Solid Tumour Section
Mini Review

Lymphangioleiomyomatosis

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Identity

Alias: LAM

Note: Lymphangioleiomyomatosis (LAM) is a multi-system disease, affecting predominantly pre-menopausal women, that is characterized by proliferation of abnormal smooth muscle-like cells (LAM cells) leading to the formation of lung cysts, fluid-filled cystic tumors in the axial lymphatics (e.g., lymphangioleiomyomas), and abdominal tumors, primarily in the kidneys, comprising adipose cells, vascular structures and LAM cells (e.g., angiomyolipomas).

Clinics and pathology

Disease

Pulmonary disease
Note
Pulmonary disease is the main cause of morbidity and mortality. LAM usually presents with progressive breathlessness or with spontaneous recurrent pneumothorax, chylous effusions (chylothorax and ascites), or hemorrhage within an angiomyolipoma. Computed tomography scans show numerous thin-walled cysts throughout the lungs (Figure 1A and 1B), renal angiomyolipomas (Figure 2), and lymphangioleiomyomas (Figure 3). Pulmonary function abnormalities include airflow obstruction and gas exchange abnormalities.
Lung lesions in LAM are characterized by nodular infiltrates and clusters of LAM cells near cystic lesions and along pulmonary blood vessels, lymphatics, and bronchioles (Figure 4A and 4B). Two types of LAM cells have been described: small spindle-shaped cells and larger, epithelioid-like

cells with abundant cytoplasm. Both types of cells react with antibodies against smooth muscle cell-specific antigens (e.g., smooth muscle a-actin, vimentin, desmin) (Figure 5). The epithelioid LAM cells react with HMB-45, a monoclonal antibody that recognizes gp100, a premelanosomal protein (Figures 5, 6 and 7). The spindle-shaped cells are more likely to react with anti-proliferation cell nuclear antigen (PCNA) antibodies, suggesting a more proliferative state. Receptors for estrogen, progesterone, and growth factors have been identified in LAM cells. LAM cells appear to have neoplastic properties and may be capable of metastasis. In addition to their presence in lungs, lymphatics and kidneys, LAM cells have been isolated from blood, chyle, and urine.

Etiology

The tumor suppressor genes TSC1 and TSC2 have been implicated in the etiology of LAM, as mutations and loss of heterozygosity in the TSC genes have been detected in LAM cells (Figure 7). TSC1 encodes hamartin, a protein that plays a role in the reorganization of the actin cytoskeleton, and TSC2 encodes tuberin, a protein with roles in cell growth and proliferation. TSC1 and TSC2 may function both individually and as a cytosolic complex.

