Brigham and Women's Hospital
Founding Member, Mass General Brigham

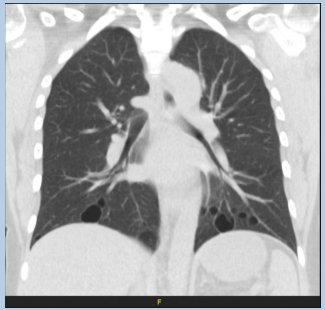
Cystic Lung Disease

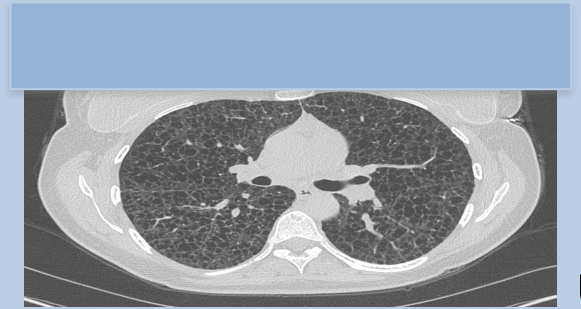
Elizabeth (Lisa) Petri Henske, MD

Director, Center for LAM Research and Clinical Care, Brigham and Women's Hospital

Medical Oncologist, Dana-Farber Cancer Institute

Professor of Medicine, Harvard Medical School





CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Elizabeth P Henske, MD

- Professor of Medicine, Harvard Medical School
- Director, Center for LAM Research and Clinical Care, Brigham and Women's Hospital
- Medical Oncologist, Dana-Farber Cancer Institute
- Henske Laboratory:
  - Tuberous sclerosis complex, LAM, Birt Hogg-Dube

Disclosure

No financial conflicts of interest

Question #1

- All women with suspected LAM should have abdominal imaging because 50% have:
  A) Hepatic angiomyolipomas
  B) Renal angiomyolipomas
  C) Ovarian cysts

Question #2

Patients with Birt-Hogg-Dube should have abdominal imaging because 25% develop:

A) Liver cysts

B) Renal cell carcinoma

C) Peritonitis

Question #3

Proven effective therapy for Lymphangioleiomyomatosis (LAM):

A) VEGF inhibition

B) mTOR inhibition

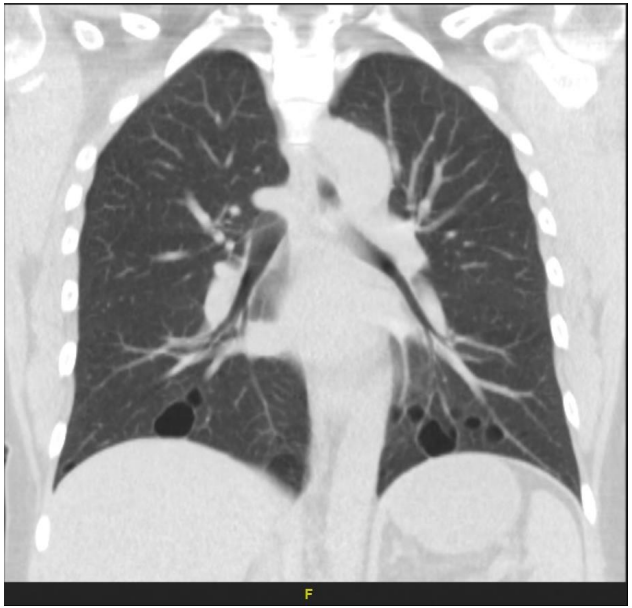
C) Corticosteroids

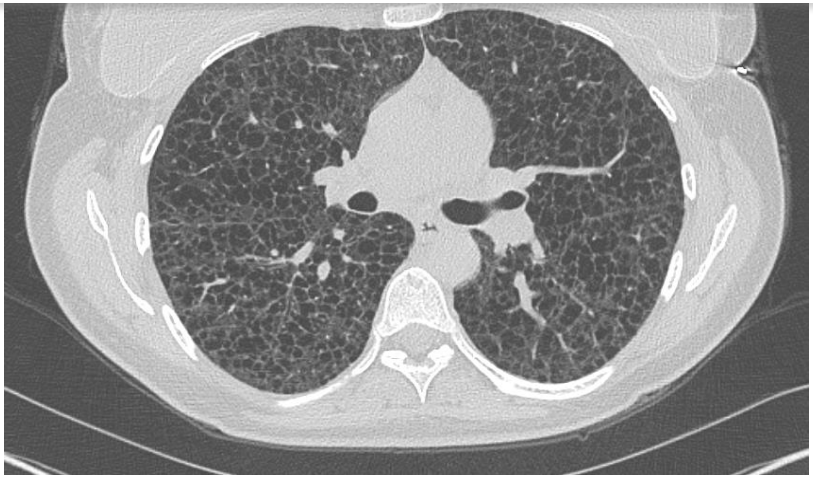
Learning Objectives

- Understand causes of cystic lung disease
- Identify cystic lung disease with specific genetic signatures:
  - Lymphangioleiomyomatosis (LAM)
  - Pulmonary Langerhans cell histiocytosis (PLCH)
  - Birt Hogg Dube syndrome (BHD)
- Recognize kidney tumors associated with cystic lung disease (LAM, BHD)
- Diagnose cystic lung disease with proven specific therapy (LAM)

What is a cyst?

