**– Luteinizing hormone**
HX	**– Histiocytosis X**
HRCT	**– High resolution computed tomography**

INTRODUCTION

Historical considerations

From 1937 to 1955, 3 papers were published reporting cases of women who all presented with chylothorax, mediastinal lymph node enlargement, and pulmonary cystic lesions combined with pneumothorax.[1,2,3] In 1956, Cornog and Enterline[4] reviewed 45 cases in which the findings were very similar to those from the previous cases and designated this condition pulmonary lymphangiomatosis syndrome. Although the initial reports questioned the malignant potential of the disease (dissemination through the lymph vessels), Cornog and Enterline believed that the absence of cellular atypia and of significant mitotic activity, together with the degree of organization of the pulmonary lesions, disproved that hypothesis. They also believed that this process was attributable to a single agent, possibly of genetic origin, which acts on smooth muscle fibers in the lungs and lymph nodes. It was then characterized as a new clinical disease, which was restricted to women of childbearing age and, therefore, likely mediated by hormones.

EPIDEMIOLOGY

The reported prevalence of pulmonary lymphangioleiomyomatosis (LAM) is about 1/1,000,000 in Great Britain,[5] France[6] and the United States[7]. However, prevalence must be higher, especially because very little is known about the disease, which delays its diagnosis. A recent survey among Canadian pulmonologists revealed that, of 118 physicians, 61 had never encountered a case of LAM. However, various reports have been published (about 300 cases registered in the literature), indicating that the global incidence is approximately 100 cases a year[7]. In Brazil, a study is ongoing in the pulmonology departments of the FMUSP Hospital das Clínicas, the Hospital São Paulo and the Hospital do Sevidor Público Estadual, in which 37 patients have been diagnosed with LAM since 1982. Of those 37, 24 are still living and are being monitored.

PATHOLOGY

A progressive cystic transformation throughout the lung parenchyma is a characteristic finding in patients with LAM. These changes seem to basically appear from the proliferation of atypical smooth muscle cells around the bronchiole structure, which results in airflow obstruction and lesions in the alveolar space, leading to pulmonary collapse. Many patients may also present with subpleural bullae. Muscular proliferation involving venules may cause primary pulmonary hypertension and obstruction of venous blood flow.[29]

Evaluation of the lesions reveals that the pulmonary architecture is progressively altered by the proliferation of atypical smooth muscle cells around bronchioles, blood vessels, and lymph nodes. According to Bionetti et al.,[30] there seem to be 3 distinct cellular forms: large fusiform cells, small fusiform cells, and epithelioid cells (Figure 1). These cellular types present distinct immunophenotypes and, according to the findings of Matsui et al.,[31] also have distinct roles in the pathogenesis of pulmonary lesions. In this study, we analyzed lung tissues obtained from 5 patients before and after therapy with progesterone or tamoxifen citrate. Epithelioid cells were most commonly found in proximity to medullary lesions and had a higher positive response to the anti-melanoma monoclonal antibody HMB-45 (an anti-glycoprotein derived from melanosomes), although they were not greatly influenced by the therapy. On the other hand, the small fusiform and oval cells showed a higher positive response to proliferating cell nuclear antigen (PCNA), matrix metalloproteinase (MMP)-2 and membrane type 1-matrix metalloproteinase (MT1-MMP). These findings were much more frequent in the pre-therapy samples, suggesting that the activation of MMP-2 by MT1-MMP is related to the hormonal activity and may play a major role in the destruction of pulmonary tissues. Other studies have also indicated an imbalance in elastic fiber degradation resulting from greater elastase (metalloproteinase) activity in the etiopathogenesis of pulmonary destruction.[32,33]

The bronchiolar narrowing that results from smooth muscle cell proliferation causes air trapping and partially explains the origin of pulmonary cysts. However, although bronchiolar narrowing obstructs airflow, Sobonya et al.,[34] using morphometric analysis, demonstrated that the loss of alveolar support

due to the destruction of the extracellular matrix seems to directly contribute to the collapse and tortuosity of the adjacent airways. This process seems to be the primary instigator of airflow obstruction and progressive cyst formation in the lungs.

