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

Diffuse Cystic Lung Diseases

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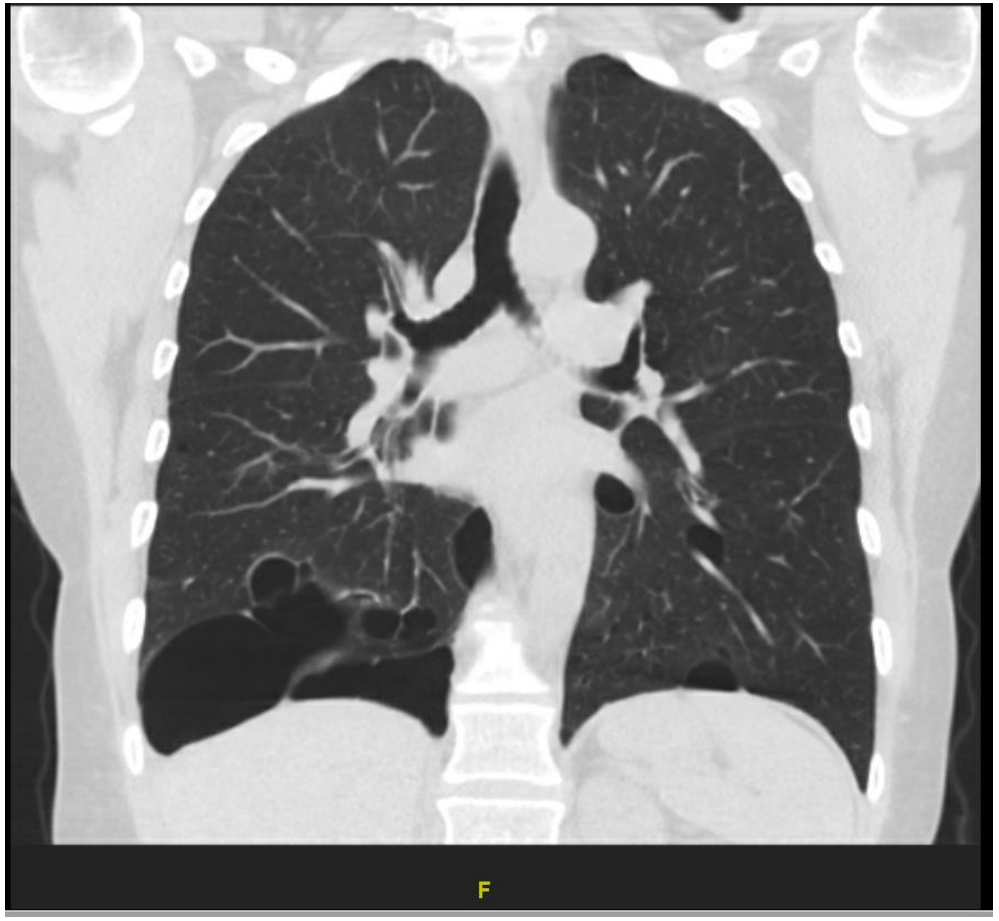
- Co-Director of the BWH Pulmonary Genetics Clinic
  - **Clinical focus:** Cystic Fibrosis, Pulmonary Genetics and Lung Transplant Medicine
  - **Research focus:** Cell signaling in Birt-Hogg-Dube and other forms of ILD/pediatric ILD

Conflicts of interest

- Site PI for Vertex VX-121 study for Cystic Fibrosis. **(Not relevant to this talk)**
- Paid lecturer on pediatric ILD for Eli Lilly. **(Not relevant to this talk)**
- **Coordinating PI on Chan-Zuckerberg Initiative grant 2002-316770** for Creating an Inflammatory Childhood Interstitial Lung Disease Cell Atlas.
- **Co-PI on Myrovlytis Trust grant MTT22_15** to **"**Developing AI solutions via Federated Learning to aid the diagnosis of Birt-Hogg-Dubé Syndrome and other rare genetic causes of pneumothorax**"**

Definition of a pulmonary cyst

- **Pathology-** A cyst is any rounded circumscribed space that is surrounded by an epithelial or fibrous wall of variable thickness.
- **Radiographs-** A cyst appears as a rounded parenchymal lucency or low attenuating area with well defined interface with normal lung…..are usually thin walled (usually <2mm) and occur without associated pulmonary emphysema.