Gas-filled round or irregular low attenuating area with a thin wall (<3mm)





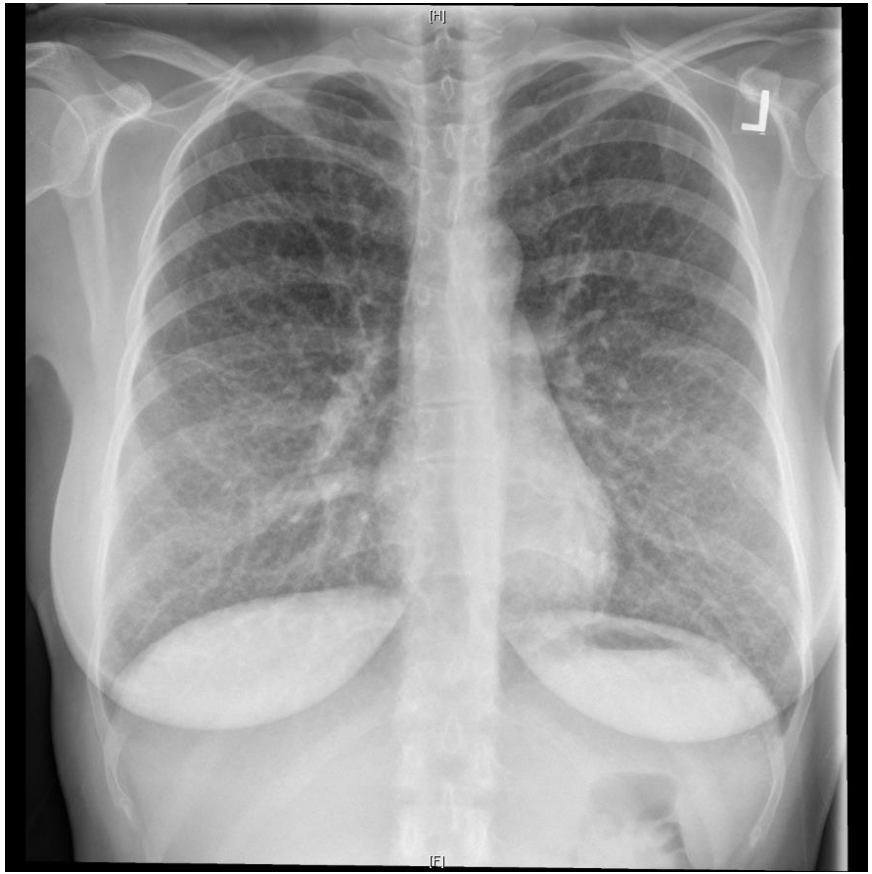
Cystic lung diseases

Lymphangioleiomyomatosis
Langerhans cell histiocytosis
Birt Hogg Dube syndrome

Emphysema
Pulmonary metastasis
Subacute (?chronic) hypersensitivity pneumonitis
Desquamative interstitial pneumonia
Barotrauma/ ARDS
Pulmonary infection- pneumatoceles
Necrobiotic nodules
Light chain disease
Lymphoid interstitial pneumonia

Beddy et al. Insights Imaging 2011

Case Study



- 34 year old
- Mother of 3
- Mountain bikes, works full time
- Progressive shortness of breath over 3 yrs
- “always feel tired”
- Severe episode shortness of breath while water skiing

Case Study: 34 year old, progressive dyspnea for 3 years

Name: [redacted] [redacted] Sex: **F** [redacted] Age: **35** Race: **W**

Ht: **65 in** (**165 cm**) Wt: **148 lb** (**67.0 Kg**) BMI: **24.7 Kg/mt** ^{2} Diagnosis: 1: **Clinical Research Trial Participant**

Location: **Center for Chest Disease** [redacted]

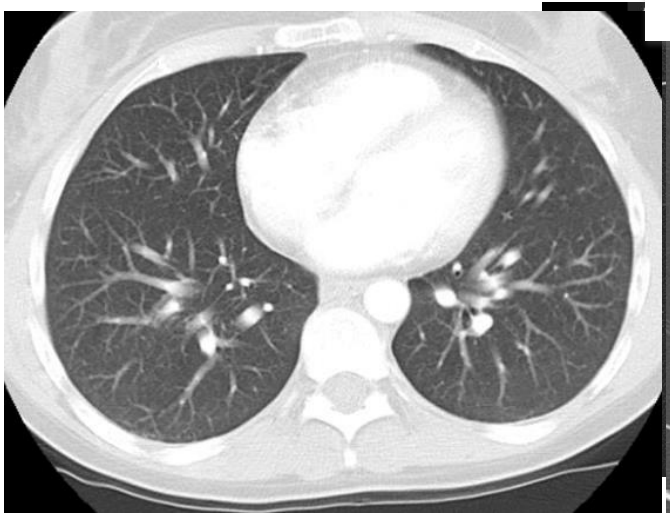
Technician: **DJ947** Attending: **Po-Shun Lee, M.D.** Referring: **Hilary J. Goldberg, M.D.**

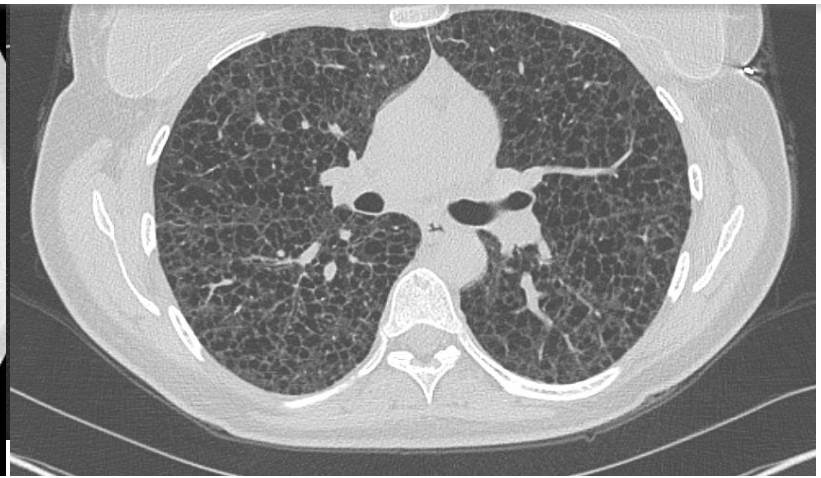
ATS compliant tests are indicated by a ✔ : **FVC** ✔ **FRC** **DLCO** **Raw**

