Lymphangioleiomyomatosis

19

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Introduction

Lymphangioleiomyomatosis (LAM) is a disease characterised by lung cysts, enlargement and obstruction of the axial lymphatics, and in many cases angiomyolipomas, benign tumours occurring mainly in the kidneys. LAM almost exclusively affects women and can occur as a sporadic disease but is also common in adults with tuberous sclerosis complex (TSC) [1]. Although the clinical course can vary, many patients lose lung function at an accelerated rate and eventually develop respiratory failure.

The prevalence in the populations studied varies between 3.4 and 7.8/million women with an incidence of 0.23–0.31/million women/per year [2]. As the symptoms of LAM are similar to a number of more common respiratory diseases, the condition is under-recognised and there is often a period of years between the initial symptoms and the correct diagnosis. LAM has been described in most racial groups: TSC and female sex are the only known risk factors for developing LAM.

Pathogenesis

The association between LAM and TSC has been a key factor in understanding the molecular basis of LAM. Both sporadic and TSC-LAM are associated with loss of function of either *TSC-1* or more commonly *TSC-2*, the genes abnormal in TSC [3]. Hamartin and tuberin, the protein products of *TSC-1* and *-2*, respectively, form a complex with multiple functions, including as a guanosine triphosphatase accelerating protein (GAP) which inactivates Rheb, a small GTPase [4]. Rheb in turn activates the mammalian target of rapamycin (mTOR). mTOR associates with raptor and other proteins in complex 1 (mTORC1) which regulates cell growth, gene translation autophagy and metabolism, and with rictor and other proteins in the mTORC2 pathway which has other less well-defined functions but has a role in control of cytoskeletal arrangement and migration via the GTPase Rho [5] (Fig. 19.1. For a detailed description see [6, 7]). Loss of TSC-1/2 function by a combination of genetic or possibly epigenetic modifications results in constitutive activation of mTORC1 and hence uncontrolled proliferation, abnormal migration and a dependence on glycolytic metabolism within a clonal population of 'LAM' cells [8]. Drugs which block the activity of mTORC1 have transformed the treatment of the disease [9, 10]. Identical genetic abnormalities in *TSC-2* have been identified in LAM cells from different sites (lung, lymph nodes, angiomyolipoma) within the same patient, suggesting LAM cells are clonal and migrate throughout the body [11] leading to the 'benign metastasis model' of LAM pathogenesis [12]. LAM cells express receptors for oestrogen and progesterone, possibly in keeping with the female preponderance of the disease [13]. In model systems, oestrogen promotes LAM cell growth and metastasis; however, anti-oestrogen therapies have not proven effective for patients [14, 15]. The hallmark of LAM is the presence of lung cysts. Lined by nodular proliferations of LAM cells, it is thought that cysts may develop as a consequence of extra-cellular matrix proteolysis resulting from the secretion of proteases by LAM cells. Consistent with this idea, it has been shown that LAM cells produce a number of proteases, including cathepsin K [16] plasmin [17] and matrix metalloproteinases-1, -2, -9 and -14 [18, 19]. These proteases are capable of degrading extra-cellular matrix proteins, including collagens, elastin and proteoglycans. They may also contribute to the disease by activating growth factors, modulating cell surface receptor activity, inflammatory cell trafficking, angiogenesis and cellular invasion. LAM nodules are complex structures composed of multiple cell types, including LAM cells, LAM-associated fibroblasts and lymphatic endothelial cells forming central lym-

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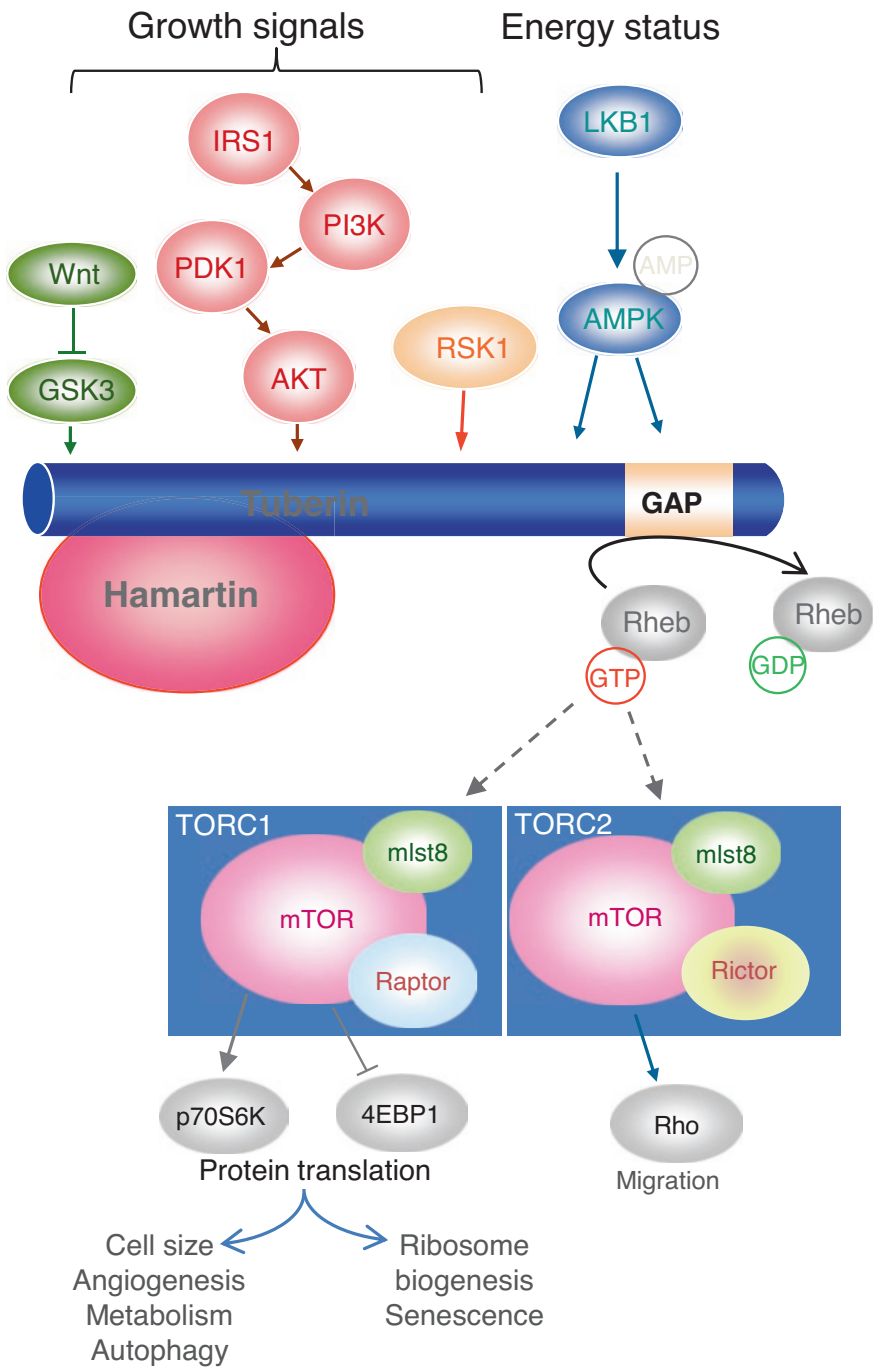


Fig. 19.1 Schematic representation of the mTOR pathway. Tuberin is phosphorylated by multiple inputs from growth signals via growth factors or as a consequence of change in cellular energy status. Phosphorylation of tuberin leads to increased guanine nucleotide hydrolysis via tuberin's GAP domain. Conversion of guanine triphosphate (GTP) to guanine diphosphate (GDP) inhibits Rheb (Ras homologue enriched in brain) activity, an activator of both mTOR complexes. Activation of the two multiprotein complexes results in differing downstream functions: for TORC1, including the translation of a selection of mRNA species changes in cell size, metabolism, proliferation, autophagy and other functions via the serine/threonine kinase p70S6K and 4EBP1, a component of the protein translation machinery. TORC2 is less well understood but functions include cell migration via the small GTPase Rho

phatic clefts, and covered by hyperplastic type 2 pneumocytes [20, 21]. Very recently, inflammatory cells have been described within LAM nodules, have been associated with disease activity and may represent future therapeutic targets [22, 23]. Many aspects of the disease mimic cancer biology and despite the benign appearance of the LAM cell, due to their uncontrolled growth, metastatic behaviour, interactions with host cells and their metabolic signature, LAM is viewed by some as a slow growing neoplasm or cancer-like disease [24]. The processes contributing towards the pathogenesis of LAM are summarised in Fig. 19.2.