K.

Hansell D.M. *et al.* Radiology *2008*

Methods for categorizing Diffuse Cystic Lung Diseases (DCLDs)

- **HRCT appearance:**
- Are cysts symmetric or irregular appearing?
- Are they evenly distributed, or do they favor one region?
- Are there nodules present with the cysts?
- Are there significant ground glass opacities present?

Table 2. Classification of DCLDs

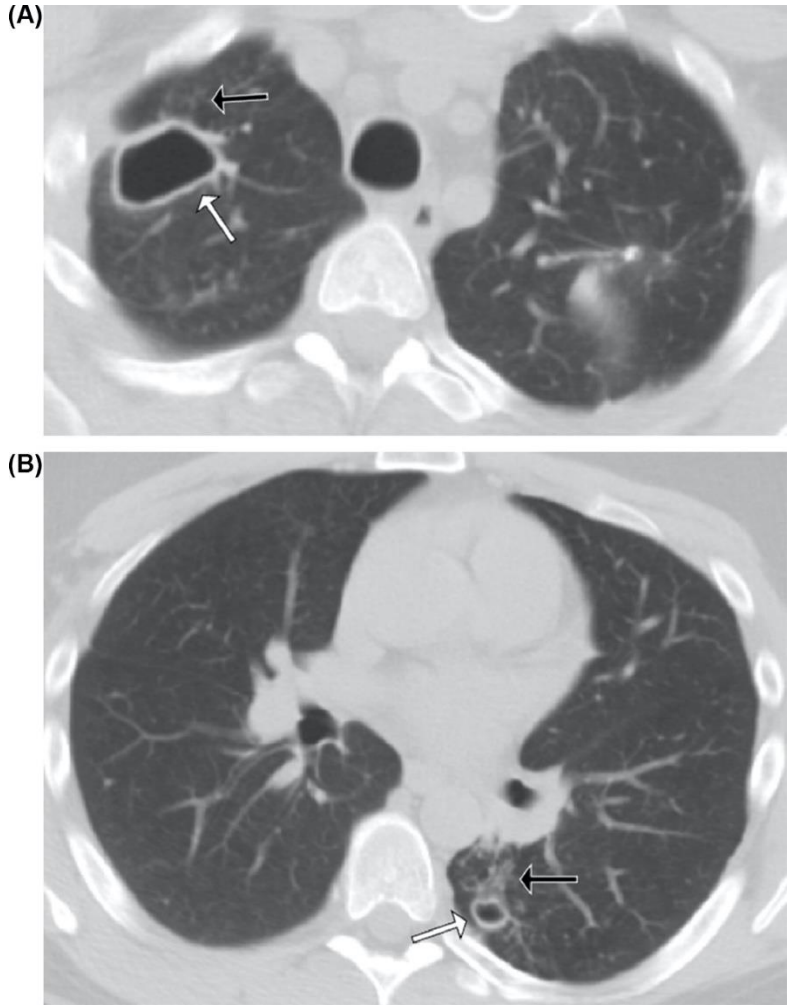
Classification	Description
1. Neoplastic	Lymphangioleiomyomatosis—sporadic as well as associated with tuberous sclerosis
	Pulmonary Langerhans cell histiocytosis, and non–Langerhans cell histiocytoses, including Erdheim Chester disease
	Other primary and metastatic neoplasms, such as sarcomas, adenocarcinomas, pleuropulmonary blastoma, etc.
2. Genetic/developmental/congenital	Birt-Hogg-Dubé syndrome
	Proteus syndrome, neurofibromatosis, Ehlers-Danlos syndrome
	Congenital pulmonary airway malformation, bronchopulmonary dysplasia, etc.
3. Associated with lymphoproliferative disorders	Lymphocytic interstitial pneumonia/Follicular bronchiolitis commonly seen in conjunction with autoimmune disorders such as Sjögren syndrome, amyloidosis, and light-chain deposition disease
4. Infectious	*Pneumocystis jiroveci*, Staphylococcal pneumonia, recurrent respiratory papillomatosis, endemic fungal diseases, especially coccidioidomycosis, paragonimiasis
5. Associated with interstitial lung diseases	Hypersensitivity pneumonitis
	Desquamative interstitial pneumonia
6. Smoking related	Pulmonary Langerhans cell histiocytosis
	Desquamative interstitial pneumonia
	Respiratory bronchiolitis
7. Other/miscellaneous	Post-traumatic pseudocysts
	Fire-eater's lung
	Hyper-IgE syndrome
8. DCLD mimics	Emphysema
	α1-antitrypsin deficiency
	Bronchiectasis
	Honeycombing seen in late-stage scarring interstitial lung diseases