Spirometry		Predicted Range		Pre Bronchodilator	
		Mean	95%	Actual	% Pred
FEV_1	L	3.17	2.61	**1.84**	58
FVC	L	3.76	3.08	**3.96**	105
FEV_1 / FVC	%	84	75	**46**	55
FEV_6	L	3.81	3.11	**3.86**	101
FEV_1 / FEV_6	%	85	76	**48**	56
FEF_{25-75}	L/s	3.61	2.25	**0.88**	24
PEFR	L/s	7.16	5.40	**7.04**	98

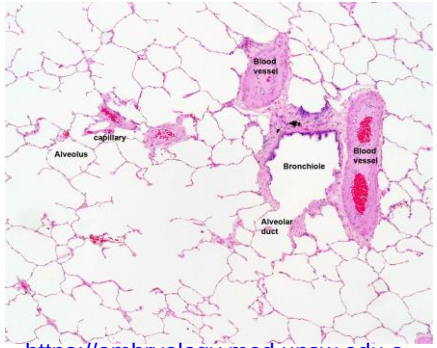
Obstructive or Restrictive?

Case Study: Chest CT





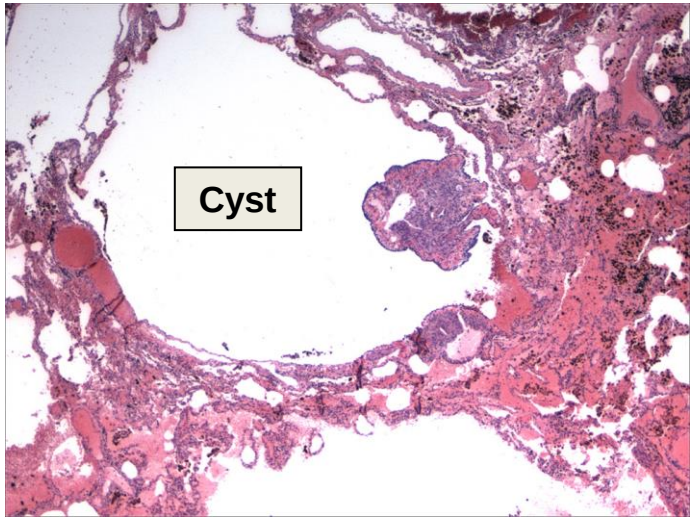
Normal Chest CT



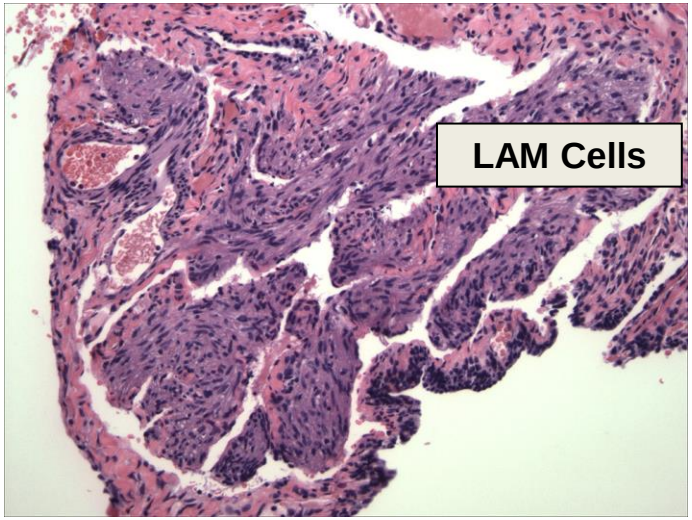
https://embryology.med.unsw.edu.au/

Case Study: Diagnostic Lung Biopsy

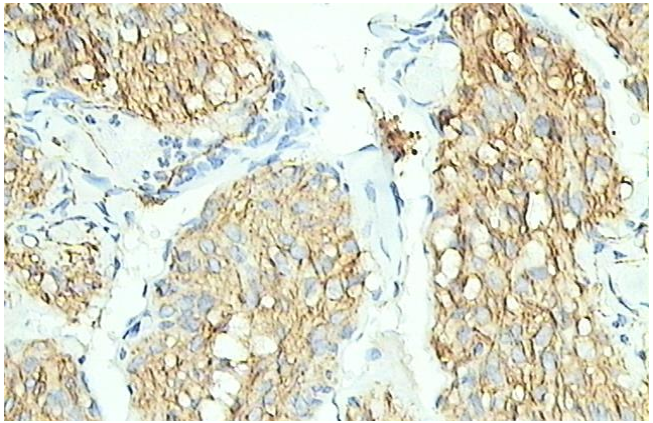
Lung transplant, died at age 37



Lung destruction/cysts



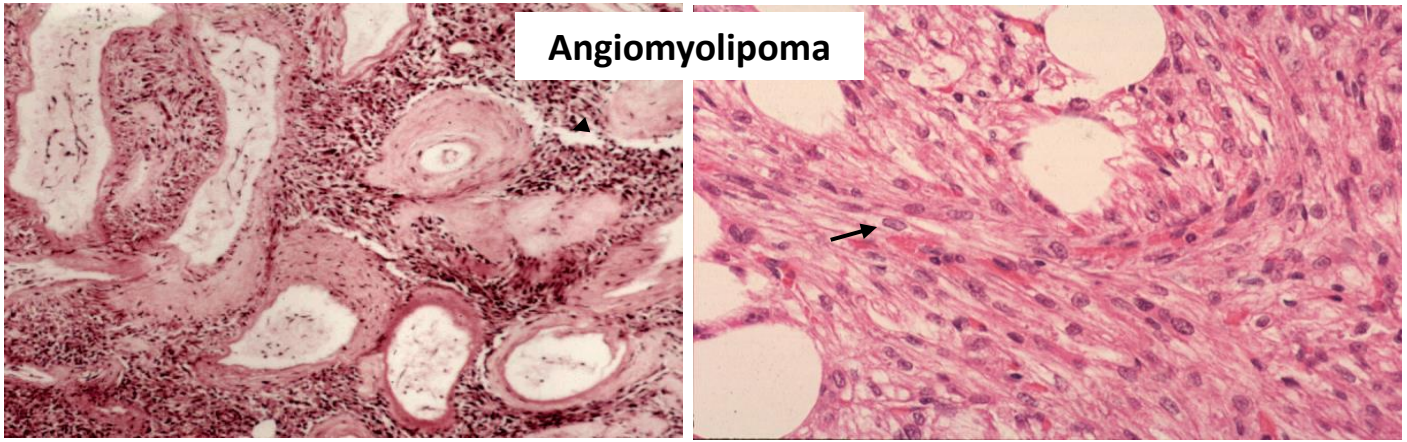
Higher power: smooth muscle-like LAM Cells



