LAM 101

Lymph-angio-leiomyomatosis

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LAM 101 Goals

• Learn some new vocabulary words

• Discuss the basics of LAM as we know it in 2017

• Understand what a supportive group of people live in this community
What is LAM?

- Rare cystic lung disease of women
Lung density coded at 15% intervals.
What is LAM?

- Rare cystic lung disease of women
  - Frequent Pneumothoraces
Pneumothorax

Common in airway obstruction
Most in cigarette smokers
Barometric pressure change
Skydiving
Scuba
Bungee Jumping
CT scan adds value
Shown cost effective in age 25-55 women
Pneumothorax and Pleurodesis

Agents used for pleurodesis
- Talc
- Surgical Abrasion
Pneumothorax in LAM

• Common
  – 57% of 1591 patients from 7 series and 2 observational cohorts
• Usually happens again
  – Recurrence is common 29-81%, most series near 70%
  – Number of recurrences 3.2 to 5.0
  – Most recurrences in first year
• Often the first manifestation of disease
• Usually on one side only
• Usually causes pain and shortness of breath
• 65% of observational series treated conservatively at first event
• In one series, average time in hospital was 1 month
What is LAM?

- Rare cystic lung disease of women
  - Frequent Pneumothoraces
  - Obstructive lung function
What is LAM?

- Rare cystic lung disease of women
  - Frequent Pneumothoraces
  - Obstructive lung function

Normal Airway

LAM Airway
LAM cells
Inflamed
Twitchy

↓

Use
Bronchodilator Medications
What is LAM?

• Rare cystic lung disease of women
  – Frequent Pneumothoraces
  – Obstructive lung function
  – Lymphatic diseases

Chylothorax
What is LAM?

- Rare cystic lung disease of women
  - Frequent Pneumothoraces
  - Obstructive lung function
  - Lymphatic diseases

Chylothorax
Lymph Node Swelling
Chylous Ascites
Lung Congestion
Swollen areas of the body
What is LAM?

• Rare cystic lung disease of women
  – Frequent Pneumothoraces
  – Obstructive lung function
  – Lymphatic diseases
  – LAM cell clusters
How are Cells Lacking TSC1 or TSC2 made?

<table>
<thead>
<tr>
<th>Tuberous Sclerosis</th>
<th>Sporadic LAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Disease</td>
<td>Spontaneous Mutations</td>
</tr>
<tr>
<td>Inherited from Parents</td>
<td>Not inheritable</td>
</tr>
<tr>
<td>Variable Penetrance</td>
<td></td>
</tr>
<tr>
<td>Prominent Skin Findings</td>
<td></td>
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<tr>
<td>Brain tubers common</td>
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</tbody>
</table>
Is LAM a cancer?

**NEOPLASM/CANCER**
- Mesenchymal neoplasm
- 30-40% associated with women with TSC
- Clonal origin in some that have LOH
- Extrapulmonary source of seeding
- Inappropriate constitutive signaling through mTOR pathway
- Rare recurrence in transplanted lung
- Lymphangiogenesis
- Cancer-like metabolism

**NOT NEOPLASM/BENIGN**
- Cystic, interstitial lung disease
- Sporadic, not associated with TSC
- No cellular atypia/histologically benign appearance
- No chromosomal abnormalities in G-banded metaphase
- Slow, indolent course of disease
- Angiomyolipomas only in minority so unlikely primary source
- Uterine origin not supported as yet
- Target organ restriction

Inappropriate proliferation and invasion

Glassberg, M 2013 Am J Respir Crit Care Med 188:397
What is LAM?

• Rare cystic lung disease of women
  – Frequent Pneumothoraces
  – Obstructive lung function
  – Lymphatic diseases
  – LAM cell clusters
  – Seen related to Tuberous Sclerosis or Spontaneously
  – Angioleiomyomas in Kidney
  – Estrogen associated
  – Almost certainly a very slow growing form of cancer
  – Complicated biochemistry

Wu, PathologyOutlines.com
ERS Definite or Probable LAM

**Definite LAM:**
1) Characteristic or compatible lung HRCT, and lung biopsy fitting the pathological criteria for LAM; or
2) Characteristic lung HRCT and any of the following: angiomyolipoma (kidney); thoracic or abdominal chylous effusion; lymphangioleiomyoma or lymph-node involved by LAM; and definite or probable TSC.

**Probable LAM**
1) Characteristic HRCT and compatible clinical history; or
2) Compatible HRCT and any of the following: angiomyolipoma (kidney); thoracic or abdominal chylous effusion; or VEGF-D >800 pg/ml at any time in the past.
How to treat LAM

Things that do not seem to work:
Most estrogen antagonists
Progestins
Corticosteroids
Other immunosuppressives
How to treat LAM

Things that do work:

- Bronchodilator inhalers
- Vaccinations for influenza, pneumonia, and shingles
- Avoiding excess estrogen
- Exercise
- mTOR inhibitors
  - sirolimus (Rapamycin®)
  - everolimus (Afinitor®)
- Oxygen
- Lung Transplantation
MILES Study Design
89 Patients with FEV1 <70% predicted
Randomized to Sirolimus or Placebo for 1 year

Primary Outcome  FEV1 Slope (ml/month)

Miles Trial (Multicenter International LAM Efficacy of Sirolimus Trial)

- Placebo-controlled
- Randomized
- Double blind

Trial on the efficacy of Sirolimus on pulmonary LAM
12 Month Spirometry Change in MILES

FEV1 Responder Analysis MILES Study

McCormack FX, NEJM 2011;364:1595-1606
VEGF-D is a biomarker for LAM

Chang WYC, Johnson SR. Clinical Utility of diagnostic guidelines and Putative biomarkers in LAM.
How to live with Sirolimus or Everolimus

Take the medication regularly, usually at low dose

Side Effects
  - Mouth ulcers
  - Elevated lipids
  - Problems with wound healing
  - Immune suppression
  - Rare lung toxicity

Monitoring
  - Controversial need for laboratory monitoring at the 1 mg daily sirolimus dose
Future Directions

• Learn the right dose of mTOR inhibitors
• Determine if there are other pathways involved in disease progression in some
• mTOR inhibitors suppress LAM cell growth but do not kill cells. What will kill these cells?
• Determine how early in the disease to begin these medications
Amazing resource for Support

Knowledge
Research
Emotional Support
Advocacy
2016 LAM Education & Support Meetings

• 18 out of 21 Regions held 28 gatherings
• 17 of those gatherings took place at a LAM Clinic or community center with LAM Clinic Directors
• Those 28 gatherings connected more than 700 LAM professionals, patients, family and friends
RLD / LAM White Papers

Available Now:

– Sirolimus
– Vaccines – posted to LAM Foundation Website
– Pleural disease management of LAM

Future:

– Contraceptives and HRT during menopause
– Tissue donation
– TSC Screening
– VEGF-D and insurance coverage
– Chylous complications
Conclusions

We will cure LAM in our lifetime

The disease is a difficult one to understand. You likely now know more than your doctor about LAM. Be an advocate for your health.

The LAM community is there for you. Ask questions.