From Reference 1, with permission.
DCLD = diffuse cystic lung diseases

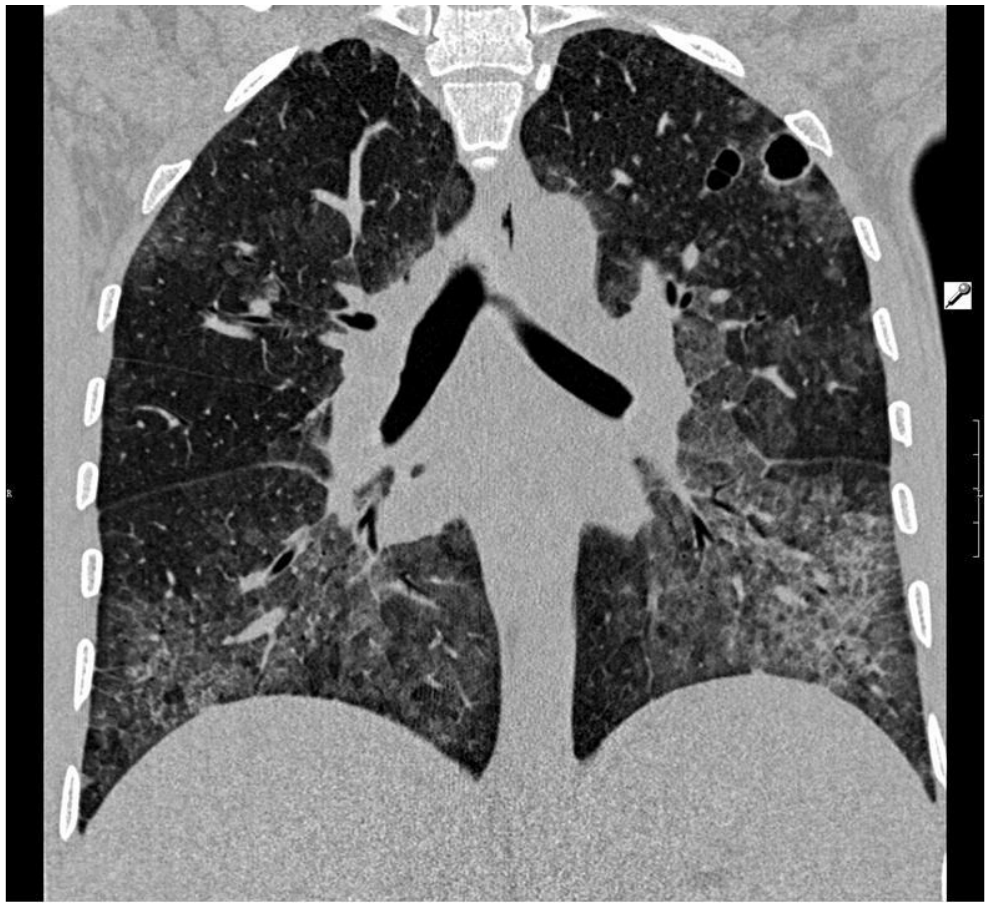
Gupta N., Vassallo R. *et al.* Am J Respir Crit Care Med 2015
Obaidat B., Yazdani D., *et al*. Respir Care 2020