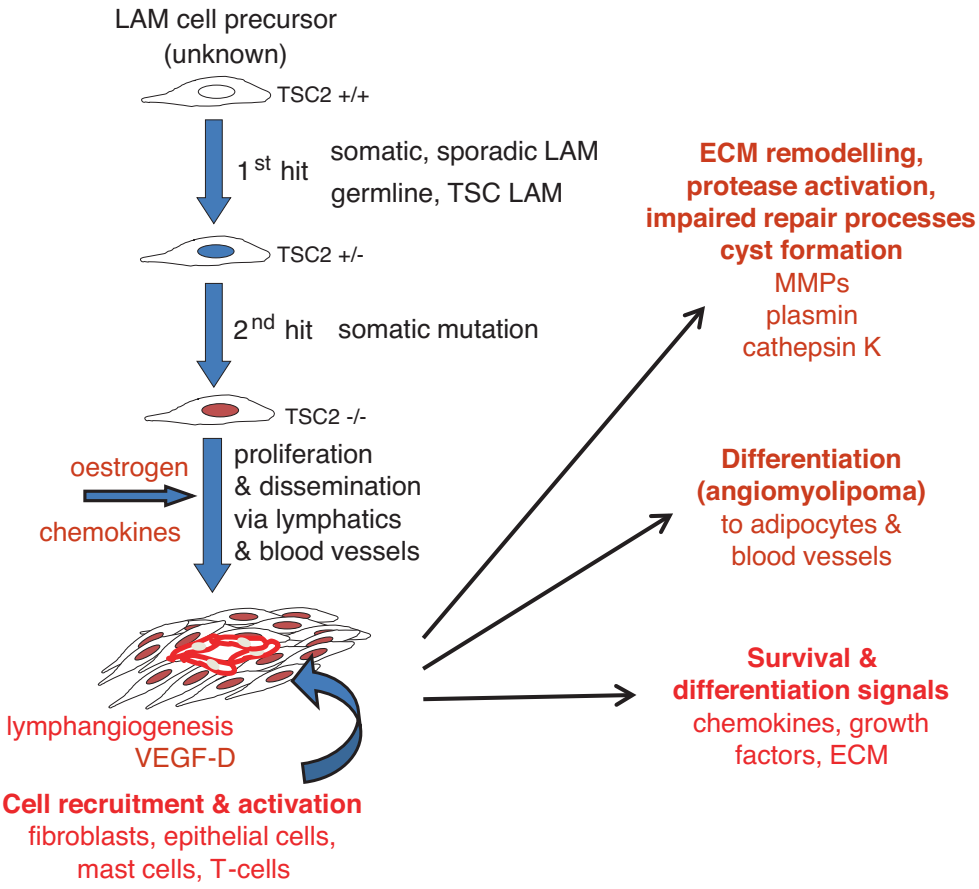


Fig. 19.2 Cellular and pathologic events contributing to the development of LAM. Biallelic inactivation of TSC-2 results in loss of functional tuberin protein in the LAM precursor cell. This confers a survival advantage and metastatic capability which is likely to be oestrogen dependent. LAM cells disseminate and form nodules acting as foci for lymphangiogenesis. The LAM nodule provides a supportive environment for LAM cell growth possibly allowing differentiation into the other components of angiomyolipoma, including blood vessels and adipocytes. LAM cells recruit stromal cells, including LAM-associated fibroblasts and inflammatory cells. The production of proteases is likely to result in cyst formation and support further LAM cell dissemination

Presentation

LAM most commonly presents with respiratory symptoms, but abdominal disease, LAM detected as a consequence of TSC and identification in asymptomatic individuals undergoing CT scanning for other problems also occur.

Cysts replace the lung parenchyma to cause breathlessness and symptoms of airway narrowing, including cough and wheezing. This collection of symptoms is the presenting feature in over 40% of patients and frequently leads to treatment for asthma: a poor response to treatment or other features not typical of asthma may then prompt further investigation. Lung cysts also cause pneumothorax which may be recurrent and difficult to treat. Dyspnoea or pneumothorax are the presenting problem in the majority of patients. Around 5% of patients present with chylous pleural effusions due to obstruction of the thoracic duct by LAM cells [1]. The combination of chylous effusions and lung cysts in women is pathognomonic of LAM. Some patients expectorate chylous secretions due to intrapulmonary lymphatic stasis, whilst others may develop haemoptysis. Onset of respiratory symptoms may occur during pregnancy particularly with refractory pneumothorax, including bilateral pneumothorax or chylopneumothorax. Symptoms may persist until surgical correction can be performed, often after delivery [25].

Abdominal disease may be the first symptom of LAM. Most commonly this is with symptomatic renal angiomyolipoma, in some patients, preceding lung symptoms by many years [26]. Sometimes large tumours present with abdominal fullness but more commonly haemorrhage causes acute flank pain with or without haematuria. The use of CT scanning to evaluate renal tumours in these situations may coincidentally reveal lung cysts. Up to 20% of patients have cystic lymphatic masses caused by occlusion of abdominal, retroperitoneal or pelvic lymphatics by LAM cells. Termed lymphangioleiomyomas, these can give rise to abdominal bloating, swelling or peripheral oedema [27]. In a small number of cases, discovery of these masses may lead to a biopsy for suspected malignant disease often resulting in persistent chylous leakage. The tissue obtained reveals characteristic histology usually leading to the correct diagnosis. In rare cases, symptoms from chylous ascites can be the presenting problem although chylous ascites is generally associated with more advanced disease.

Table 19.1 Clinical scenarios suggestive of LAM

'Asthma' with poor response to treatment, especially with fixed airway obstruction
Early onset 'emphysema', especially in non-smokers
Recurrent or bilateral pneumothorax in women
Pneumothorax in pregnancy
Chylothorax or chylous ascites
Respiratory symptoms in TSC
Angiomyolipoma in women
Asymptomatic lung cysts identified during medical imaging

The prevalence of LAM in TSC increases with age: at 40 years cysts are present in up to 80% of women [28]. Although respiratory symptoms occur in many, only a minority of these women develop severe respiratory disease [29–31]. The presenting symptoms in TSC-LAM are similar to sporadic LAM with dyspnoea and pneumothorax. Treatment guidelines for TSC recommend screening adult women for TSC at 18 years [32]. This, as well as CT performed for non-respiratory problems in both TSC and sporadic LAM, inevitably results in the detection of patients with early and asymptomatic disease. Occasionally, patients with severe learning difficulties may present with advanced disease and even cyanosis or behavioural change due to pneumothorax. The majority of patients with TSC-LAM have renal angiomyolipomas which may be very large, multiple and bilateral and may be the presenting feature [33]. Lymphatic disease appears less common in TSC-LAM than sporadic disease [34]. Clinical presentations suggestive of LAM are listed in Table 19.1.