TISSUE MARKERS AND RECEPTORS

Various immunohistochemical markers have been used in the diagnosis and evaluation of the physiopathology of lymphangiomatosis-related lesions. However, a protein with sensitivity and specificity sufficient to ensure diagnosis of the disease has not been found to date.

Among tissue markers, the monoclonal antibody HMB-45, which was initially raised against an extract of melanoma cells (reaction against the glycoconjugate portion of immature melanosomes), is the most commonly used for the immunohistochemical study of LAM.[33] In LAM samples, HMB-45 generally reacts with epithelial-like cells, which present with lower mitotic activity, are located closer to airways and are, therefore, more easily accessed through transbronchial biopsy. This antibody also reacts with renal angiomyolipoma cells.

Another tool used in the investigation of LAM is α-smooth muscle actin (α-SMA), which, although less specific, strongly reacts with the cytoplasm of cells in areas of cellular proliferation. It is used as an ectopic marker of smooth muscle cell proliferation in the lungs.

More recently, the idea of an imbalance between proteases and antiproteases has yielded to the investigation of enzymes involved in the process of the destruction of the pulmonary extracellular matrix. Matsui et al.[35] measured PCNA and MMP-2 and MT1-MMP enzymes in 2 patient groups (those treated with progesterone, tamoxifen or both, and those not treated) and found a higher positivity for the untreated group. Since these enzymes and PCNA are preferably found in fusiform (spindle-shaped) cells, the authors concluded that a larger number of fusiform cells found to be positive for proliferation markers correlates with a higher degree of parenchymal destruction.

Since the initial observations confirming the almost exclusive incidence of the disease in women (reports on male cases refer to patients presenting nonandrogenic hormones), the correlation between hormonal activity and the incidence of LAM has always been taken into consideration. The first study involving LAM patients that showed the presence of hormone receptors in the cytoplasm of the lungs was performed at the FMUSP Hospital das Clínicas by Brentani et al. in 1984.[36] Later, Graham et al.,[37] using radioimmunoassay techniques, found specific nuclear progesterone binding sites as well as cytosolic estrogen receptors. More recently, immunohistochemical studies of LAM patients performed by Colley et al.[38] demonstrated that the nuclei of smooth muscle cells, unlike those of normal smooth muscle cells, showed pronounced marking by anti-estrogen and anti-progesterone antibodies. These findings, together with the discovery of mutations in tuberous sclerosis complex (TSC) 1 and 2 genes, reinforce the hypothesis that the role of hormones in LAM may depend upon cytosolic and nuclear receptors, which interfere with their expression in these chromosomal regions. In 2001, Flores-Delgado et al. demonstrated the nongenomic action of estrogen through the inactivation of nuclear phosphatases, which would destabilize TSC genes.[39]

The proto-oncogene Bcl-2, initially identified in B cell leukemia and non-Hodgkin's follicular lymphoma, seems to be one of the most effective genes in controlling apoptosis. Its potential correlation with the development of LAM lesions was established by Usuki et al.,[40] who identified higher Bcl-2 positivity in LAM cells than in vascular and bronchiolar smooth muscle cells. In this study, the higher positivity of Bcl-2 in LAM cells coincides with the presence of estrogen and progesterone receptors, thereby resembling breast neoplasia and suggesting that the expression of this proto-oncogene may be related to hormone control.

CLINICAL MANIFESTATIONS

Cases of LAM are most common among women of childbearing age. In a series of 50 patients in Great Britain, Johnson and Tattersfield[5] found that symptoms first appear at a mean age of 35. A retrospective analysis of a subgroup of 20 patients from our clinic showed a mean age of 32 for the onset of symptoms and 34 for diagnosis. However, there are reports of the disease in children, in

postmenopausal women and (2 cases) in men.[9,10] The male cases were patients who presented nonandrogenic hormones.

Although the disease is typically diagnosed in patients who are in their 30s or 40s,[11,12,13] symptoms may precede the diagnosis by months or years. The disease is often mistaken for asthma, chronic obstructive pulmonary disease (COPD) or bronchiolitis. Taylor et al.[14] showed that, in a group of 32 patients, diagnoses were not made until 44 months after the onset of symptoms.