Excluding infectious causes of pulmonary cysts

Chronic Coccidioidomycosis infection



- Pulmonary *Pneumocystis jiroveci* infection



Desai, Radiopaedia.org, rID:5751

Green D.B. *et al.* Current Problems in Diagnostic Radiology 2022

ABIM Pulmonary Boards Blueprint

Diffuse cystic lung diseases (DCLDs)	<2%
Lymphangioleiomyomatosis	
Langerhans cell histiocytosis	
Birt-Hogg-Dube syndrome	
Follicular bronchiolitis and cystic LIP	
Light-chain deposition disease, neurofibromatosis, Marfan syndrome, and other DCLDs	

American Board of Internal Medicine

Pulmonary Disease

Certification Examination Blueprint

October 2024

PULMONARY DISEASE Blueprint

For traditional, 10-year Maintenance of Certification (MOC) exam and Longitudinal Knowledge Assessment (LKA™)

DIFFUSE CYSTIC LUNG DISEASES (DCLDs) *(<2% of exam)*

Lymphangioleiomyomatosis	LF	⊘	⊘	⊘	⊘	⊘
Langerhans cell histiocytosis	LF	⊘	⊘	⊘	⊘	⊗
Birt-Hogg-Dube syndrome	LF	⊘	⊘	⊗	⊗	⊗

✓ – ***High Importance***: *At least 65% of questions will address topics and tasks with this designation.*

⊘ – ***Medium Importance***: *No more than 35% of questions will address topics and tasks with this designation.*

⊗ – ***Low Importance***: *No questions will address topics and tasks with this designation.*

LF – ***Low Frequency***: *No more than 30% of questions will address topics with this designation, regardless of task or importance.*

DIFFUSE PARENCHYMAL LUNG DISEASE (DPLD) *continued… (10% of exam)*		**Diagnosis**	**Testing**	**Treatment/ Care Decisions**	**Risk Assessment/ Prognosis/ Epidemiology**	**Pathophysiology/ Basic Science**
DIFFUSE CYSTIC LUNG DISEASES (DCLDS) *continued… (<2% of exam)*						
Follicular bronchiolitis and cystic LIP	LF	⊘	⊘	⊘	⊗	⊗
Light-chain deposition disease, neurofibromatosis, Marfan syndrome, and other DCLDs	LF	⊘	⊘	⊘	⊗	⊗