Diagnosis and Workup

Interstitial changes and preserved lung volumes may be present on chest radiograph (Fig. 19.3) although plain X-rays are often normal at diagnosis. In patients with suspected LAM, high-resolution CT scanning is the investigation of choice. The characteristic features are of thin-walled cysts. Cysts are evenly distributed throughout the lung fields, are generally round and vary in diameter between 0.5 and 5 cm. The intervening lung parenchyma is normal although occasionally small areas of airspace shadowing representing haemorrhage or chyle may be present [35] (Fig. 19.4). Widespread alveolar shadowing, however, is not typical of LAM. Chylous pleural effusions and pneumothorax may also be present (Fig. 19.5). In patients with TSC, nodules of proliferating type 2 pneumocytes, termed multifocal micronodular pneumocyte hyperplasia, may coexist with LAM or occur without LAM [36]. The presence of interstitial abnormalities, thick-walled cysts or unevenly distributed cysts is not typical of LAM. CT alone is not diagnostic of LAM and once LAM is suspected, confirmatory features are required to make a definite diagnosis, including either the presence of renal angiomyolipomas, chylous pleural or abdominal effusions, lymphatics involved by LAM or the presence of TSC. Current diagnostic criteria are summarised in Box 19.1 [37]. A previous history of renal tumours and symptoms of TSC should be sought. A careful clinical examination should be made for signs of TSC, including facial angiofibromas, periungual fibromas, hypomelanotic macules and shagreen patches. In some patients, skin abnormalities are subtle and where there is no history of epilepsy or learning difficulties the diagnosis can be difficult to make and evaluation by a TSC specialist or dermatologist may be helpful. Diagnostic criteria for TSC have been clearly defined [38] but where doubt exists referral to a clinical geneticist is advised. To detect the abdominopelvic manifestations to aid diagnosis and management, once LAM is suspected, contrast CT scanning of the abdomen and pelvis is recommended to detect angiomyolipoma, lymphangioleiomyoma, lymphadenopathy or ascites which are collectively present in over half of patients [39].

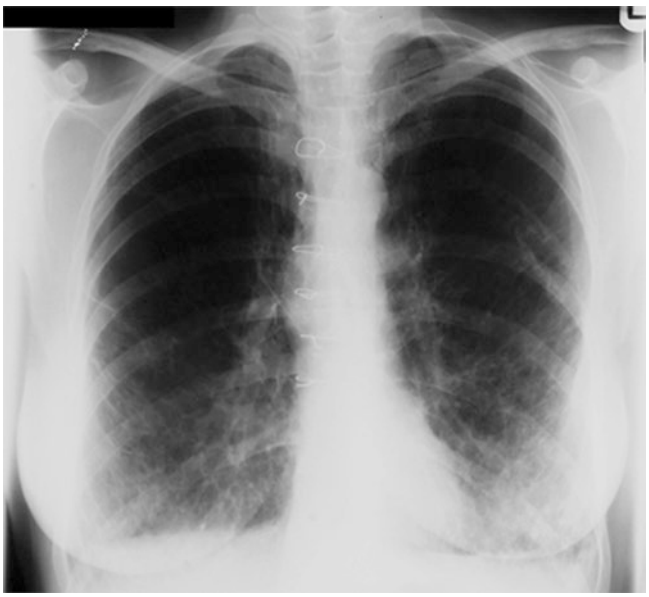


Fig. 19.3 Chest radiograph of a patient with advanced LAM. Reticular shadowing with preserved lung volumes, sternal wires from pleural surgery are visible

Pulmonary function testing may be normal in early disease, but DL_{CO} is often reduced even in early disease [40]. As the disease progresses, airflow obstruction develops. Lung volumes are generally preserved [41]. Cardiopulmonary exercise testing (CPET) provides more information on physiological derangement in early disease although is seldom performed [42]. The 6 min walk test is more practical than CPET and provides useful information about disability and exertional hypoxaemia.

Women with both sporadic and TSC-LAM are at increased risk of meningioma being present in 8 of 250 patients

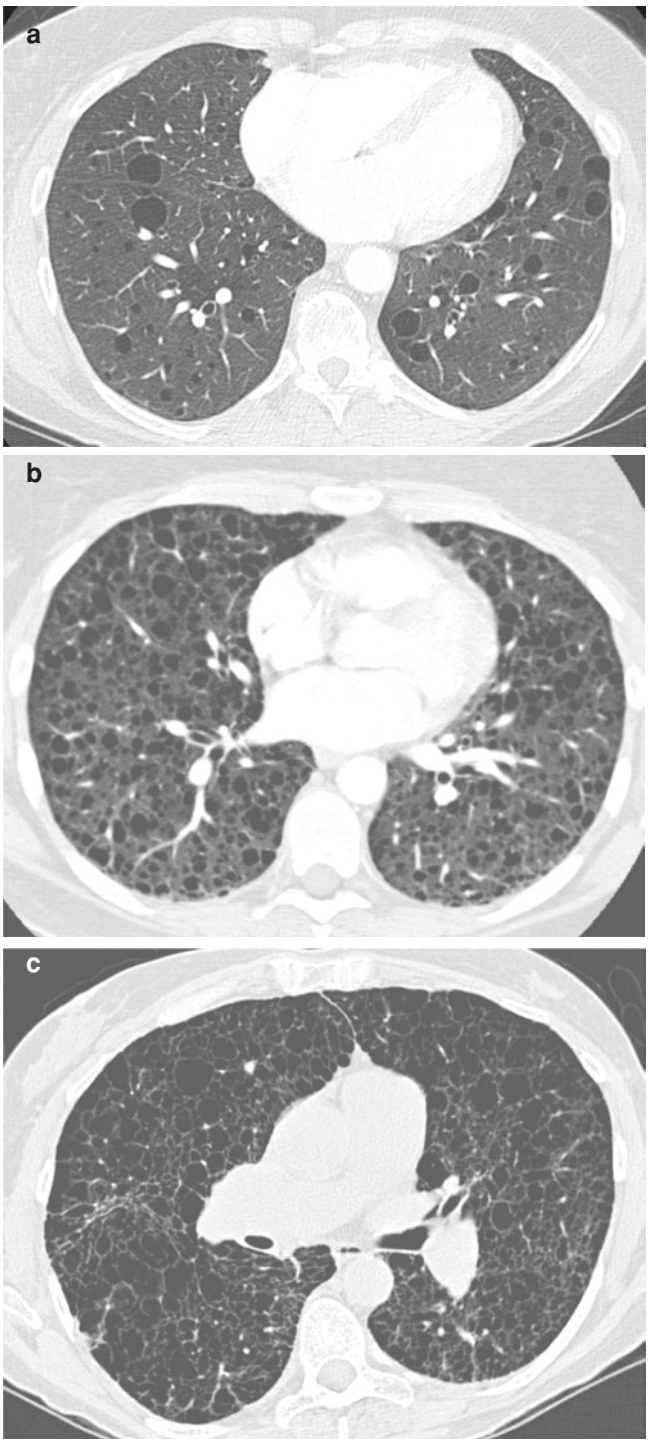


Fig. 19.4 High-resolution CT appearances in LAM. (**a**) A patient with very slowly progressive disease who has normal spirometry and mildly reduced gas transfer. (**b**) A patient with progressive LAM with significant airflow obstruction and impaired gas transfer. (**c**) Advanced lung disease with very little lung parenchyma visible

