

## Solid Tumour Section

### Mini Review

## Lymphangioliomyoma

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### Classification

#### Note

Lymphangioliomyoma is a benign neoplasm of lymphatic vessels characterized as a PEComa (perivascular epithelioid cell tumour), involving the proliferation of epithelioid cells, with mutations in the tuberous sclerosis complex (TSC) genes TSC1 and TSC2.

### Clinics and pathology

#### Note

Lymphangioliomyomas are commonly associated with lymphangioliomyomatosis (LAM), a multi-system disorder primarily affecting women of child-bearing age. Initial presentation of LAM may

result from pulmonary or extrapulmonary lesions. Pulmonary LAM is characterized by thin-walled cysts, which are diffused throughout the lungs. Patients with these lesions experience deterioration of lung function that can lead to oxygen dependency, lung transplantation or death. Extrapulmonary LAM involves the axial lymphatics of the abdomen and thorax (lymphangioliomyomas, adenopathy), and abdominal organs, especially the kidneys (angiomyolipomas).

Abdomino-pelvic lymphangioliomyomas may present with abdominal pain as an acute abdomen, with a neuropathy or with abdominal bloating. Thoraco-abdominal lymphadenopathy and lymphangioliomyomas, along with chylothorax (Figure 1) or ascites may suggest the presence of a malignant lymphoproliferative disease.

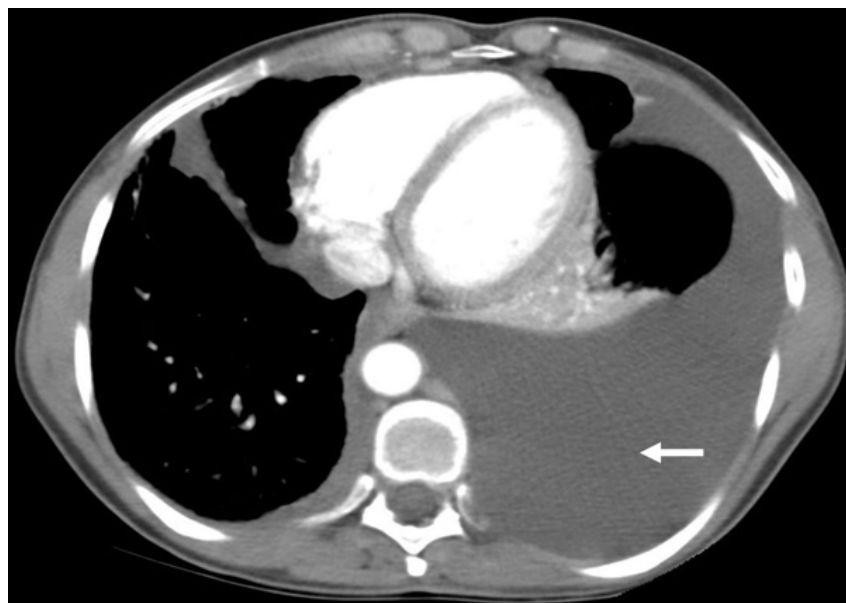


Figure 1: Large left chylothorax (white arrow) in a patient with LAM.