LAM cells in lymph node, muscle actin stain

LAM is a multi-system disease

Renal angiomyolipomas: 60%
Lymph nodes: 70%
Chylous pleural effusions: <10%

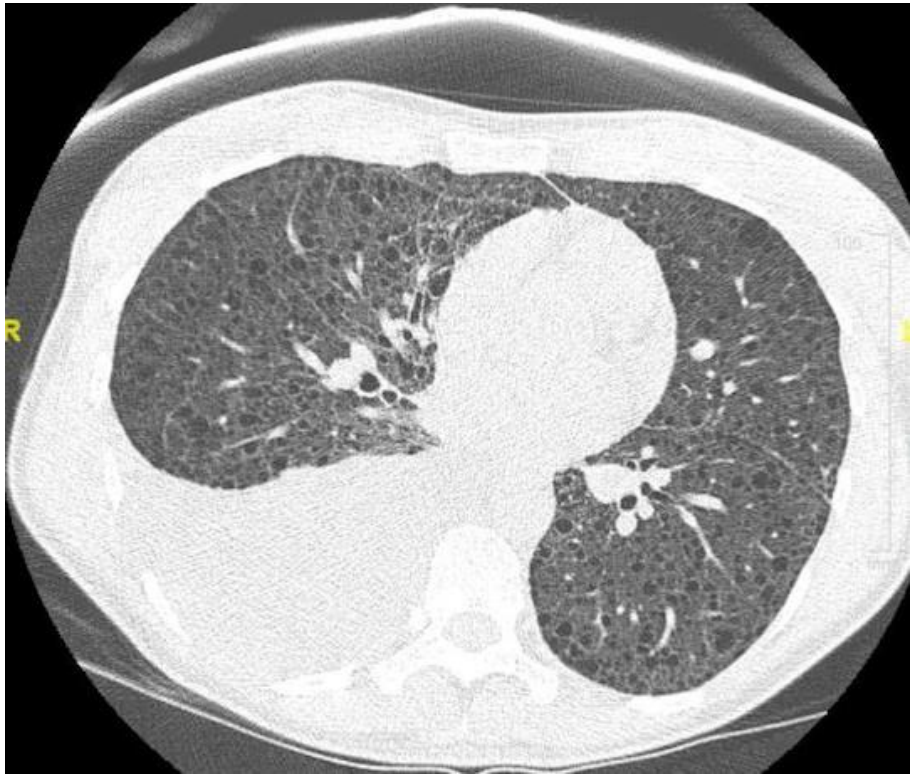


Karbowniczek … Henske Am J Pathol 2003

LAM-associated chylous effusion

30 year old

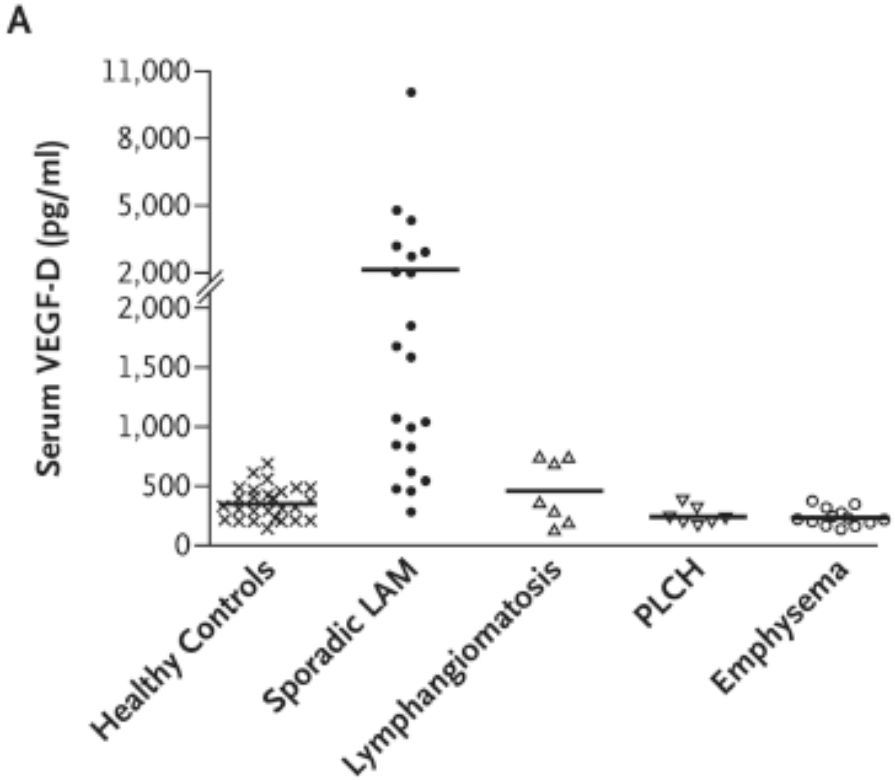