October 2024

Gupta DCLD Classification

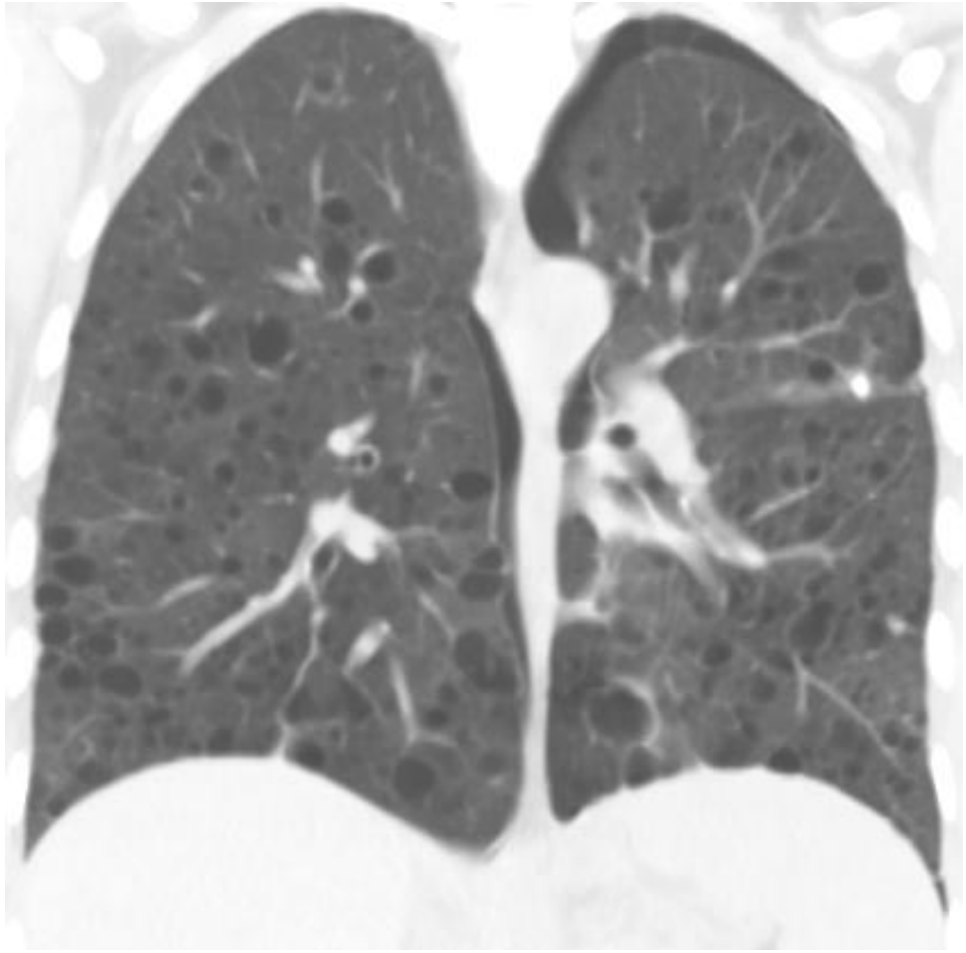
Neoplastic

Somatic mutations

Lymphangioleiomyomatosis (LAM)

- Typical presentation: F mid-30s with worsening dyspnea or spontaneous pneumothorax
- Associated with renal angiomyolipoma and pneumo/chylothorax

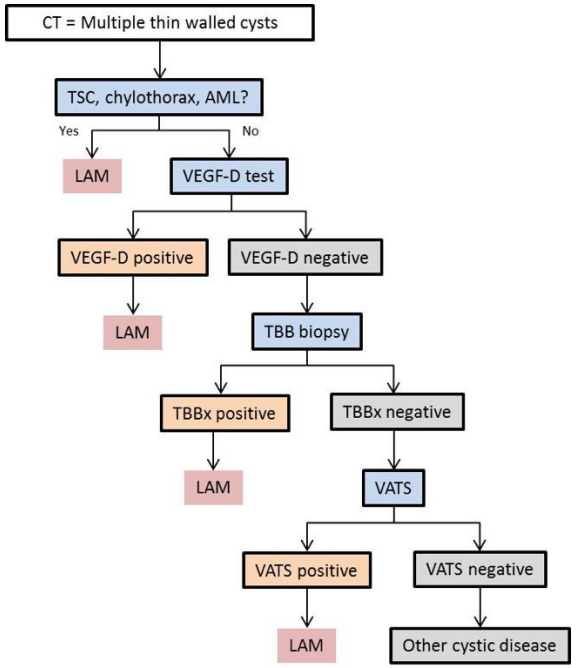
- Elevated serum VEGF-D >800pg/ml is diagnostic i/s/o appropriate imaging