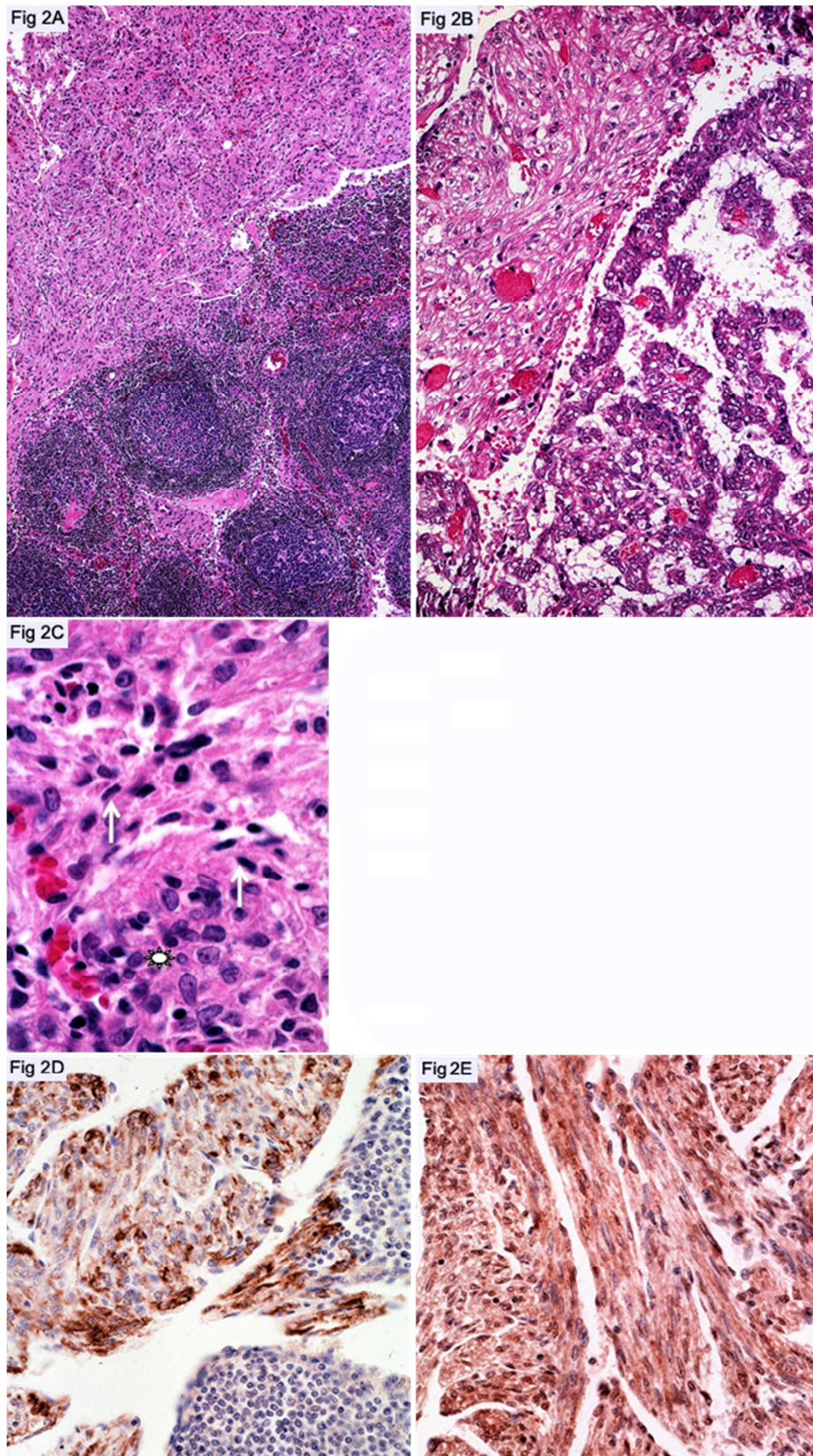


Figure 2 A, B, C, D, and E. Histological characterization of extrapulmonary LAM. LAM cells form fascicles separated by lymphatic channels (A). (HE, original magnification x 100) An example of LAM cells arranged in trabecular bundles and irregular papillary patterns (B). (H&E, original magnification x 250) Image representing morphological heterogeneity of LAM cells; large epithelioid LAM cells (asterisk) and smaller, round to oval cells (arrows) (C). (H&E, original magnification x 1,000) Positive reactivity of LAM cells to HMB-45 (D). (immunoperoxidase with hematoxylin counterstain, original magnification x 400) Positive reactivity of LAM cells to SMMHC (E). (original magnification x 400). (from Matsui et al., *Hum Pathol.* 2000 October;31(10):1242-1248).

## Etiology

LAM results from proliferation of an abnormal cell, termed the LAM cell. LAM occurs in 30-40% of patients with tuberous sclerosis complex, an autosomal dominant disorder associated with mutations in the TSC1 or TSC2 genes. Sporadic LAM is caused presumably by cells with mutations of the TSC2 gene. Lymphatic involvement (including lymphangioliomyomas) occurs less frequently in patients with LAM/TSC, than in patients with sporadic LAM.

## Epidemiology

Lymphangioliomyomas are present in about 16-21% of patients with LAM.

## Pathology

Histological examination of the cells lining the walls of the extrapulmonary lesions reveal common characteristics with pulmonary LAM cells, abnormal smooth muscle-like cells with a mixture of epithelioid and spindle-shaped morphologies. Cells react with HMB-45, a monoclonal antibody against gp100 (a premelanosomal marker), and with antibodies against SMMHC, a smooth muscle-cell marker. Unlike the nodular collections of the pulmonary LAM cells, the extrapulmonary cells usually form fascicles or papillary patterns. Both types of lesions contain slit-like lymphatic channels (Figure 2A, B, C, D, and E).

