LYMPHANGIOLEIOMYOMATOSIS

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Key:

LAM – Lymphangioleiomyomatosis
TSC – Tuberous Sclerosis Complex
AML – Angioleiomyomatosis
BHD – Birt Hogg-Dube
VEGF-D – Vascular Endothelial Growth Factor
mTOR – Mechanistic Target of Rapamycin
MMP – Matrix Metalloproteinasesmatrix
GF – Growth Factors
LDH - Lactate Dehydrogenase

Lymphangioleiomyomatosis:

Low-grade, metastasising neoplasm leading to cystic lung disease, AML & lymphatic complications
Either sporadic (S-LAM) or associated with TSC (TSC-LAM)
Female-predominant during reproductive years
Case reports of LAM in men
3-8 cases/million women approx., likely underestimated

Pathophysiology:

Natural history incompletely understood

Clusters of smooth muscle-like LAM cells transported via lymphatics, enter circulation and travel to infiltrate lung: Proliferation, lymphangiogenesis, and lymphatic spread, implantation, tissue destruction

Mutations in the tumour suppressor genes TSC1 & TSC 2, encoding hamartin and tuberin respectively, lead to inappropriate signalling through the mTOR pathway driving abnormal cell proliferation

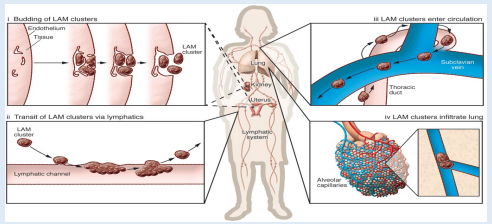
Pathways involved in regulation of cellular functions including growth, motility, and survival

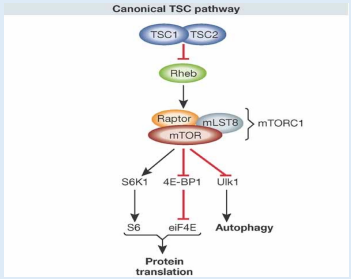
LAM cells also express lymphangiogenic growth factors VEGF-C & VEGF-D

These GF involved in the metastatic spread of LAM cells & breakdown of the extracellular MMPs, contribute to cyst formation

MMP-2 and MMP-9 have been found in tissue at cystic areas in the lung.

Female sex hormones implicated: predominance of LAM in females, exacerbations of LAM during exposures to surges in female sex hormones i.e. pregnancy/ hormonal contraception/ menstruation/ disease stabilises in post-menopausal period





Henske EP, McCormack FX. *J Clin Invest.* 2012;122(11):3807–3816

Clinical Features:

Consider in females of reproductive age with unexplained dyspnoea
Progressive dyspnoea (2/3 patients)
Cough/ LRTI/ Chest pain (25%), Fatigue, Haemoptysis/ Chyloptysis

Clinical exam:

Normal/ Wheeze/ Crackles
Abdominal mass (AML)
TSC (angiofibromas, shagreen patch, periungual fibromas, retinal astrocytoma)
BHD (facial acrochordons and trichodiscomas)

Pneumothorax

x 1000 times higher in LAM
Presenting feature in 1/3 patients
50-80% = pneumothorax during the course of the disease (often recurrent)

Pleural Effusion

10-30% of patients
Chylous effusions (chylothorax) predominate
Unilateral (76%)/ Right sided (63.2%)
Hallmarks of chylous effusions: high triglyceride, cholesterol, chylomicrons
Exudative lymphocytic fluid; Protein > LDH

Renal Angiomyolipomas (AML)

Non-contrast CT Abdomen: Contains smooth muscle, blood vessels & fat
Presence of fat = characteristic CT appearance: Biopsy rarely necessary
30% of patients with S-LAM and ~ 80% of those with TSC-LAM
S-LAM: unilateral and asymptomatic
TSC-LAM: bilateral
Haemorrhage (presenting complaint in a small subset)

Lymphatic Manifestations

Lymphangioleiomyomas: fluid filled structures (16 – 38%)
Symptomatic/ related to location (pain, oedema of lower extremities, bloating)
Lymphadenopathy (pelvis/ retroperitoneum; 25-77% of LAM patients)

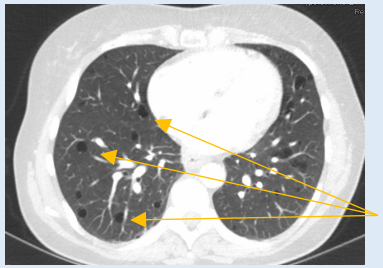
Pulmonary Function Tests

Reversible airflow obstruction (1/3)
FEV_1 & DLCO used as markers of disease severity

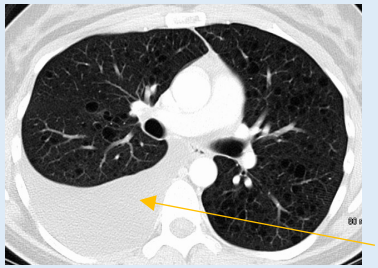
Diagnostic Criteria: **HRCT chest with characteristic thin walled cysts *PLUS one of:***

- Elevated serum VEGF-D ≥ 800pg/ml (elevated in 70% patients)
- Presence of Tuberous Sclerosis Complex
- Presence of renal angiomyolipomas
- Chylous effusions
- Lymphangioleiomyomas

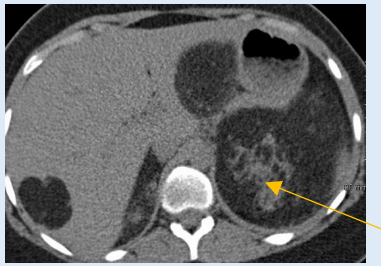
Biopsy where VEGF-D normal and no other manifestations to diagnose LAM



Characteristic HRCT in patient with LAM showing thin walled cysts



Example of chylous effusion in LAM



Renal AML in LAM patient

Treatment

Lifestyle advice/ Smoking cessation

mTOR inhibitors: slow rate of lung function decline
Can resolve chylous effusion & regress AMLs

Pneumothorax: definite management (pleurodesis) recommended; risk of recurrence is high

Prognosis

Average decline FEV_1 ~90mL/ year
Higher FEV_1/ DLCO at baseline = better prognosis
Post-menopausal participants = slower decline

Higher cyst score on CT = ↓ prognosis & ↑ FEV_1 decline
Bronchodilator response = deteriorate more rapidly

Mean transplant-free survival >20 years from diagnosis

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