A diagnosis of LAM should be considered when a woman of childbearing age without a history of cardiorespiratory disease or other inducing factors presents progressive dyspnea and dry cough, especially if combined with spontaneous pneumothorax. In Great Britain, Johnson and Tattersfield,[5] while studying 50 female patients, found that pneumothorax was the most prevalent clinical manifestation (in 19), followed by dyspnea (in 18). Dry cough was seen in 2 women, and chylothorax and chest pain in 3 women. Other less frequent symptoms are hemoptysis, chylous pleural effusions, chylous ascites, pericardial effusion, pneumoperitoneum, acute abdomen, and lymphedema. Chest auscultation can be normal or reveal crepitations (in the lower lobes) and ronchi.[14,15,16] Digital clubbing is rarely seen. Tables 1 and 2 show the summary of the clinical findings published in the literature and the ones found in our patients. Diffuse cysts were found in all of our patients (Figure 3).

RENAL ANGIOMYOLIPOMA

Renal angiomyolipoma is a rare hamartomatous tumor made of fat, rich in vascular proliferation and smooth muscle cells. It can be generally found in patients with LAM and tuberous sclerosis, and, together with changes in chest radiographs, provides strong evidence for the diagnosis (Figure 4). In the 50 patients studied in Great Britain, 6 cases of renal angiomyolipoma were found.[5] Other recent series[17,18,19,20] found renal angiomyolipoma in 23 (44%) out of 52 patients. Of those 23, 11 presented bilateral kidney involvement. This tumor generally grows slowly and silently but can cause lower back pain, hematuria, and palpable masses in the flanks. The differentiation from other renal tumors is not always easy, and the main differential diagnosis is hypernephroma. Since there may be growth, local invasion and compression of abdominal structures, partial or total removal of the affected kidney might be necessary. Arterial embolization can be an alternative to nephrectomy. Since the mass may recur and affect the contralateral kidney, the conservative procedure is more appropriate.

LABORATORY TESTS

There are no specific changes seen in the results of laboratory tests for LAM patients. Higher levels of angiotensin-converting enzyme (ACE) were found in 2 of the 3 patients evaluated by Lieberman et al.[21]. Since most studies do not include ACE dosage, references are scarce. One study reported a persistent increase in CA-125,[22] and another reported a case of hyperparathyroidism and LAM.[23]

PREGNANCY AND HORMONE REPLACEMENT THERAPY

There are reports in the literature of patients who suffered onset or worsening of LAM symptoms during pregnancy.[24] However, it is not clear whether the hormonal changes during pregnancy provoke the progression and deterioration of the pulmonary conditions or whether symptoms become more intense and pronounced because of the ventilatory and hemodynamic changes that naturally occur during pregnancy. In Johnson and Tattersfield's[5] review, 28 of the 50 patients studied were pregnant. Gestation was interrupted in 1 patient. Of the 27 who delivered, 7 presented with symptom onset during pregnancy or immediately after delivery. Of the other 20 pregnant patients, only 2 suffered a worsening of their condition during pregnancy. Urban[6] reported that 16 (23%) of the 69 patients in his study presented initial pulmonary manifestations during pregnancy. However, overall condition worsened during pregnancy in only 2.

Of the 20 patients observed at the FMUSP Hospital das Clínicas and at the UNIFESP Hospital São Paulo, 1 became pregnant after diagnosis but presented no clinical deterioration during pregnancy, and 2 had spontaneous pneumothorax within 2 months after delivery.

There have been reports on the exogenous use of estrogen and the onset or worsening of LAM-related symptoms.[25,26,27] This has also been reported in postmenopausal women and in those who have taken oral contraceptives. Despite this possible association, an extensive British survey published in 1994[28] found no correlation between oral contraceptives and LAM.

PULMONARY FUNCTION

Unlike most interstitial diseases, LAM results in progressive airway obstruction. The continuous decrease in forced expiratory volume in 1 second (FEV_1) and forced vital capacity are combined with a progressive increase in residual volume, which results in normal, or even enhanced, total lung capacity (TLC). The restrictive process is rarely seen and, when present, is usually followed by pneumothorax or chylothorax. An clear indication of the severity of the disease is reduced diffusion capacity for carbon monoxide (DLCO) occurring together with increased residual volume, a situation which usually results from the acini being replaced by cysts. Kitaichi et al.[15] correlated functional findings with anatomopathological profiles, showing that reduced DLCO combined with increased residual volume correlates with the anatomopathological profile of a more severe form of the disease.