First noted dyspnea about 6 months post-partum



Diagnosis of LAM: VEGF-D Serum Biomarker

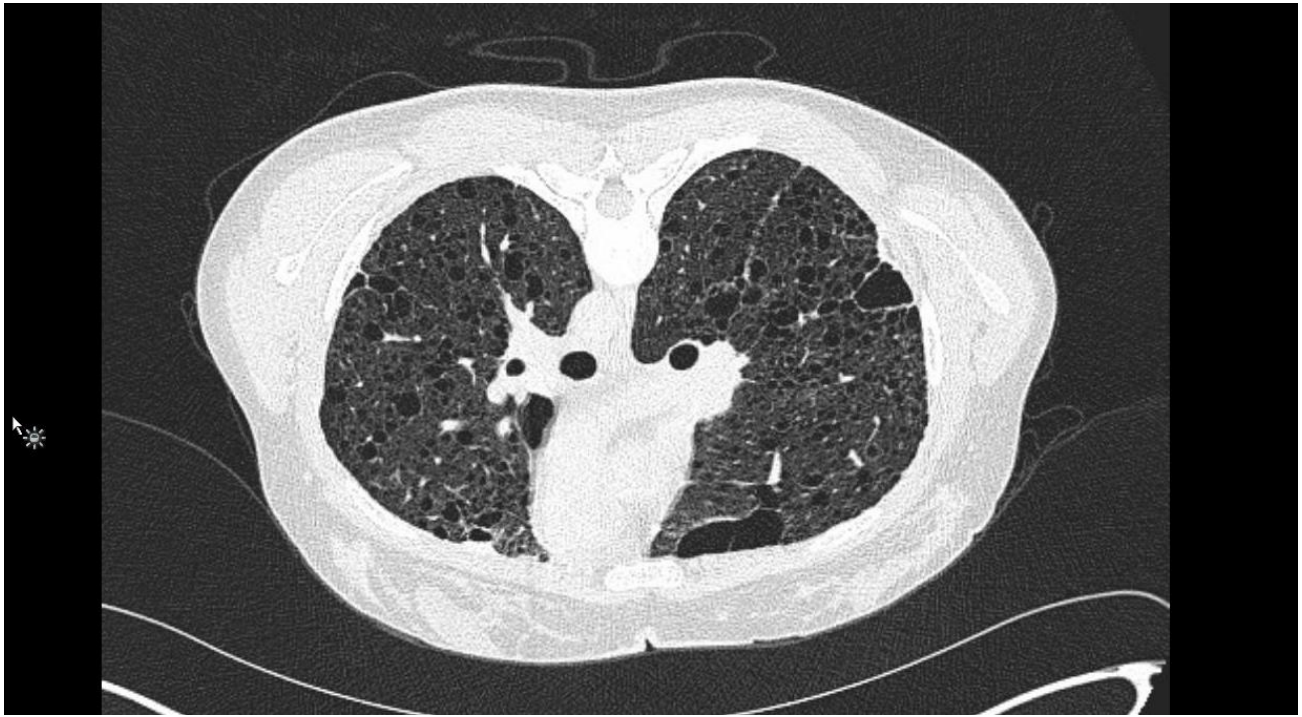
- Typical cystic changes plus

- Renal angiomyolipoma or
- Chylous effusion or
- VEGF-D >800pg/ml



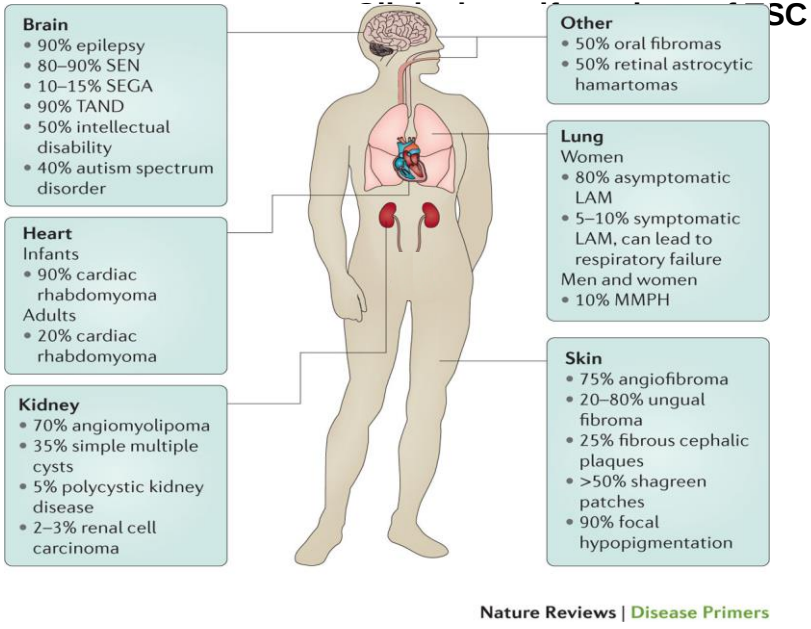
McCormack et al. Am J Respir Crit Care Med 2016 Young et al. N Engl J Med (2008)