Epidemiology

LAM occurs in about one third of women with tuberous sclerosis complex (TSC), an autosomal dominant syndrome characterized by hamartoma-like tumor growths in various organs, cerebral calcifications, seizures, and mental retardation, that occurs in one of 5800 live births. Sporadic LAM is a relatively uncommon disease with a prevalence that has been estimated at 1-2.6/million women.
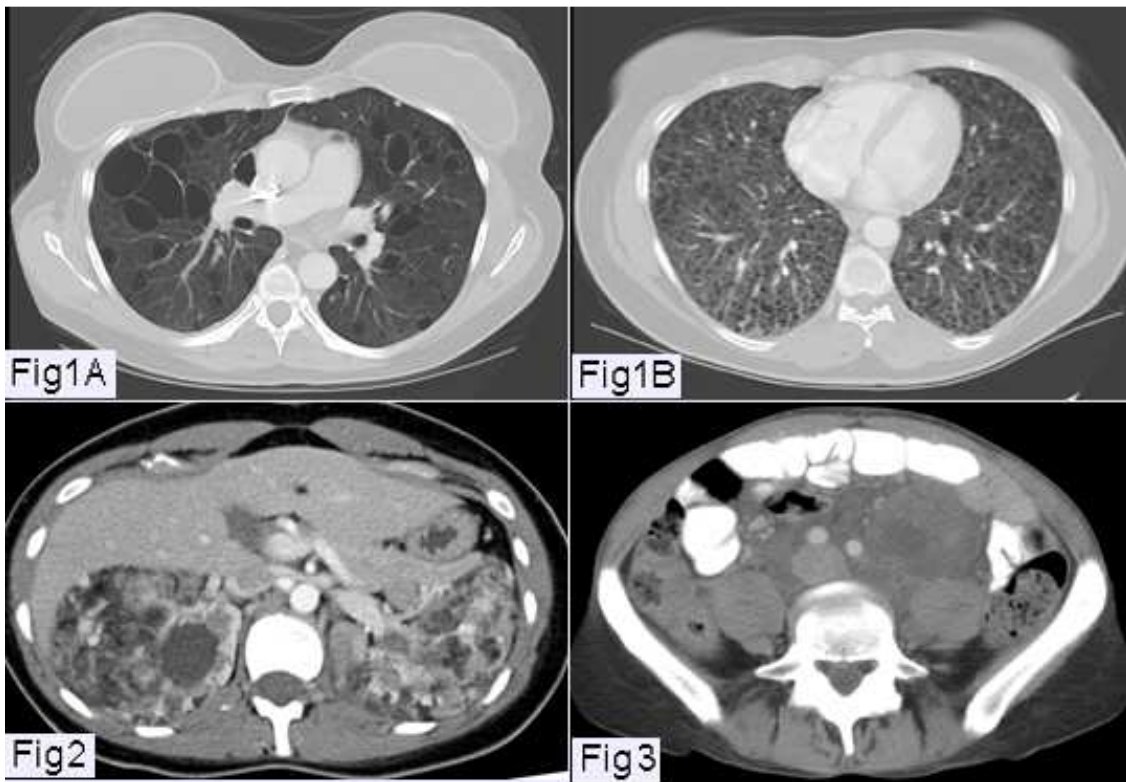
Figure 1. Chest CT scan of a patient with LAM (A) showing numerous thin-walled cysts distributed throughout the lungs. (B) The lung parenchyma is almost completely replaced by very small cysts.
Figure 2. Abdominal CT scan of a patient with LAM showing angiomyolipomas involving both kidneys.
Figure 3. Abdominal CT scan of a patient with LAM showing a large lymphangioleiomyoma located in the retroperitoneal area and surrounding the aorta and inferior vena cava.
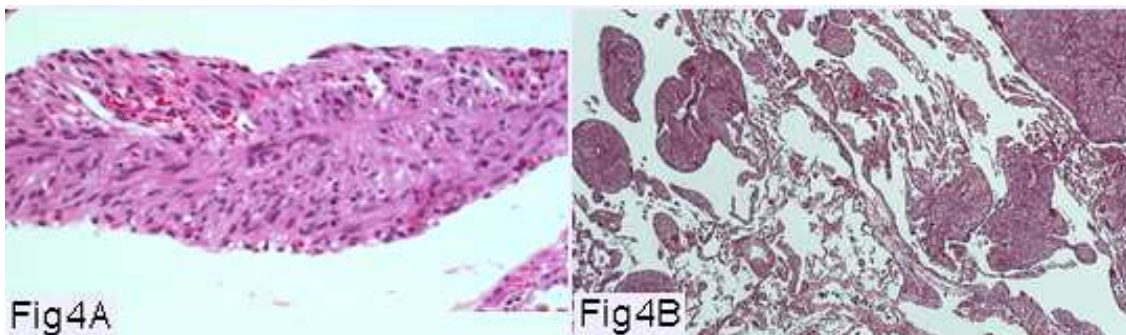

Figure 4 A and B. LAM nodule comprising spindle-shaped cells and larger epithelioid cells (A). Nodules of various sizes (B) are seen in involved lung (hematoxylin-eosin; original magnification x50).
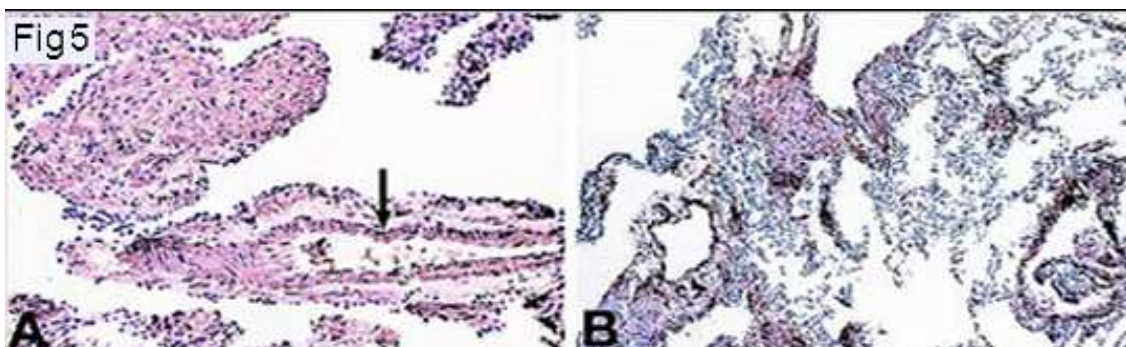