DIAGNOSIS

The diagnosis of LAM, of necessity, depends upon clinical and radiological findings. The presence of dyspnea and dry cough in young women of childbearing age, combined with spontaneous pneumothorax, raises the suspicion of LAM. Although chest radiographs may facilitate the diagnosis by suggesting cystic lesions or chylothorax – or by confirming pneumothorax (Figure 1) – only a (conventional or high-resolution) CT scan of the chest will reveal the diffuse cystic lesions throughout the lung parenchyma (Figure 3). The LAM cysts are usually found in the peribronchovascular region, have thin walls and are distributed diffusely throughout the lungs. Retroperitoneal lymph node enlargement may be present but is not typical of the disease. Renal angiomyolipoma strongly suggests LAM and should be investigated through tomography of the abdomen. A diagnosis of tuberous sclerosis, which may present in varying degrees of genetic penetrance and, therefore, may not always present in its classical form (convulsions and mental retardation), should be ruled out (Figure 5).

DIFFERENTIAL DIAGNOSIS

Differential diagnosis with other cystic diseases is imperative, mainly with Langerhans cell granulomatosis, or histiocytosis X (HX), which, unlike LAM, preserves the lower third of the lungs and the costophrenic region. In addition, HX/eosinophilic granuloma generally presents with a larger number of nodules in the chest radiograph and tomography, some of which may present with cavitations. The adult form of HX correlates closely with tobacco use (smoking), a correlation not found in LAM.

Some manifestations of panacinar emphysema may simulate cystic formations, but analysis of high-resolution CT (HRCT) scans usually eliminates diagnostic doubts. Pulmonary sarcoidosis, primary Sjögren's syndrome, and other proliferative aspects of pulmonary lymphangiomatosis (leiomyosarcomas and metastatic leiomyomas, diffuse lymphangiomatosis, lymphangiomas and lymphangiectasis, as well as cystic and fibroleiomyomatous hamartomas), may also appear with pulmonary cystic formations in young women. In such cases, pulmonary biopsy is almost indispensable in making an accurate diagnosis. Histopathological analysis, together with immunohistochemical techniques, routinely HMB-45 and alpha-actin testing, allow the evaluation of samples obtained through transbronchial, thoracoscopic or open lung biopsy. Since most alterations are predominantly in the peribronchovascular area, histological analysis can be initiated through transbronchial biopsy. Nevertheless, physicians should always consider that the samples may not be truly representative of the affected areas, and a subsequent open lung biopsy may be necessary.

TUBEROUS SCLEROSIS AND LAM

Tuberous sclerosis (TS) is a dominant autosomal disease, associated with 2 genes: TSC-1 in chromosome 9 and TSC-2 in chromosome 16. These genes are oncogene suppressors, and mutations in their alleles may lead to cellular proliferation, resulting in the characteristic hamartomas of this disease. Despite its variable expressivity, TS has high penetrance, which has significant implications for post-diagnosis genetic counseling. Genetic counseling is based on clinical findings according to the criteria described by the National Tuberous Sclerosis Association.[41] To diagnose the disease, it is necessary that 1 primary feature, 2 secondary features, or 1 secondary and 2 tertiary features be present (Table 2). Angiomyolipomas and pulmonary LAM are secondary criteria in the diagnosis of TS, which could make us believe that LAM would be only 1 of the symptoms of TS. However, since children from patients with LAM do not present the disease, we believe that there is no mutation of the TSC genes in the germ cells of those patients. Smolarek's et al.[42] recent discovery regarding the homozygosity of the mutant TSC-2 gene in renal angiomyolipoma cells in 7 patients with LAM make us think that these may be point mutations and that these patients are true mosaics of this alteration. In any case, a diagnosis of LAM requires that other evidence of TS, such as changes in the central nervous system (hamartomas and seizure foci), be sought, and that reasoned pregnancy counseling be given.[43]

TREATMENT

Emergency situations

Treatment of clinical complications such as pneumothorax, chylothorax, and chylous ascites may become the focus of initial treatment of LAM. In addition to chest drainage, patients who present with pneumothorax may be submitted to pleurodesis (chemical or surgical). However, considering the possible future need for lung transplant, pleurodesis should be avoided if possible. Only 1 of the 6 patients who recently presented with repetitive pneumothorax at our clinic underwent pleurodesis. Anti-hormone therapy was used to control the condition in the other 5. The control of chylous pleural effusions can be more difficult and, despite the adoption of diets containing medium-chain triglycerides, thoracic duct ligation is often necessary. Hormone therapy and a diet containing medium-chain triglycerides were successfully used to control the one case of chylothorax that appeared at our clinic. Other treatments based on radiotherapy and corticosteroid use proved to have no clinical value.