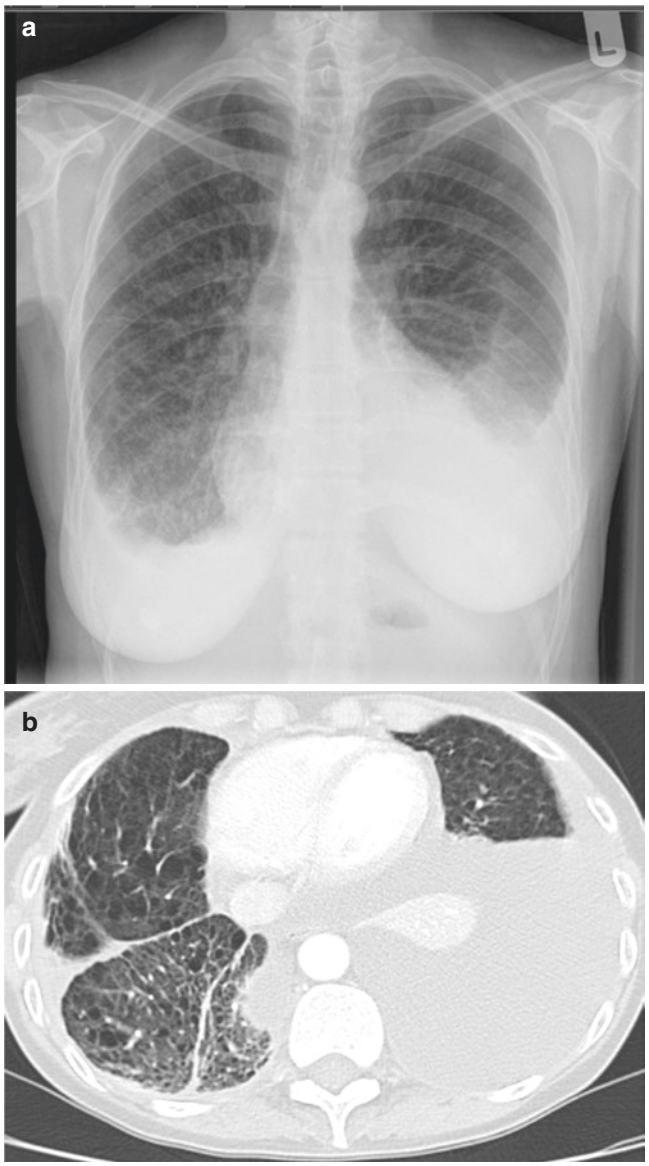


Fig. 19.5 Chylous complications. (**a**) Chest X-ray and (**b**) CT from the same patient showing bilateral pleural effusions and parenchymal changes due to LAM

screened by MRI scanning in one series [43]. Some meningiomas can cause symptoms and require surgery. MRI of the brain may be performed at baseline especially in the presence of headache, seizures or other neurological symptoms. In patients with TSC-LAM and those presenting with LAM who are suspected of having TSC, brain MRI scanning should also be performed where subependymal giant cell astrocytoma (SEGA), subependymal nodules and white matter abnormalities may be present [39].

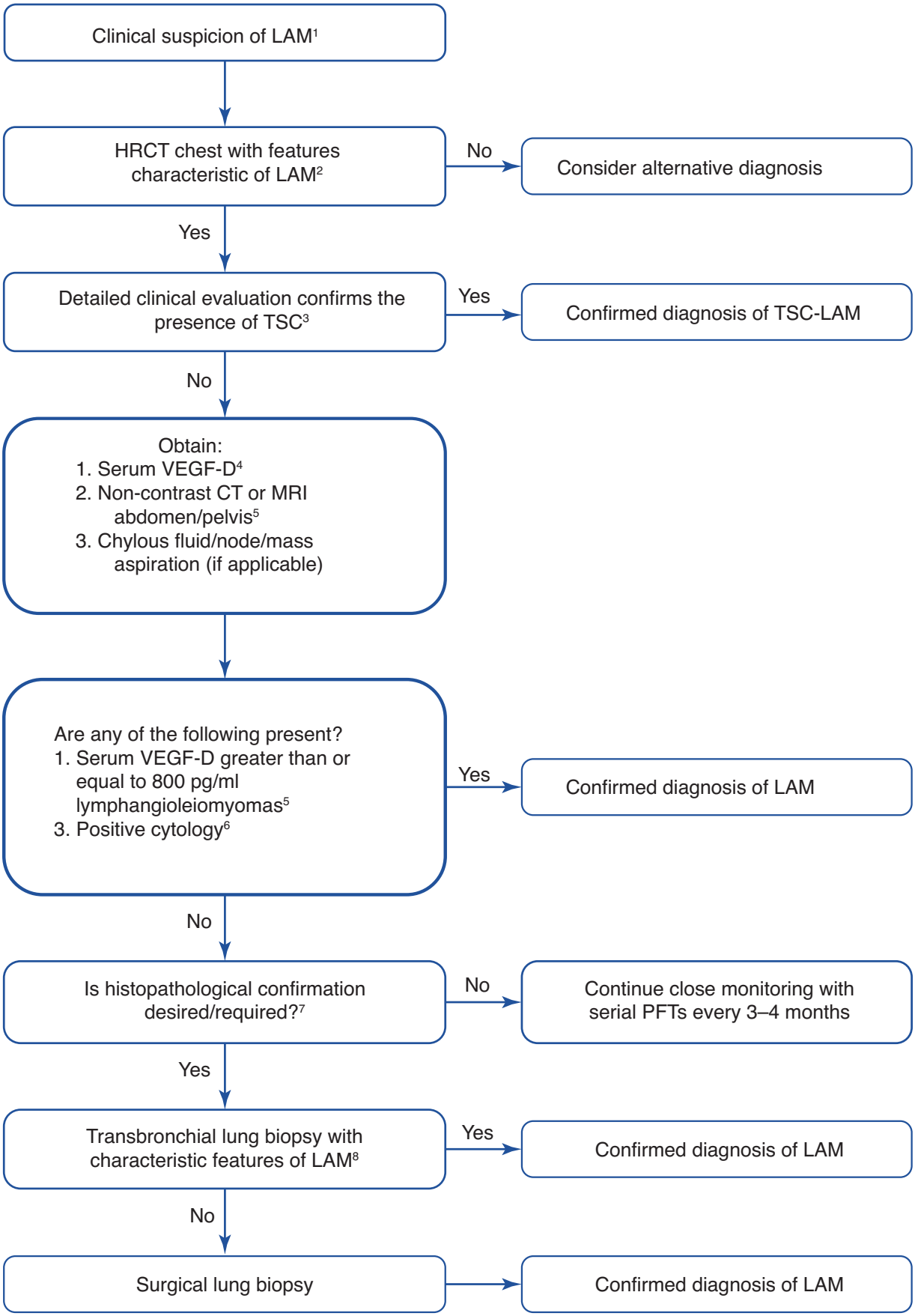
A definite diagnosis of LAM can be made without lung biopsy in around 2/3 of patients [44]. The lymphangiogenic growth factor, vascular endothelial growth factor-D (VEGF-D), is elevated in around 2/3 of patients with LAM, particularly those with lymphatic involvement [45]. A serum VEGF-D level of greater than 800 pg/mL has been shown to differentiate LAM from other cystic lung diseases when used

in combination with other clinical features, avoiding the need for lung biopsy [44, 46]. VEGF-D has also been correlated with disease severity and response to treatment with mTOR inhibitors [47]. At the time of writing, the test is not routinely available in all centres.

In those with suspected LAM and low VEGF-D levels, a lung biopsy is required to make a firm diagnosis. Whether to perform a lung biopsy or not should be discussed with the patient. In general terms, it is important to obtain a definite diagnosis in patients with progressive disease who require (or may require in the future) specific treatment for LAM. Those with few symptoms and stable lung function may be observed with biopsy being performed if the disease progresses [39]. Lung biopsy may be hazardous for patients with advanced disease and should only be considered if essential to management. Lung tissue may be obtained by transbronchial biopsy and when combined with immunostaining with the monoclonal antibody HMB45 can be diagnostic in some cases and avoid the need for a surgical biopsy [48, 49]. Video-assisted thoracoscopic biopsy is performed more often, gives a better indication of the tissue architecture which provides some prognostic information and has better sensitivity and specificity. The American Thoracic Society and Japanese Respiratory Society LAM Guidelines outline the diagnostic strategy and workup for those with suspected LAM (Fig. 19.6) [37].

In most cases the appearance of cysts surrounded by nodular proliferations of mesenchymal cells is sufficient to make the diagnosis in the correct clinical context. In early disease, LAM cells may be sparse and their detection can be improved by immunostaining for the smooth muscle markers α-smooth muscle actin and desmin, oestrogen and progesterone receptors [50, 51] (Fig. 19.7). HMB45 stains 30–70% of LAM cells in biopsy tissue. HMB45 is particularly useful diagnostically, not being expressed in normal lung.