Figure 5. Immunohistochemistry of LAM cells. Immunoperoxidase method and counterstaining with hematoxylin. A and B: Immunoreactivity with a-smooth muscle actin antibodies. LAM cells show strong reactivity (A). Pulmonary vascular smooth muscle cells are also strongly positive (arrow). LAM cells in the walls of the lung cysts are also strongly reactive (arrow) (B) (original magnification x250 for each).
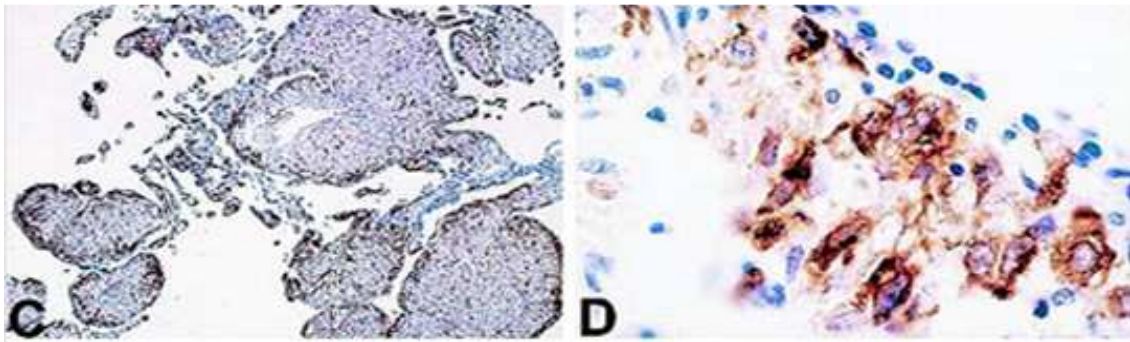
C: Immunoreactivity with monoclonal antibody HMB-45. Immunoreactive cells are distributed in the periphery of LAM lung nodules (arrow) (original magnification x250). D: Immunoreactivity with monoclonal antibody HMB-45. Higher-magnification view of tissue shown in C. A strong granular reaction is present in large epithelioid LAM cells adjacent to epithelial cells covering LAM lung nodules (arrow) (D) (original magnification x1000).
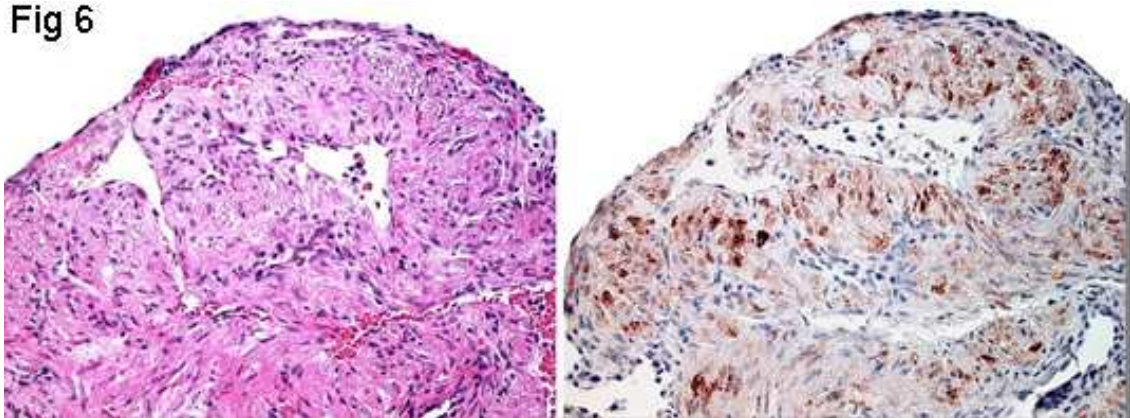