**Radiologic Imaging:** Retroperitoneal lymphangioliomyomas have a distinctive radiologic appearance (Figures 3-7), and diurnal variation in size of the tumor masses can be demonstrated by ultrasonography or computed tomography scans (Figure 8).

Lymphangioliomyomas are well characterized by either ultrasonography or computed tomography scanning, appearing as well-circumscribed lobular, thin or thick-walled masses without evidence of necrosis or hemorrhage. Masses greater than 3 cm in diameter are usually cystic in appearance and many contain fluid, presumably chyle. Lesions as large as 20 cm in diameter have been observed. In patients with LAM, the lesions most often occur in the retroperitoneal region.

## Treatment

There is no effective treatment for lymphangioliomyomas. The lesions are usually asymptomatic, however, ascites, peripheral edema, and compression of the bladder, bowel, pelvic veins and other viscera by large lymphangioliomyomata may cause severe symptomatology, including pain, obstipation, urinary frequency, and peripheral edema. Although surgery is sometimes contemplated to ameliorate symptoms caused by visceral compression, it is contraindicated, as, in our experience; it may lead to persistent lymphatic

leakage and intractable chylothorax and ascites. Chylous effusions including pleural effusions are particularly difficult to treat. Repeated thora-centeses lead to malnutrition and may result in infectious complications. Low fat diet with medium-chain triglycerides and therapeutic thora-centesis should be attempted initially. However, most patients require pleurodesis, which may be effective if the rate of chyle generation can be reduced. Patients should be placed on a fat-free parenteral nutrition regimen prior to, during, and after surgery. It is essential that good lung expansion be obtained to ensure complete apposition of the visceral and parietal pleura to avoid residual pleural pockets. After a successful pleurodesis, a low fat diet with mid-chain triglycerides is recommended. A peritoneal-venous shunt may be considered for most severe cases when the ascites is disabling and is causing mechanical/ nutritional problems, but little experience with this therapeutic modality in LAM is reported. Treatment with octreotide may be considered for those patients with disabling ascites and large lymph-angioliomyomata. Previous studies with somato-statin and octreotide in other clinical settings (e.g., traumatic damage to the lymphatics, yellow nail syndrome) have shown a successful reduction in chylous effusions, chyluria, ascites, and peripheral lymphedema.

**Sirolimus:** The TSC1 and TSC2 genes encode respectively, hamartin and tuberin. Although Hamartin and tuberin may have individual functions, they are also known to interact in a cytosolic complex. Hamartin may play a role in the reorganization of the actin cytoskeleton. Tuberin has roles in pathways controlling cell growth and proliferation. 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. Tuberin also integrates signals from growth factors and energy stores through its interaction with mTOR (mammalian target of rapamycin). Tuberin has Rheb GAP (Ras homolog enriched in brain GTPase-activating protein) activity, which converts active Rheb-GTP to inactive Rheb-GDP. Rheb regulates 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 activated by growth factors, leads to inhibition of tuberin, resulting in cell growth and proliferation. Phosphorylation of tuberin by AMPK (AMP-activated kinase) activates tuberin and further promotes inhibition of cell growth in conditions of energy deprivation.