ANTIHORMONAL THERAPY

A progressive decrease in FEV_1, together with pulmonary diffusion, is an important sign of aggravation and lack of control of the disease. In addition, some authors consider the positive response to bronchodilators to be correlated with hormone-mediated growth of smooth muscle cells and with a cyst histopathology pattern showing a tendency for poor prognosis.[15] Since the disease affects mainly women of childbearing age, antihormonal therapy has been used since its initial description. Assuming the hypothesis that myofibroblastic cells have estrogen and progesterone receptors and that these receptors act on the growth process, antihormonal therapies have been based on suppression of estrogen secretion. Traditionally, this has been done through the use of intramuscular progesterone. More recently, gonadotropin-releasing hormone (GnRH) analogs have been used to suppress the secretion of follicle stimulating hormone (FSH), and luteinizing hormone (LH) has been used for the subsequent suppression of estrogen synthesis. In addition, oophorectomy is used to suppress estrogen production, while maintaining high levels of FSH and LH, and estrogen-receptor antagonists such as tamoxifen citrate and raloxifene are used because of their direct effect on myofibroblastic cells. Primarily because the disease is rare, there have been to date no controlled, randomized, double-blind placebo clinical trials evaluating the response of LAM patients to antihormonal therapy.

PROGESTERONE

The first report on the use of progesterone was made by McCarthy et al.[44] in 1980, in which a 33-year-old patient was treated with 400 mg of medroxyprogesterone monthly, and had clinical and functional improvement. In the largest British case series published, Tattersfield and Johnson[5] showed that there was functional and clinical worsening in 50 patients despite the therapy (GnRH analogs were not used), but the rate of FEV_1 reduction was slowed from its average of 118 mL/year. Taylor et al.[13] showed that, of 19 patients treated with progesterone, 2 improved while therapy was still underway, 6 stabilized, and 11 deteriorated. The recommended dosage of progesterone (Depo-Provera) is (intramuscular) from 400 mg to 1600 mg monthly or (oral) from 10 mg to 60 mg daily. Contraceptive drugs containing estrogen should be banned during such treatment regimens.[45]

GONADOTROPIN-RELEASING HORMONE ANALOGS

The use of hormone analogs is a recent advent. In 1991, Rossi et al.[46] reported the case of a LAM patient whose disease was stabilized for 19 months through the use of subcutaneous goserelin (partial agonist to GnRH analog). Since then, there have been conflicting reports concerning the use of hormone analogs in the treatment of LAM.[47,48,49,50] Hormone analogs interfere with GnRH pulse secretion, and consequently with FSH and LH synthesis, thereby causing chemically-induced menopause. Unlike oophorectomy, which maintains gonadotropin levels high, hormone analogs, through suppression of FSH and LH synthesis, block any other peripheral effect, perhaps by stimulating myofibroblasts or interfering in the synthesis of extraglandular estrogen.

Since 1992, all patients diagnosed with LAM at our hospital have been submitted to a regimen of goserelin (subcutaneous, 3.6 mg/month). During the same period, patients diagnosed with LAM at the Hospital São Paulo have been submitted to a regimen of progesterone (intramuscular, 500-800 mg/month). Retrospective analysis of the data regarding functional evolution of patients suggest there is a more positive evolution in the group treated with goserelin, but the difference is not statistically significant.

TAMOXIFEN AND RALOXIFENE

The use of tamoxifen has not proven beneficial when used in isolation. There are reports of clinical improvement when it is used in combination with progesterone. The utility of selective aromatase inhibitors (anastrozole) and new estrogen receptor modulators such as raloxifene is still unknown.