Figure 6. Left panel: close-up of LAM nodule (hematoxylin-eosin). Right panel: same nodule showing positive immunocytochemistry stain for HMB 45 (original magnification x200).
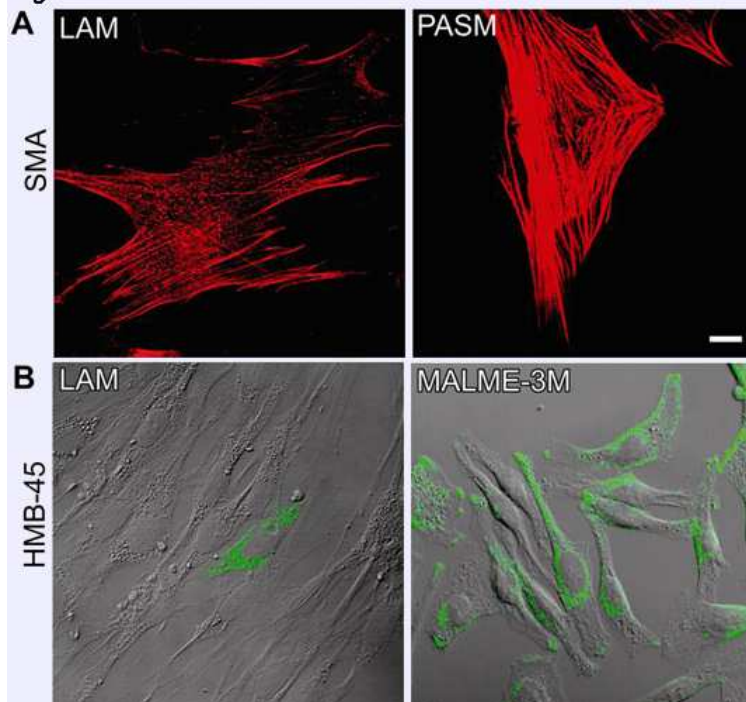
Figure 7. Characteristics of LAM cells (A-C). Reaction of LAM cells cultured from lung and pulmonary artery smooth muscle cells (PASM) with monoclonal antibody against SMA (A). Reaction of cultured LAM cells and melanoma cells (MALME-3M) with monoclonal antibody HMB-45 (B). Fluorescence in situ hybridization (FISH) for TSC1 (green) and TSC2 (red) in LAM cells showing normal presence of two of each alleles as well as abnormal presence of TSC2 alleles (left)
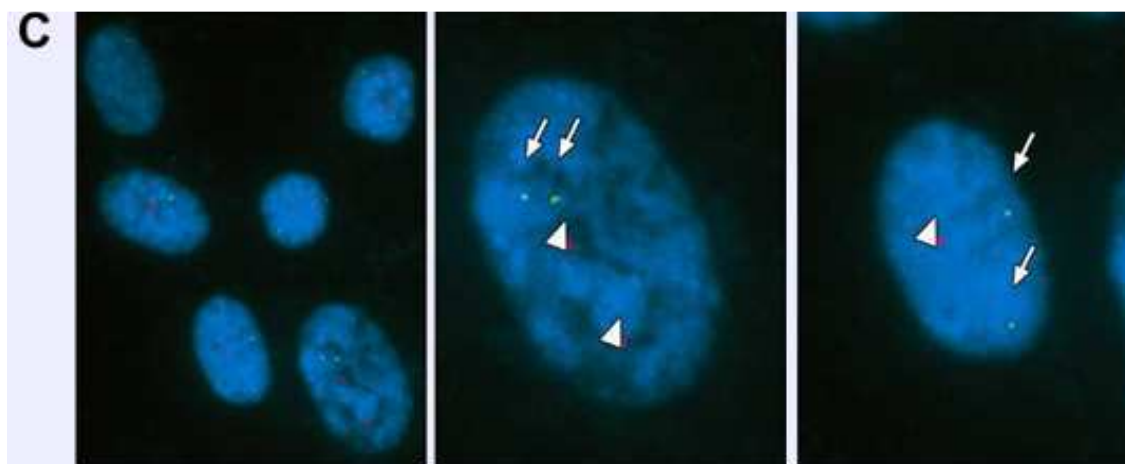
(C). FISH for TSC1 (green, arrow) and TSC2 (red, arrowhead) in LAM cell with one (right) or two TSC2 (left) alleles (C). Bar, 20 µm.