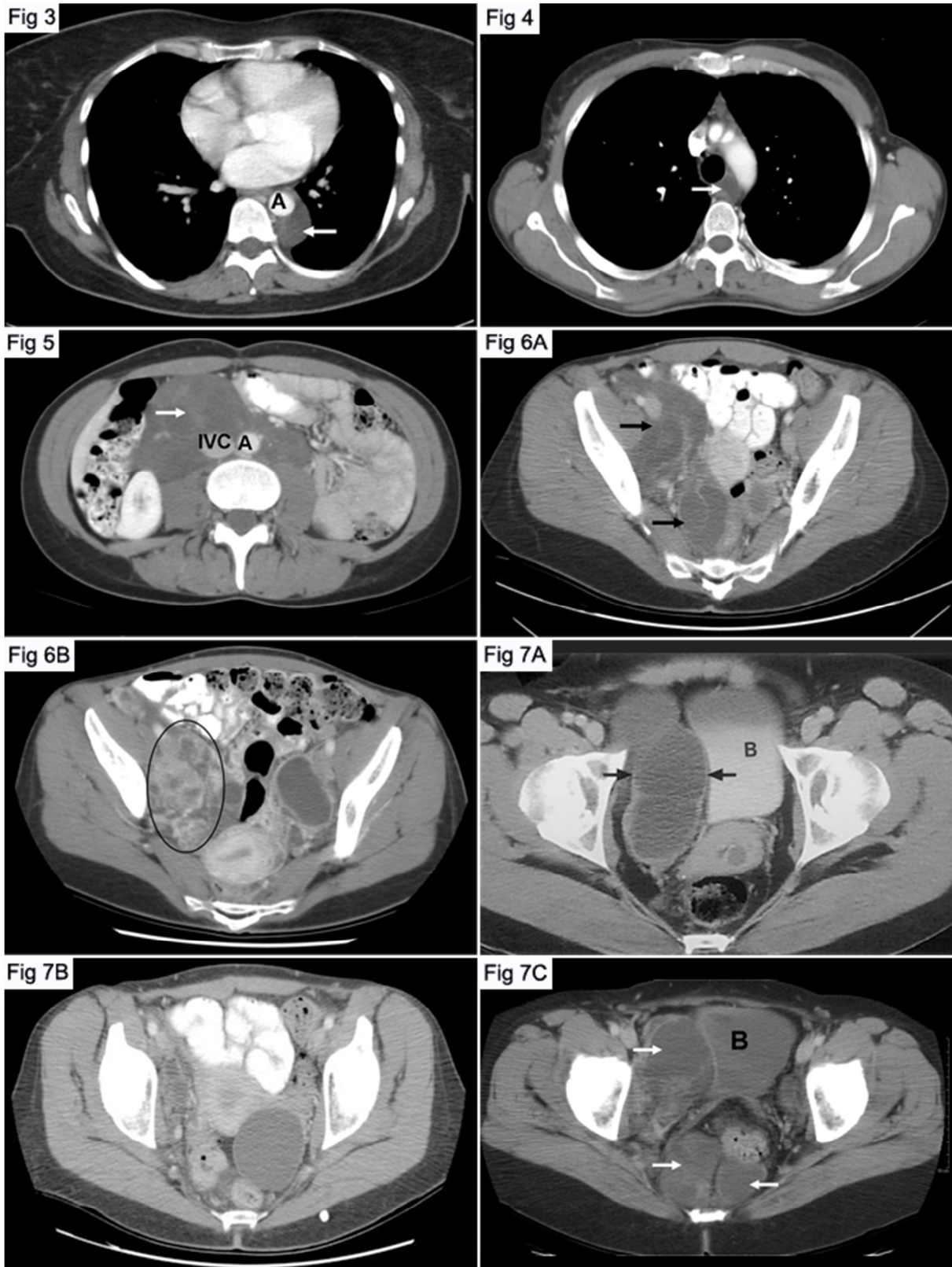


Figure 3. Mediastinal lymphangioliomyoma (white arrow), located posteriorly to the descending thoracic aorta. A: aorta.  
 Figure 4. Mediastinal lymphangioliomyomas (white arrow), located posteriorly to the trachea.  
 Figure 5. Large retroperitoneal lymphangioliomyoma (white arrow) surrounding the aorta and inferior vena cava. A: aorta; IVC: inferior vena cava.  
 Figure 6A and B. Black arrows point to large pelvic lymphangioliomyoma (A). A complex lymphangioliomyoma is shown marked by circle on panel B.  
 Figure 7A, B and C. Evidence of bladder and bowel compression caused by the tumors. B: bladder.