Fig. 19.6 ATS/JRS diagnostic algorithm. The proposed strategy aims to confirm the diagnosis of LAM using the least invasive approach. (1) Suspect LAM in women presenting with worsening dyspnoea and/or pneumothorax/chylothorax. Most patients with LAM will have an obstructive defect on PFTs. Some patients, especially early in their disease course, may be asymptomatic and have normal PFTs. (2) Characteristic HRCT features are the presence of multiple, bilateral, round, well-defined, relatively uniform, thin-walled cysts in a diffuse distribution. The intervening lung parenchyma often appears normal. Other features sometimes present on CT scanning are chylous pleural effusions, pneumothorax, ground-glass opacities suggestive of chylous congestion, or multiple tiny nodules characteristic of multifocal micronodular pneumocyte hyperplasia in TSC-LAM. (3) Features suggestive of TSC include subungual fibromas, facial angiofibromas, hypomelanotic macules, confetti lesions, shagreen patches, positive family history of TSC, history of seizures or cognitive impairment, or presence of cortical dysplasias, subependymal nodules and/or subependymal giant cell astrocytomas on brain imaging. (4) Serum VEGF-D is currently available in a limited number of Centres including Cincinnati Children's Hospital Medical Center: www.cincinnatichildrens.org/ttdsl. (5) The diagnosis of angiomyolipoma can usually be made radiographically on the basis of the presence of fat in the tumours. Lymphangioleiomyomas can typically be diagnosed on the basis of characteristic radiographic appearance. (6) Cytological analysis of pleural fluid for the diagnosis of LAM is only available at select centres. (7) The decision to obtain tissue confirmation via invasive means should be made on a case by case basis. For some patients with mild disease and few symptoms, a clinical diagnosis of probable LAM with serial monitoring may be sufficient if a definitive diagnosis of LAM would not change management and some level of diagnostic uncertainty is acceptable to the patient and clinician. Every attempt should be made to establish the diagnosis of LAM with certainty before initiation of pharmacologic therapy with mTOR inhibitors. (8) Transbronchial biopsy has an estimated yield of greater than 50% for the diagnosis of LAM. Consultation with an expert centre is recommended in cases where transbronchial biopsy is being considered, including for the interpretation of the biopsy. *AML* angiomyolipoma, *CT* computed tomography, DI_{CO} diffusion capacity of the lung for carbon monoxide, *HRCT* high-resolution computed tomography, *MRI* magnetic resonance imaging, *mTOR* mechanistic target of rapamycin, *PFTs* pulmonary function tests, *TSC* tuberous sclerosis complex, *VEGF-D* vascular endothelial growth factor-D. (Adapted and reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society. Gupta, N., et al. (2017). "Lymphangioleiomyomatosis Diagnosis and Management: High-Resolution Chest Computed Tomography, Transbronchial Lung Biopsy, and Pleural Disease Management. An Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guideline." American Journal of Respiratory and Critical Care Medicine 196 (10): 1337–1348. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society)


Clinical suspicion of LAM[1]
HRCT chest with features characteristic of LAM[2]
No
Consider alternative diagnosis
Yes
Detailed clinical evaluation confirms the presence of TSC[3]
Yes
Confirmed diagnosis of TSC-LAM
No
Obtain:
1. Serum VEGF-D[4]
2. Non-contrast CT or MRI abdomen/pelvis[5]
3. Chylous fluid/node/mass aspiration (if applicable)
Are any of the following present?
1. Serum VEGF-D greater than or equal to 800 pg/ml lymphangioleiomyomas[5]
3. Positive cytology[6]
Yes
Confirmed diagnosis of LAM
No
Is histopathological confirmation desired/required?[7]
No
Continue close monitoring with serial PFTs every 3–4 months
Yes
Transbronchial lung biopsy with characteristic features of LAM[8]
Yes
Confirmed diagnosis of LAM
No
Surgical lung biopsy
Confirmed diagnosis of LAM

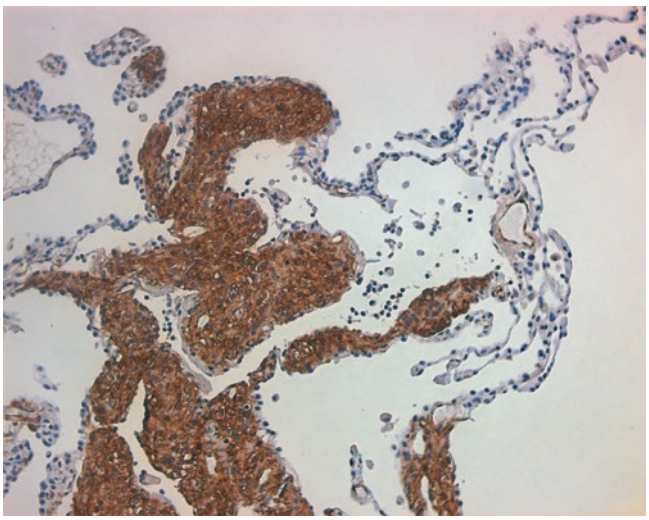


Fig. 19.7 Histological appearance of LAM. Lung section showing lung infiltrated by nodular proliferations of LAM cells which stain strongly for the smooth muscle marker, α-smooth muscle actin (brown)

Prognosis

It is currently difficult to predict prognosis accurately at diagnosis in individual patients. Various studies have associated clinical and pathologic features with outcome and it is reported that pre-menopausal status, presentation with breathlessness rather than pneumothorax, low K_{CO} at presentation, extensive LAM involvement of the lung biopsy and the presence of bronchodilator reversibility have been associated with more rapid disease progression in cohort studies [52–57]. However, these factors lack predictive power in individuals and in practice, calculation of the disease trajectory by estimating the change in lung function from the onset of symptoms or over a period of observation is probably the most reliable approach but risks an irreversible fall in lung function. Estimating survival for women with LAM is difficult as older studies have tended to over-represent patients with severe disease and worse outcome and it is important to put these studies into context for patients. Recent studies based on larger patient cohorts have estimated median transplant-free survival to be between 20 and 30 years [2, 58]. Improvements in lung transplant outcome and the impact of mTOR inhibitors mean that the prognosis for many patients with a recent diagnosis of LAM should continue to improve.

Management

General Measures

Women with definite or probable LAM are likely to benefit from general measures applicable to other chronic respiratory diseases and should be advised to maintain a normal weight, refrain from smoking, receive prophylactic vaccinations against influenza, pneumococcus and COVID19 and in those limited by dyspnoea undertake pulmonary rehabilitation [59]. Patients with LAM should receive advice on the symptoms of pneumothorax and what to do should these occur. Where relevant, symptoms of bleeding angiomyolipoma should also be discussed. Patients should avoid supplemental oestrogen, particularly in the form of the combined oral contraceptive and post-menopausal hormone replacement therapy [39].

The diagnosis of a rare or orphan disease can lead to a feeling of isolation and helplessness. This may be compounded if incorrect information is given about the disease at diagnosis or the patient is left to find out about the disease themselves. At this time, support from other patients through patient organisations can be very helpful. Strong patient groups exist in many countries, including the UK (www.LAMaction.org), the USA (www.thelamfoundation.org), France (http://asso.orpha.net/FLAM/) and others. In addition rare disease organisations, such as Orphanet (http://www.orpha.net/consor/cgi-bin/index.php), provide disease specific information.

Parenchymal Lung Disease

Longer-term management should be aimed at determining rate of disease progression and avoiding complications. During the course of the disease, lung function, particularly rate of decline of FEV_1, DL_{CO} and exercise tolerance should be assessed regularly. Routine follow-up, including spirometry and gas transfer, is generally scheduled between one to four times a year, with the interval between follow-up dependent upon the individual patient's previous rate of disease progression. On average patients lose FEV_1 by around 60–120 mL/year [41, 60], with loss most rapid in pre-menopausal women [57].