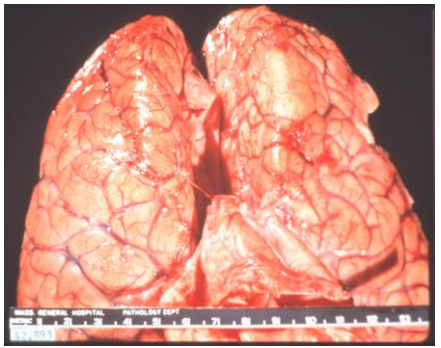
Lymphangioleiomyomatosis (LAM): Occurs in women with Tuberous Sclerosis Complex (TSC)



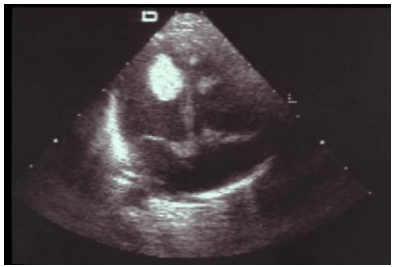
FEV1 fell from 77% to 50% in 2 years

Tuberous Sclerosis Complex is a Cause of Lymphangioleiomytomatosis (LAM)





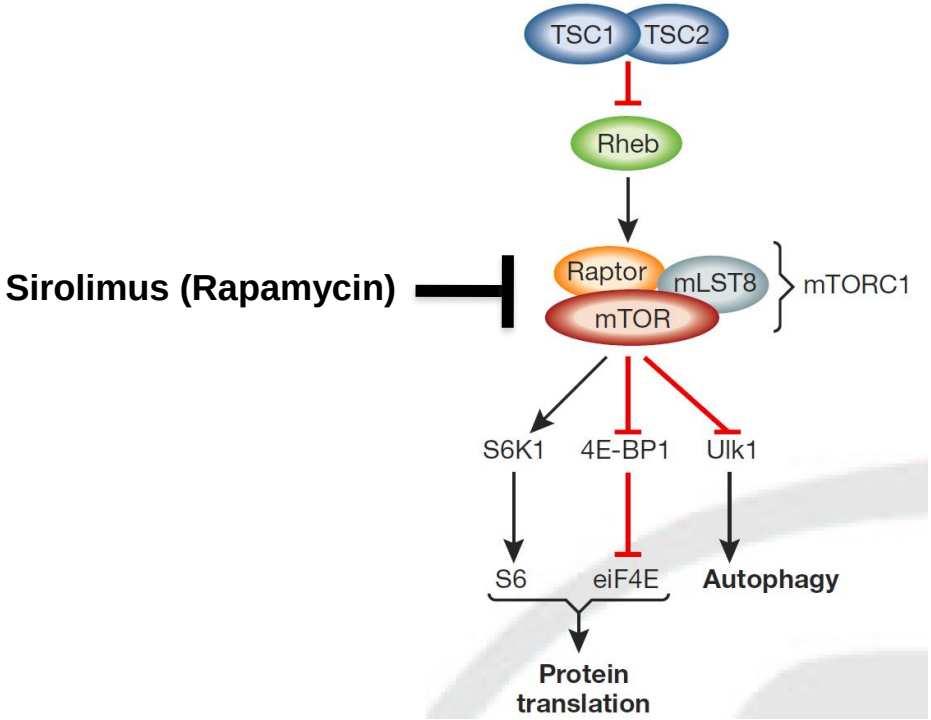
Cerebral Cortical Tuber



Cardiac Rhabdomyoma (prenatal)