LUNG TRANSPLANT

Even with hormonal therapy, there is progressive deterioration of the pulmonary function in most LAM patients. Therefore, lung transplant is a therapeutic alternative in the most severe cases. The indications for transplant in LAM are similar to those for other terminal respiratory diseases. However, during postoperative follow-up, in addition to infectious complications due to immunosuppression and the possibility of rejection, recurrence of the disease in the transplanted lung has been reported. O'Brien et al.[52] even reported recurrence in the transplanted lung of a male donor.

FINAL CONSIDERATIONS

Pulmonary lymphangioleiomyomatosis is a rare disease that primarily affects women of childbearing age. The clinical symptoms are progressive dyspnea, dry cough, spontaneous pneumothorax, and chylothorax. Approximately half of all patients may present with renal angiomyolipomas. Functionally, the disease evolves through a progressive obstructive process. Tomography scans show characteristic, multiple thin-walled cysts throughout the lung parenchyma. Although there is no definitive treatment, the use of antihormonal therapies has slowed loss of function and prolonged survival in some series. Recent findings regarding the genetic association between LAM and TS have brought new perspectives on the etiopathogenesis. Further studies of the interaction between oncogene activation and hormone "status" are warranted.

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TABLE 1

Summary of clinical and radiological findings (pulmonary and extrapulmonary). Analysis of international case studies and of cases studied at the HC-FMUSP and HSP-UNIFESP interstitial diseases clinics

SIGNS AND SYMPTOMS	LITERATURE REVIEW		HC-FMUSP AND HSP-UNIFESP	
	Number of patients presenting the symptom	Number of patients evaluated	Number of patients presenting the symptom	Number of patients evaluated
Dyspnea	142	164	20	20
Dry cough	84	164	20	20
Pneumothorax	138	213	15	20
Chest pain	56	164	12	20
Chylothorax	60	213	2	20
Hemoptysis	36	164	2	20
Renal angiomyolipoma	77	146	5	20

TABLE 2
Clinical criteria for diagnosis of tuberous sclerosis complex
According to the National Tuberous Sclerosis Association[37]

Primary features	Secondary features	Tertiary features
Facial angiofibromas	**First-degree relative affected**	**Hypomelanotic macules**
Mutiple ungual fibromas	**cardiac rhabdomyoma**	***Confetti* skin lesions**
Cortical tuber	**Cerebral tuber**	**Hamartomatous rectal polyps**
Calcified subependymal nodules	**Other retinal hamartomas or achromic patch**	**Bone cysts**
Multiple retinal astrocytomas	**Forehead plaque**	**Gingival fibromas**
Subependymal nodules or giant cell astrocytoma	**Renal cysts**	**LAM**
	LAM	**Non-renal hamartomas**
	Renal angiomyolipoma	**Cerebral white matter migration lines or heteropias**
	Shagreen patch	**Infantile spasms**
	Non-calcified subependymal nodules	

At least: 1 primary feature;
2 secondary features; or
1 secondary feature and 2 tertiary features

LAM: (pulmonary) lymphangioleiomyomatosis

Figure 1 – *Open lung biopsy of a 42-year-old patient*

A*) – 20x magnification showing a large thin-walled cyst near the axial axis , normal alveolar structures (10 and 11 o'clock), terminal bronchiole (5 o'clock), and oval structure in the internal face which corresponds to new smooth cell growth;* ***B****) and* ***C****) – Details of smooth muscle cells and their relation to the cyst, which has expanded to obstruct the bronchioles and partially destroy the extracellular matrix;* ***D****) – 40x magnification, showing the myofibroblast foci with smooth muscle cell clusters.*

Figure 2 – *Right Pneumothorax with visible contralateral mediastinal deviation in a 32-year-old patient*

Figure 3 – *High-resolution computed tomography of a 32-year-old patient, showing multiple thin-walled cysts of various sizes, some confluent, that are diffusely distributed and are supplanting the pulmonary cortex and medulla. Pleural irregularities on the right (arrow – adherence in an area with prior pneumothorax) and left pneumothorax.*

Figure 4 – *Renal angiomyolipoma in a 32-year-old patient which appeared after the birth of her second child. Image taken with the help of intravenous injection of non-ionic contrast media. In the bottom left-hand corner, different average attenuations can be seen, ranging from –27.7 (area 1 – fat) to 47.8 (area 3 – soft parts).*