Pleural Disease

Patients with LAM are at high risk of pneumothorax. Pneumothorax occurs in 70% of patients and is recurrent in the majority of these. On average, patients have four pneumothoraces with each episode requiring 7 days in hospital [61]. Surgical intervention reduces recurrence rates and should be considered after the patient's first pneumothorax [37]. Evidence is only available from case series but suggests that surgical approaches may be more effective than pleurodesis via chest tube [25, 61]. In a significant number of cases, more than one surgical procedure is required. There is no clear evidence to suggest one procedure is superior to

another in patients with LAM. It is therefore appropriate to perform the minimal degree of pleural intervention which will prevent recurrence. Although pleural surgery results in increased peri-operative bleeding during transplant procedures, it does not seem to affect overall survival [62] and patients with pneumothorax should be treated with the most appropriate surgical procedure to treat pneumothorax [37].

Clinically significant chylous pleural effusions affect around one in ten patients. Occasionally these are stable and can merely be observed. Simple drainage usually results in rapid re-accumulation of the fluid [63]. Rates of fluid formation may be reduced by a low fat diet. Supplementation of medium chain triglycerides, that are not absorbed through the lymphatic system, has been used to avoid insufficient intake of lipids and the lipid soluble vitamins A, D, E and K. The use of the mTOR inhibitor rapamycin has been shown to reduce the volume of chylous pleural effusions and reduce the need for thoracentesis and other surgical interventions in these patients and is now the first-line treatment for these complications [64].

Renal Angiomyolipoma

Patients with angiomyolipomas should have their renal tumours monitored regularly. Once initial cross-sectional imaging using either CT or MRI has been performed, follow-up imaging in uncomplicated cases, where a straight forward measurement of growth is required, may be performed by ultrasound (Fig. 19.8). For small tumours with a low risk of bleeding, renal imaging once a year is recommended. For tumours at higher risk of bleeding, specifically, those greater than 4–5 cm in their longest axis, those with aneurysmal blood vessels and symptomatic tumours should be evaluated by a urologist, ideally with expertise in conservative management of these lesions [65]. As angiomyolipomas are frequently bilateral, treatment of large and symptomatic lesions should aim to conserve healthy renal tissue where possible. Those with TSC-LAM almost always have renal angiomyolipomas which tend to be bigger and more likely to bleed than those in patients with sporadic LAM [33] (Fig. 19.9). Current guidelines for those with TSC now suggest the consideration of mTOR inhibitor therapy for angiomyolipomas greater than 3 cm [32]. Physical approaches can be used particularly where risk of haemorrhage is high and include selective transcatheter embolisation or conservative nephron sparing surgery. Outcomes are similar between techniques although embolisation may be performed without the use of

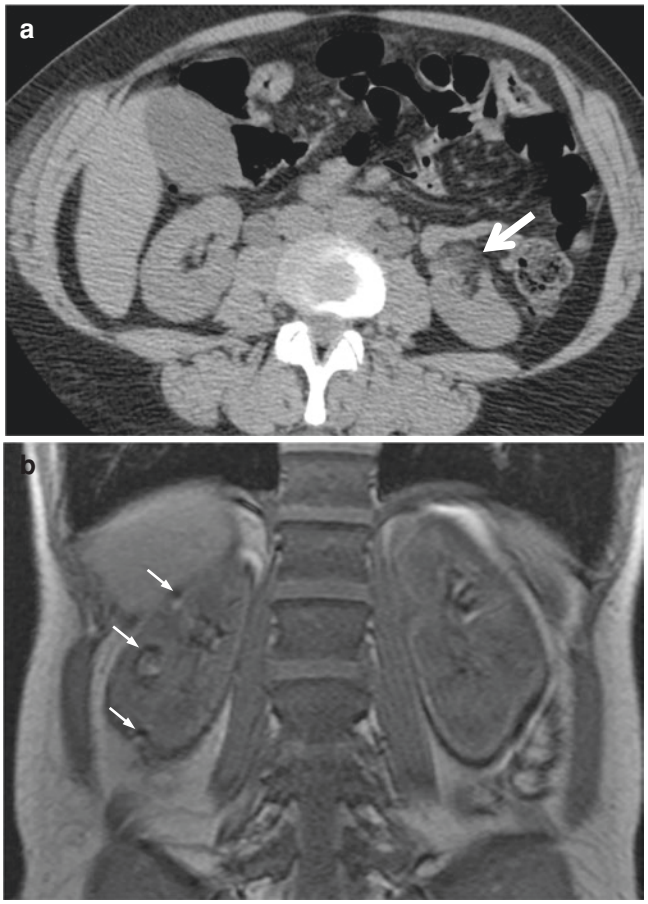


Fig. 19.8 CT appearances of angiomyolipoma in patients with sporadic LAM. (**a**) A characteristic small asymptomatic lesion in the anterolateral aspect of the left kidney (arrow). The low density areas containing fat are characteristic of angiomyolipoma. (**b**) Coronal section of a T1-weighted MRI image showing multiple small angiomyolipomas in the right kidney (arrows)

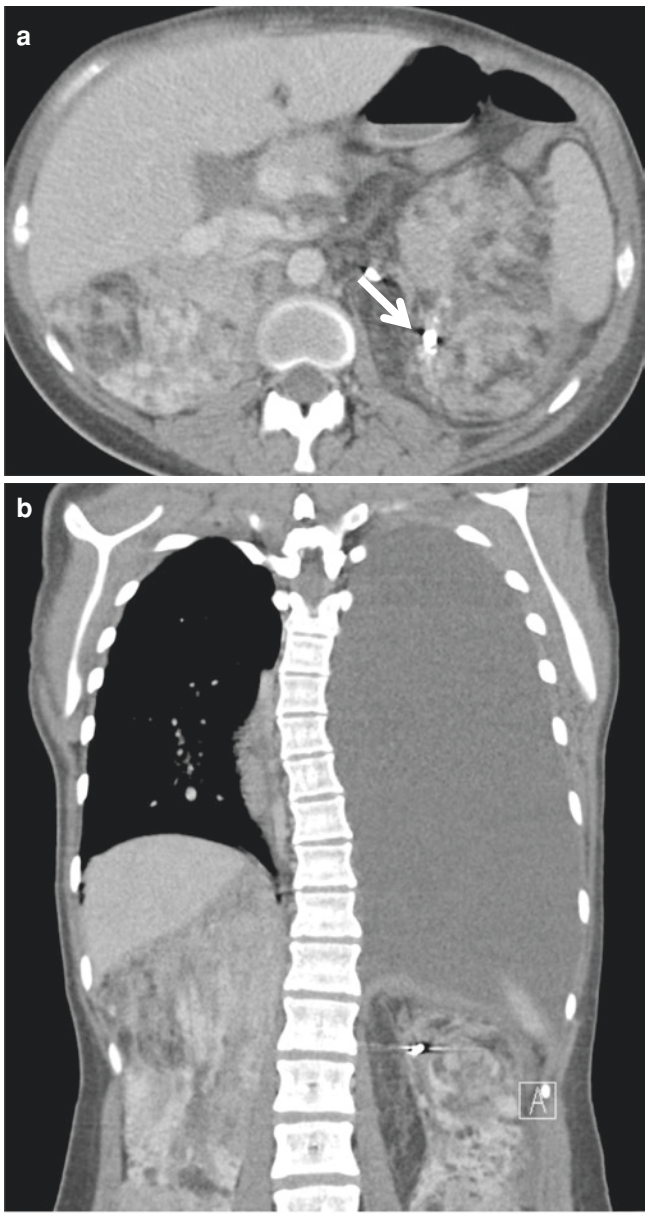


Fig. 19.9 Angiomyolipomas in TSC-LAM. (**a**) A cross-sectional image of a patient with TSC-LAM and multiple, bilateral angiomyolipomas greatly enlarging both kidneys. The arrow highlights an embolisation coil, used to treat a bleeding lesion. (**b**) A coronal CT of the same patient who presented with dyspnoea due to a large left chylous effusion

a general anaesthetic, including during episodes of haemorrhage and pregnancy [66].