Treatment

Because LAM is predominantly a disease of pre-menopausal women and may worsen during pregnancy, or following the administration of exogenous estrogens, hormonal manipulations have been employed. However, no controlled studies have been undertaken to determine their efficacy. A retrospective study of 275 patients found no difference in disease progression between patients treated with progesterone and patients who received no progesterone. There is also no evidence that suppression of ovarian function, either by oophorectomy or use of gonadotrophin-releasing hormone analogs, benefit patients with LAM.

Progress about the mechanisms regulating cell proliferation and migration, and angiogenesis and lymphangiogenesis, have provided a foundation for the development of new therapies.

The mammalian target of rapamycin (mTOR) appears to play a role in regulating the growth and multiplication of LAM cells (Figure 8). An inhibitor of mTOR, sirolimus (rapamycin), an antifungal macrolide antibiotic approved for immunosuppression after solid organ transplantation, has been studied as a possible treatment for LAM. In a rat model of TSC (Eker rat) with a functionally null germline mutation of tsc2, which spontaneously develops renal cell carcinomas, treatment with sirolimus resulted in a decrease in size of kidney tumors by both a reduction in the percentage of proliferating cells, and extensive tumor cell death. An open label study with sirolimus undertaken in twenty patients with angiomyolipomas showed a reduction in tumor size to 53.2+/-26.6 % of baseline at one year. An improvement in some lung function parameters was also observed. A clinical trial [MILES trial (Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus Trial)], to examine the effect of rapamycin on pulmonary function, is underway.

Patients with severe LAM or those who show an accelerated rate of decline in lung function may be referred to a lung transplantation center.

Evolution

LAM is a chronic disease, which may span decades. A retrospective analysis of 402 patients seen at NIH from 1995 to 2006 showed that 22 had died, eight of whom had undergone lung transplantation. The mortality in this large cohort was 5.5%. Of the surviving 380 patients, 38 (10%) had lung transplantation. A recent study reported a ten year survival greater than 90%.

Genes involved and proteins

TSC genes

Note

TSC1 and TSC2 are tumor suppressor genes. TSC1 (9q34) encodes the 130kDa protein hamartin, while TSC2 (16p13.3) encodes the 200kDa protein tuberin. Hamartin and tuberin may have individual functions, but they also interact to form a cytosolic complex. Loss of heterozygosity of TSC2 has been detected in LAM lesions from lung and kidney, and mutations in TSC2 occur more frequently than those in TSC1 in patients with sporadic LAM. Hamartin may play a role in the reorganization of the actin cytoskeleton, with a lack of hamartin leading to a loss of focal adhesions and detachment from substrate, resulting in cell rounding. Hamartin induces an increase in the levels of RhoGTP , an activator of ERM (ezrin-radixin-moesin) proteins, and binds to activated ERM proteins. ERM proteins bind both filamentous actin and integral membrane proteins, thereby bridging the plasma membrane and cortical actin filaments.