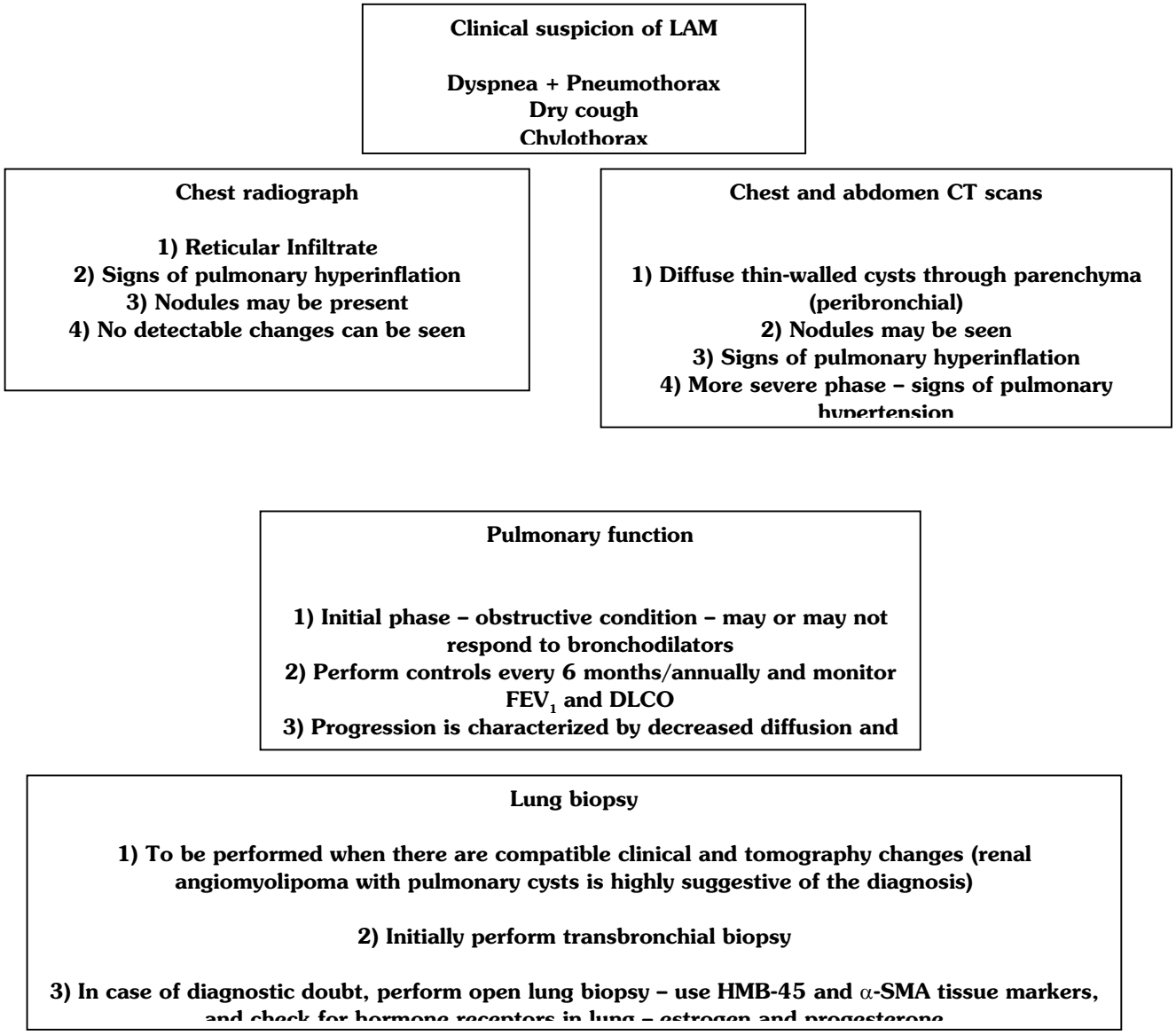

Figure 5 – LAM: pulmonary lymphangioleiomyomatosis; CT: computed tomography; FEV_1: forced expiratory volume in one second; DLCO: diffusion capacity for carbon monoxide; HMB-45: anti-melanoma monoclonal antibody; α-SMA: alpha-smooth muscle actin