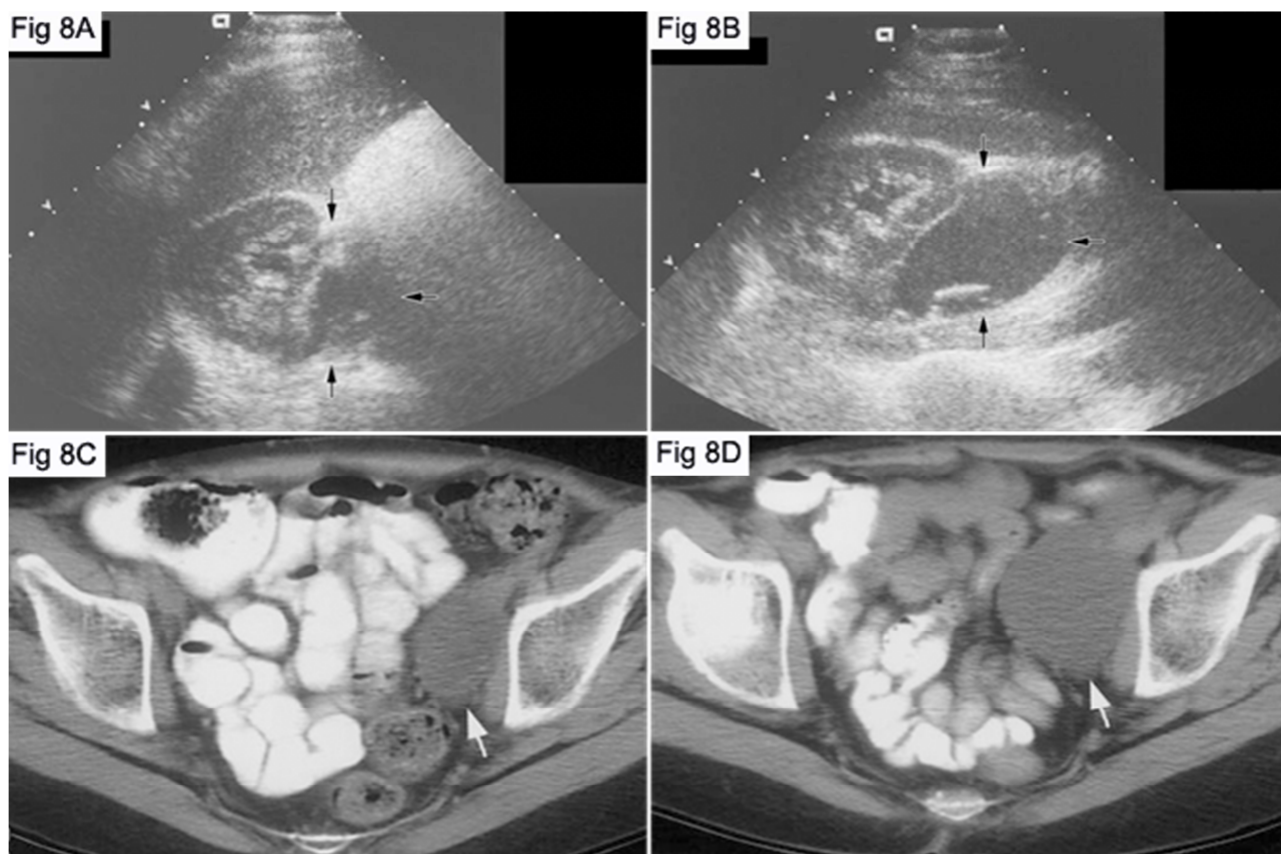


Figure 8A, B, C and D. Diurnal variation of lymphangioliomyomas. Abdominal ultrasound shows that the size of a lymphangioliomyoma is greater in the evening (panel B) than in the morning (panel A). Abdominal CT scan showing also diurnal variation in tumor size from morning (panel C) to evening (panel D).

Sirolimus, an immunosuppressive agent, inactivates mTOR. Sirolimus has been shown to induce apoptosis of tumors in rodents and decrease the size of renal angiomyolipomas in patients with lymphangioliomyomatosis or TSC. Further, sirolimus was effective in decreasing the size of chylous effusions and lymphangioliomyomas in one patient with LAM and improved chylous effusions in another patient who underwent lung transplantation.

### Evolution

Lymphangioliomyomas are thought to occur due to the proliferation of LAM cells in lymphatic vessels, causing obstruction and dilatation of the vessels leading to collection of chylous material in cyst-like structures. The cysts, when overdistended, may rupture resulting in chylous ascites. Lymphangioliomyomas can exhibit diurnal variation, (visualized by CT or sonography) with lesions increasing in size during the day. This phenomenon can be an aid in a differential diagnosis of a probable lymphangioliomyoma with thick walls and no fluid, from other mass lesions such as a lymphoma or a sarcoma.

### Prognosis

Lymphatic involvement (defined by the presence of adenopathy and/or lymphangioliomyomas) in patients

with LAM, is correlated with more severe lung disease assessed by computed tomography scans.

## Genes involved and proteins

### Note

Serum levels of VEGF-D, a lymphangiogenic growth factor, are higher in patients with LAM than those in healthy volunteers. In addition, serum levels of VEGF-D in patients with LAM who have lymphangioliomyomas and adenopathy are higher than in patients without lymphangioliomyomas. LAM lung nodules demonstrate immunoreactivity for VEGF-D. Because of these findings and reported observations of LAM cell clusters in lymphatic channels, it has been hypothesized that LAM-associated lymphangiogenesis, driven by VEGF-D, may account for the dissemination of LAM cells through the shedding of LAM cell clusters into the lymphatic system.

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