Tuberin has roles in pathways controlling cell growth and proliferation (Figure 8). It is a negative regulator of cell cycle progression, and loss of tuberin function shortens the G1 phase of the cell cycle. Tuberin binds p27KIP1, a cyclin-dependent kinase inhibitor, thereby preventing its degradation and leading to inhibition of the cell cycle. Upon mutation of tuberin, p27 becomes mislocalized in the cytoplasm, allowing the cell cycle to progress.
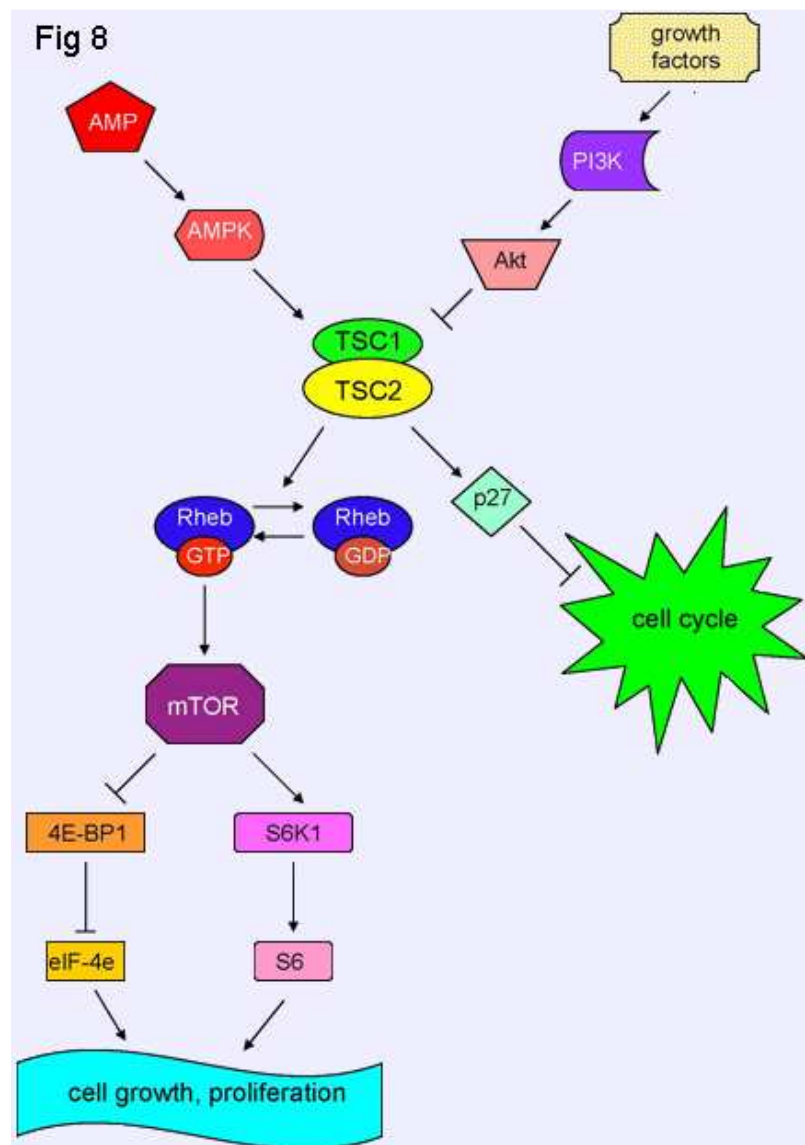
Figure 8. Schematic model of TSC1 and TSC2 pathways. The TSC1/TSC2 complex has roles in cell cycle progression and in cell growth and proliferation. Tuberin binds p27KIP1, a cyclin-dependent kinase inhibitor, stabilizing it and resulting in inhibition of cell cycle progression. Tuberin also has Rheb GAP activity, which converts Rheb-GTP to Rheb-GDP, resulting in inactive Rheb. Rheb controls mTOR, which is a kinase that controls translation through the phosphorylation of 4E-BP1 and S6K1. Akt, when activated by growth factors, phosphorylates tuberin, leading to an inhibition of tuberin and resulting in cell growth and proliferation. However, when a state of low cellular energy exists, AMPK phosphorylates tuberin, activating it, and thereby inhibiting cell growth.

Tuberin also integrates signals from growth factors and energy stores through its interaction with mTOR (mammalian target of rapamycin) (Figure 8). Tuberin has Rheb GAP (Ras homolog enriched in brain GTPase-activating protein) activity, which converts Rheb-GTP to Rheb-GDP, thereby inactivating Rheb. Rheb controls mTOR, a serine/threonine kinase that phosphorylates at least two substrates: 4E-BP1, allowing cap-dependent translation, and S6K1, leading to translation of 5' TOP (terminal oligopyrimidine tract)-containing RNAs. Phosphorylation of tuberin by Akt, which is known to be activated by growth factors, leads to inhibition of tuberin and results in cell growth and proliferation. Phosphorylation of tuberin by AMPK

(AMP-activated kinase) activates tuberin and further promotes inhibition of cell growth in states of energy deprivation.

Tuberin may also have roles in endocytosis through its interaction with rabaptin-5 and in transcriptional activation through interaction with members of the retinoid X receptor (RXR) family.

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