Abdominopelvic Lymphatic Disease

Occlusion of the axial lymphatics by LAM cells can result in retroperitoneal cystic structures termed lymphangioleiomyomas. Although often asymptomatic, these lesions can be associated with abdominal distension and bloating [67] and characteristically enlarge throughout the day, which can be associated with worsening symptoms in the afternoon [68]. Rarely, larger lesions can cause pressure symptoms on other organs including the bladder. Abdominal lymphatic disease may be associated with chylous ascites which can also cause abdominal symptoms (Fig. 19.10). Surgical treatment of abdominal lymphatic masses can be followed by prolonged chylous leakage and is best avoided. A number of case reports and series have suggested that treatment with mTOR inhibitors is effective for symptomatic abdominopelvic lymphatic disease resulting in resolution of symptomatic chy-

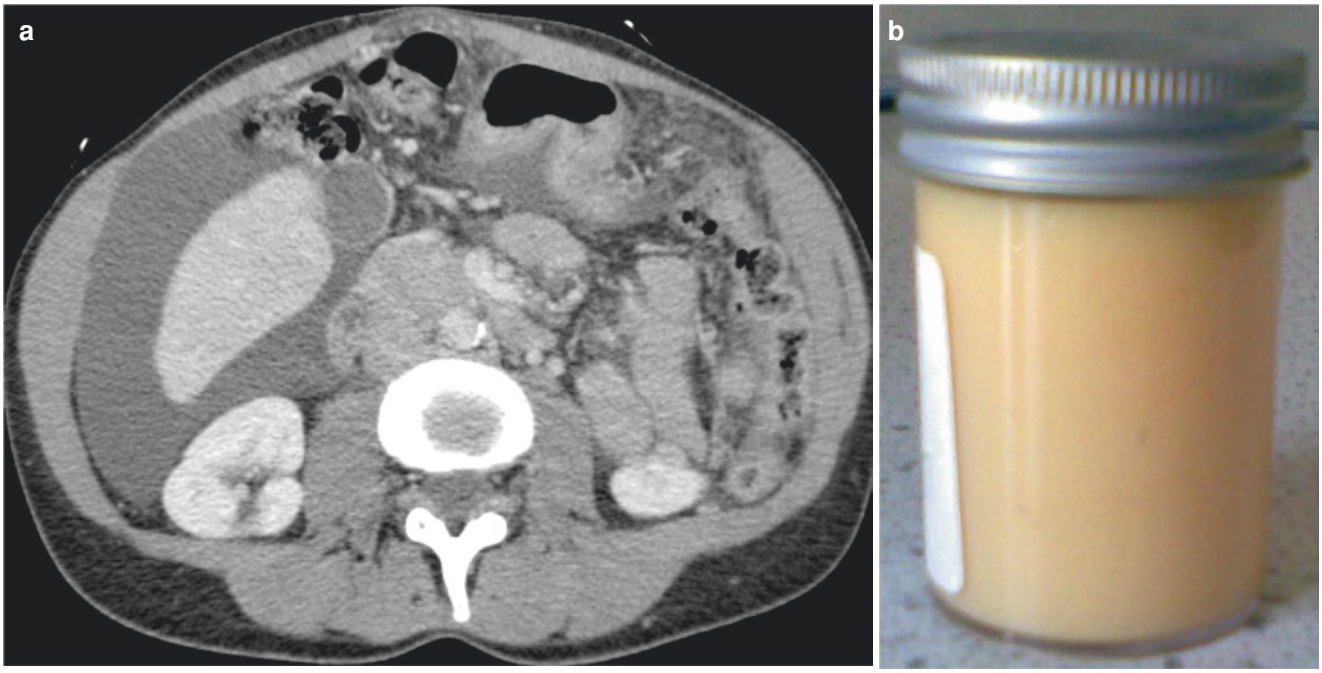


Fig. 19.10 Abdominal lymphatic disease. (**a**) CT showing dilated retroperitoneal lymphatics and chylous ascites. (**b**) The appearance of chylous fluid from a patient with LAM

lous ascites and lymphangioleiomyomas [64]. In resistant cases, imaging of the lymphatic circulation with a view to selective embolization rather than a 'blind approach' is essential.

Pregnancy

During pregnancy, women with LAM have an increased risk of pneumothorax, chylous effusion and possibly bleeding angiomyolipoma [25]. Patients with TSC-LAM have a 50% chance of having a child with TSC and these risks should all be discussed prior to pregnancy. The risks of pregnancy to the mother are likely to depend upon her lung function. At present it is unknown if pregnancy influences the course of LAM in the long term although one retrospective study suggests that pregnancy does not significantly accelerate the disease in most cases [69].

Tuberous Sclerosis

Patients with LAM presenting to chest physicians may have TSC, including previously undiagnosed disease. It is now recognised that LAM and angiomyolipoma are two of the leading causes of morbidity and mortality in adults with TSC [70, 71]. Although some patients with TSC may be under a TSC specialist, those with LAM as their main clinical manifestation of TSC may not. The main screening investigations for patients with TSC have been described in consensus statements and are summarised in Table 19.2 [32]. Those requiring genetic counselling, those with symptomatic epilepsy,

Table 19.2 Baseline investigations for patients with TSC

Clinical feature	Timing of assessment	Initial testing
Cognitive function	At diagnosis and at school entry	Neurodevelopmental testing
Retinal hamartomas	At diagnosis	Fundoscopy
Epilepsy	If seizures occur	Electroencephalography
Cardiac rhabdomyomas	At diagnosis or if cardiac dysfunction occurs	Electrocardiography Echocardiography
Renal angiomyolipomas and cysts	At diagnosis	Renal MRI
LAM	Women in adulthood and if pulmonary dysfunction occurs	High-resolution CT and baseline pulmonary function
Cerebral hamartomas and tumours	At diagnosis	Cranial MRI

Adapted from [32]

brain tumours, cognitive and other neurologic disorders, including autism, disfiguring skin lesions and renal disease, including polycystic kidneys, are all likely to benefit from specific interventions and monitoring by specialists in these areas. TSC patients with mutations in either *TSC-1* or *TSC-2* may develop LAM and those with mutations in *TSC-2* tend to have more lung cysts, worse lung function and are more likely to develop severe lung disease. *TSC-2* patients are also more likely to have large and symptomatic angiomyolipomas. *TSC-2* is located on chromosome 16 adjacent to *PKD1,* the gene associated with adult polycystic kidney disease. In some patients with large deletions in *TSC-2* there is also disruption of *PKD1* and these patients have a syndrome comprising TSC (including LAM and angiomyolipomas) and renal cysts with a high prevalence of renal failure [72, 73].

Lung disease in those with TSC may be as severe as in patients with sporadic LAM, presenting at a similar age with the same symptoms and resulting in respiratory failure and death [70]. However, this is not the case for the majority of those with TSC-LAM for whom the disease is mild and may not progress. Although over one-third of women with TSC will have lung cysts compatible with LAM, only a small minority of these patients will have significant pulmonary symptoms and a progressive fall in lung function. The increased use of CT screening in adult women with TSC has identified many of these patients with mild disease and their management should involve general measures for LAM, such as advice about pneumothorax and oestrogen avoidance [32]. Lung cysts also occur in men with TSC, but cysts tend to be few in number and very seldom cause symptoms or progressive disease [74, 75] and screening for LAM with thoracic CT scanning is only recommended for men with respiratory symptoms [32]. Whilst LAM can be the major health problem in adult women with TSC, for the majority of patients, LAM may be only one of their medical problems possibly with epilepsy, autism and learning difficulties being their major clinical issues with non-respiratory clinicians being their main care providers.