Henske, EP et al., Nat Reviews Disease Primers, 2016

mTOR Kinase is Activated in LAM Cells

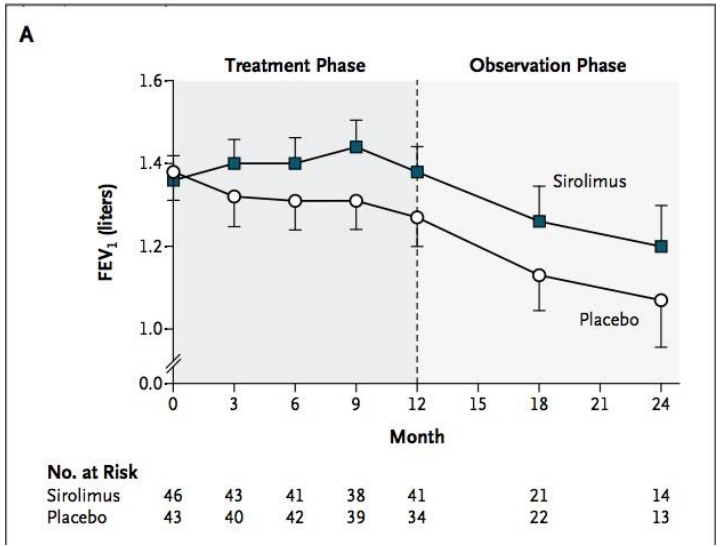


Neuman and Henske, EMBO Molec Med 2011

The NEW ENGLAND JOURNAL *of* MEDICINE **March 2011**

Efficacy and Safety of Sirolimus in Lymphangioleiomyomatosis

Francis X. McCormack, M.D., Yoshikazu Inoue, M.D., Ph.D., Joel Moss, M.D., Ph.D., Lianne G. Singer, M.D., Charlie Strange, M.D., Koh Nakata, M.D., Ph.D., Alan F. Barker, M.D., Jeffrey T. Chapman, M.D., Mark L. Brantly, M.D., James M. Stocks, M.D., Kevin K. Brown, M.D., Joseph P. Lynch, III, M.D., Hilary J. Goldberg, M.D., Lisa R. Young, M.D., Brent W. Kinder, M.D., Gregory P. Downey, M.D., Eugene J. Sullivan, M.D., Thomas V. Colby, M.D., Roy T. McKay, Ph.D., Marsha M. Cohen, M.D., Leslie Korbee, B.S.,Angelo M. Taveira-DaSilva, M.D., Ph.D., Hye-Seung Lee, Ph.D., Jeffrey P. Krischer, Ph.D., and Bruce C. Trapnell, M.D., for the National Institutes of Health Rare Lung Diseases Consortium and the MILES Trial Group*

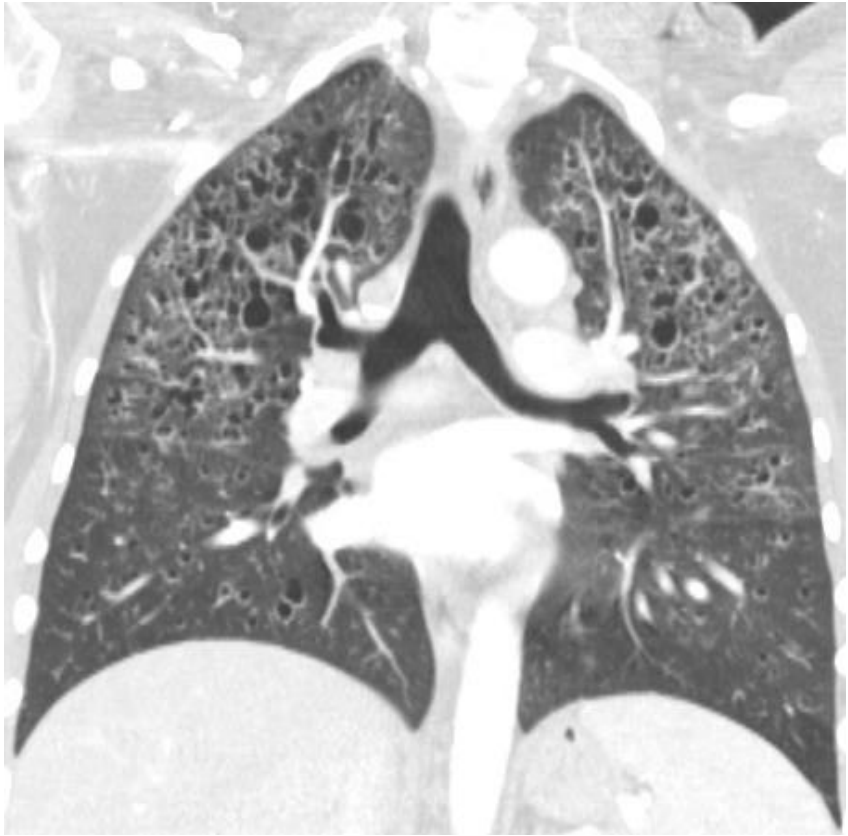


Double blind, placebo control
Sirolimus n = 43
Placebo n = 46

Moderate to severe LAM
Mean FEV1: 1367 ml (48%)
Mean age: 45 yrs
34% postmenopausal

FDA-approved

Langerhans Cell Histiocytosis



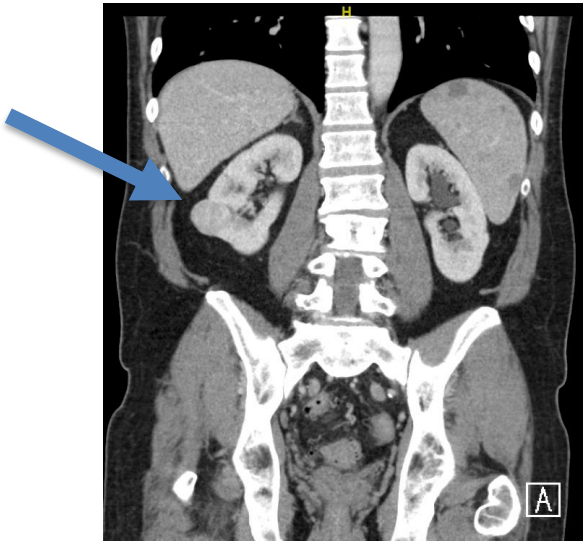
Pulmonary Langerhans Cell Histiocytosis

- Inflammatory myeloid neoplasm, arising from dendritic cells of the monocyte-macrophage lineage that resemble Langerhans cells
- >90% cigarette smoke history
- Often present with incidentally detected cysts or pneumothorax; symptoms include cough, dyspnea , fatigue
  - 20% have extrapulmonary manifestations (cystic bone lesions, diabetes insipidus)
- Somatic mutations activating the MAPK pathway in almost all cases
  - BRAF V600E (50%); MAPK2K1 (25) plus others