Drug Treatment

Bronchodilators

Around 25% of patients have a positive bronchodilator response according to American Thoracic Society criteria, particularly those with airflow obstruction [25, 53]. One recent study evidence suggests beta agonists might also alter disease progression in LAM, although this needs confirmation [76]. Although anti-muscarinic drugs are untested in LAM, long-acting beta agonist and anti-muscarinic combinations are frequently used in LAM [77].

mTOR Inhibitors

LAM cells have constitutive activation of the mTORC1 complex and in a randomised placebo controlled trial the mTOR inhibitor rapamycin (sirolimus) reduced the decline in FEV_1 of patients with impaired lung function [60]. Rapamycin also reduces the volume of angiomyolipomas [78, 79] and subependymal giant cell astrocytoma (SEGA) in patients with TSC [80]. Randomised controlled trials of other mTOR inhibitors, including everolimus, show good efficacy in other indications in patients with TSC, including angiomyolipoma [81], SEGA [82] and epilepsy [83]. Although evidence in pulmonary LAM is not as strong, everolimus appears effective for pulmonary [84] and extra-pulmonary disease [85]. mTOR inhibitors cause side effects in the majority of patients treated, particularly mouth ulcers, hyperlipidaemia, nausea, diarrhoea, proteinuria and peripheral oedema. Pneumonitis may also occur less commonly. An increased susceptibility to infections was an initial concern although this has not emerged as a significant problem [86]. For LAM, rapamycin is generally dosed to achieve a serum level of 5–10 ng/mL although some case series have suggested serum levels of 2–5 ng/mL might be equally efficacious and reduce side effects [87, 88]. Serum levels should be monitored at the start of therapy after 14 days, and at routine clinical review at least twice annually or if toxicity is suspected [89]. Current indications for use of mTOR inhibitors in LAM include an FEV_1 of less than 70% predicted [10], or decline in FEV_1 of 90 mL/year or greater [10, 60], chylous collections unresponsive to other therapies [64] and angiomyolipoma endangering renal function which are not suitable for surgical therapy [79]. In current practice the decision to use an mTOR inhibitor may also be influenced by the patient's likely future course, with those with younger, pre-menopausal subjects tending to have more active disease than post-menopausal women [57].

Anti-Oestrogen Therapy

Although LAM appears to be an oestrogen-dependent disease, observational and retrospective studies have suggested that blocking oestrogen production by oophorectomy, GnRH agonists [90], progesterone [41, 91] or oestrogen receptor binding drugs, such as tamoxifen, does not affect disease progression in the majority with established disease. Moreover, as these drugs are commonly associated with adverse effects, including increased growth of meningioma [92] and reduced bone density [90], they are not recommended for routine use [10, 39]. A small study has examined aromatase inhibition in post-menopausal women with LAM suggesting it was safe and worthy of further study [93].

Experimental Therapies

Studies of the molecular pathology of LAM have suggested a number of potential candidate drugs for LAM, both as stand-alone agents and as adjuncts to mTOR inhibition. Initial safety studies have been performed for simvastatin, chloroquine [94] with studies of resveratrol and tyrosine kinase inhibitors in progress.

Interventions for Advanced Disease

Those with severe disease are likely to develop hypoxaemia and secondary pulmonary hypertension and seem particularly prone to respiratory infections.

Oxygen Therapy

Hypoxaemia at rest, on exertion and overnight are common in patients with moderate to advanced disease. As patients with LAM are relatively young and may have few comorbidities they are frequently keen to keep active. It is therefore important to assess exercise-induced hypoxaemia and consider ambulatory oxygen therapy. At present there are no evidence-based guidelines for the use of oxygen therapy in LAM and not unreasonably, patients with LAM are often prescribed oxygen as for other patients with obstructive lung diseases.

Pulmonary Hypertension

A small proportion of patients with LAM develop pulmonary hypertension secondary to advanced lung disease and hypoxaemia [95]. LAM cells can infiltrate small pulmonary arteries to involve the pulmonary vasculature and rarely patients can develop pulmonary hypertension earlier in the course of the disease [96]. Screening for pulmonary hypertension by echocardiography may be useful for those with advanced disease, but is only likely to be helpful in patients with early disease if dyspnoea is out of proportion to their lung function defect.

Although not well described or studied, it is apparent that patients with advanced disease often suffer respiratory infections, both with typical organisms but also *Pseudomonas* and atypical mycobacteria. Aggressive investigation and treatment of infections in these patients can improve quality of life.

Patients with LAM and advanced disease may be treated by lung transplantation, including those with TSC-LAM. Patients with LAM represent around 1% of lung transplantees and the overall survival for these patients is favourable when compared with lung transplantation for other lung diseases [97, 98]. At the time of transplant, patients generally have limited exercise tolerance with New York Heart Association functional class III or IV and severe impairment in lung function with resting hypoxaemia [62, 97]. Particular aspects of the pre-transplant assessment for these patients should include a thorough assessment of renal angiomyolipomas. Although angiomyolipomas are not associated with post-transplant renal failure, pre-transplant embolisation may be needed to prevent renal haemorrhage postoperatively. Women with LAM tend to be at risk of low bone density due to chronic lung disease and anti-oestrogen therapies [99]. As many of these patients require transplantation close to the menopause, bone mineral density should be assessed and where necessary treated with bisphosphonates as appropriate. Prior pleural interventions, particularly surgical treatment of pneumothorax and pleural effusions increases the incidence of peri-operative bleeding and operative duration but not overall survival [62]. The effect of mTOR inhibitors on wound healing post-transplantation has been a concern for transplant centres [100]. This must be balanced against the risk that withdrawal of mTOR inhibitors results in accelerated lung function decline. The evidence in this area is still evolving and currently varies with the individual transplant centre. Currently, many centres require cessation of mTOR inhibitors when patients are listed for transplant although some will continue sirolimus until the day of transplant, whilst others recommend the use of everolimus in pre-transplant patients as the shorter half-life is considered to reduce the risk of post-transplant wound dehiscence [101]. Although studies have suggested there is no overall differ-

Box 19.1 ATS/JRS Diagnostic Criteria for LAM

A definite diagnosis of LAM can be established when there is a compatible clinical history and characteristic HRCT *plus* one or more of the following:

- TSC
- Renal angiomyolipoma*
- Serum VEGF-D ≥ 800 pg/mL
- Chylous pleural effusion or ascites (confirmed by biochemical fluid analysis)
- Lymphangioleiomyomas*
- Cytology showing LAM cells or LAM cell clusters in chylous effusions or lymph nodes
- Lung or extra-pulmonary biopsy confirming LAM

*Angiomyolipoma and lymphangioleiomyomas can normally be diagnosed by a characteristic radiographic appearance. Adapted from [37].

Case Vignette

A 41-year-old woman developed exertional dyspnoea at the age of 18 and was treated for asthma. Breathlessness worsened over years and was poorly responsive to treatment. Over this period she worked as a technician and gave birth to five children. Some years later she developed abdominal discomfort and became aware of a fullness in her abdomen: irritable bowel syndrome was diagnosed. Four years later, following severe flank pain, she was admitted to hospital. A CT scan showed an 18-cm bleeding angiomyolipoma arising from the right kidney: the tumour was treated successfully by two-stage embolisation. The abdominal CT scan also revealed multiple lung cysts in the lung bases and a high-resolution chest CT was performed which showed changes consistent with advanced LAM. There were no signs of TSC and *TSC* gene analysis was normal. Sporadic LAM with renal angiomyolipoma was diagnosed. Lung function showed irreversible airflow obstruction with an FEV_1/FVC ratio of 34% and a gas transfer of 49% predicted. The history suggests LAM that has been present for over 20 years during which time her FEV_1 has deteriorated by >100 mL/year. Due to advanced and progressive lung disease she was treated with bronchodilators and sirolimus.

ence in survival between those treated with single or double lung transplant, occasionally over-inflation of the native lung can impair the function of the graft after single lung transplantation. Post-transplant, normal practice is to use tacrolimus-based regimens rather than sirolimus as this is likely to be optimal for graft function long term [102]. The outcome for women with LAM is at least as good as other lung diseases [103], and whilst recurrent LAM post-transplant has been reported, this is seldom clinically relevant and not a contraindication to transplant.

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