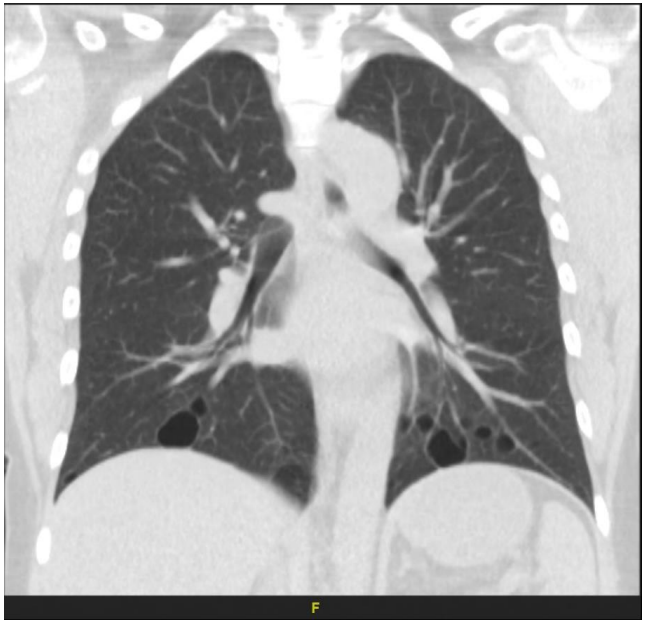
Pulmonary Langerhans Cell Histiocytosis: Treatment

- 40-50% spontaneous resolution with smoking cessation alone
- Steroids – limited responses
- Consider clinical trial for progressive disease (including trials of MAPK pathway inhibitors)

Birt-Hogg-Dubé (BHD)

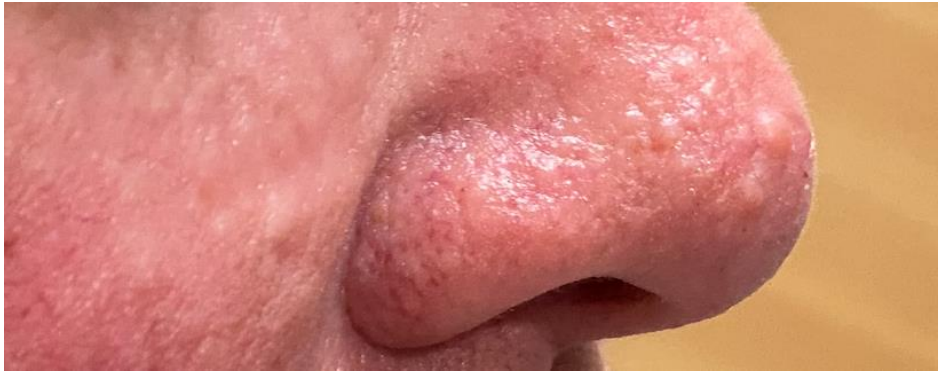


Renal Cell Carcinoma



Birt Hogg Dube

- Autosomal dominant
  - Incidence around 1/3,500
- Lung cysts ~80% by age 50; ~40% pneumothorax
- Facial fibrofolliculomas (flesh colored)
- Kidney cancer in ~25%
- Mutations in the folliculin (FLCN) gene



Cystic Lung Disease: Overview

	Lymphangioleiomyomatosis (LAM)	Pulmonary Langerhans	Birt-Hogg-Dube (BHD)
Lung cysts	Round, Thin-walled Diffuse	Irregular shapes, thin-walls Often upper zone predominant	Round or ellipse-shaped Often medial
Other features	Women-only Chylous effusion Renal angiomyolipoma VEGF-D> 800 pg/ml	Skin and bone lesions	Kidney cancer Skin lesions
Pneumothorax	60%	10-20%	40%
Genes	TSC1 or TSC2	BRAF, MAPK	FLCN
Targeted Therapy	mTOR inhibition (Rapamycin/Sirolimus)	Kinase Inhibitors?	

Cystic Lung Disease: MOC Reflective Statement

- Many causes of cystic lung disease
- Three cystic lung disease have specific genetic signatures and non-pulmonary manifestations:
  - Lymphangioleiomyomatosis (LAM) (*TSC1/2*)
  - Pulmonary Langerhans cell histiocytosis (PLCH) (*B-RAF*)
  - Birt Hogg Dube syndrome (BHD) (*FLCN*)
- Kidney tumors in LAM (angiomyolipoma) and BHD (carcinoma)
- LAM has a specific, FDA-approved therapy: Rapamycin/sirolimus

Question #1

- All women with suspected LAM should have abdominal imaging because 50% have:
  A) Hepatic angiomyolipomas
  B) Renal angiomyolipomas
  C) Ovarian cysts

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- All women with LAM should have abdominal imaging because 50% have:
  A) Hepatic angiomyolipomas
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Question #2

Patients with Birt-Hogg-Dube should have abdominal imaging because 25% develop:

A) Liver cysts

B) Renal cell carcinoma

C) Peritonitis

Question #2

Patients with Birt-Hogg-Dube should have abdominal imaging because of the risk of:

A) Liver cysts

B) Renal cell carcinoma

C) Peritonitis

Question #3

Proven effective therapy for Lymphangioleiomyomatosis (LAM):

A) VEGF inhibition

B) mTOR inhibition

C) Corticosteroids

Question #3

Proven effective therapy for Lymphangioleiomyomatosis (LAM):

A) VEGF inhibition

B) mTOR inhibition (Rapamycin/Sirolimus)

C) Corticosteroids