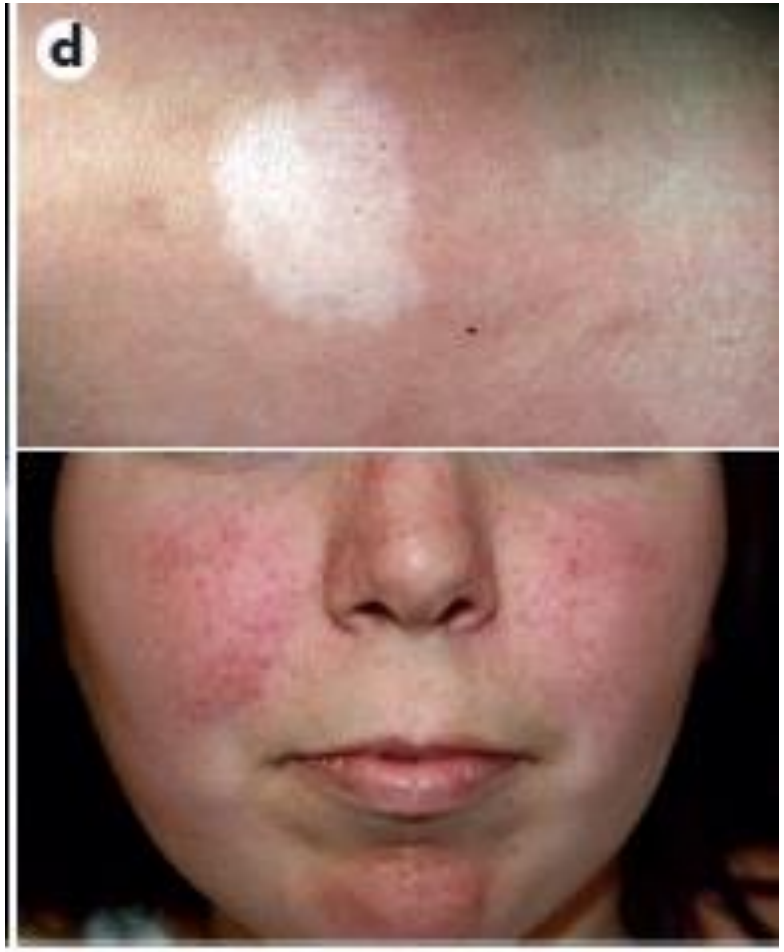


Leal C. dos Santos R. *et al.* ESTI poster P-0100

Lymphangioleiomyomatosis (LAM)

- Seen with (TSC-LAM) or without (s-LAM) an underlying diagnosis of Tuberous sclerosis complex (TSC).
- History and physical focused on signs of TSC

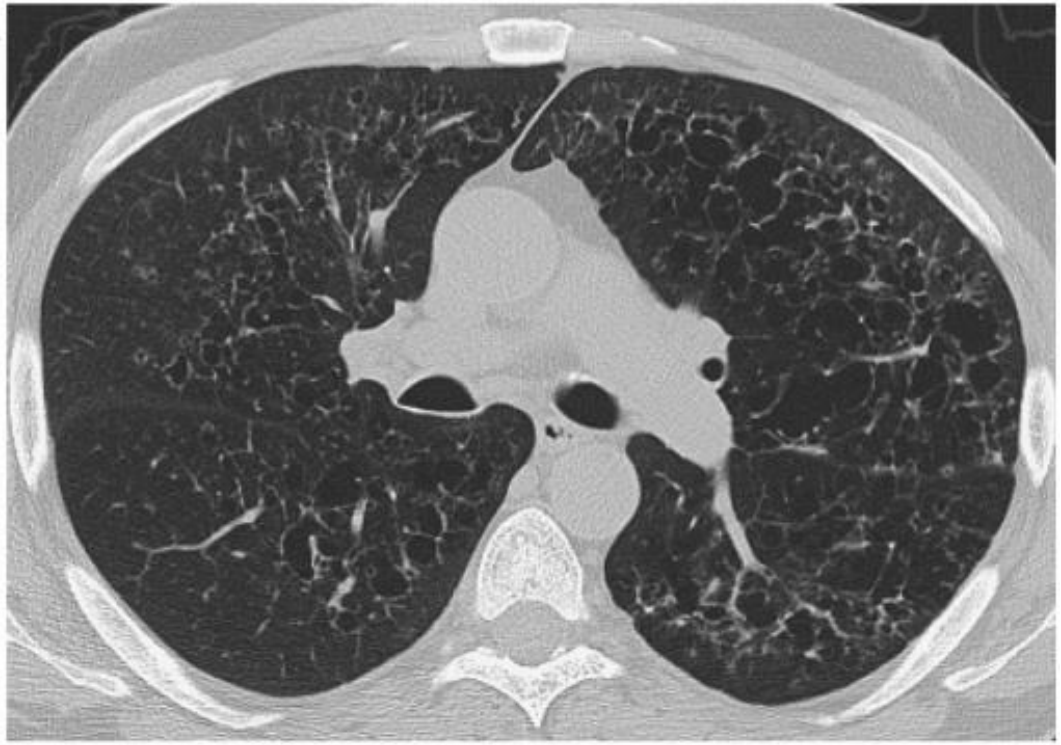




Henske *et al.* Nature Reviews 2016; Carsillo *et al.* PNAS 2000
thelamfoundation.org

Langerhans cell histiocytosis

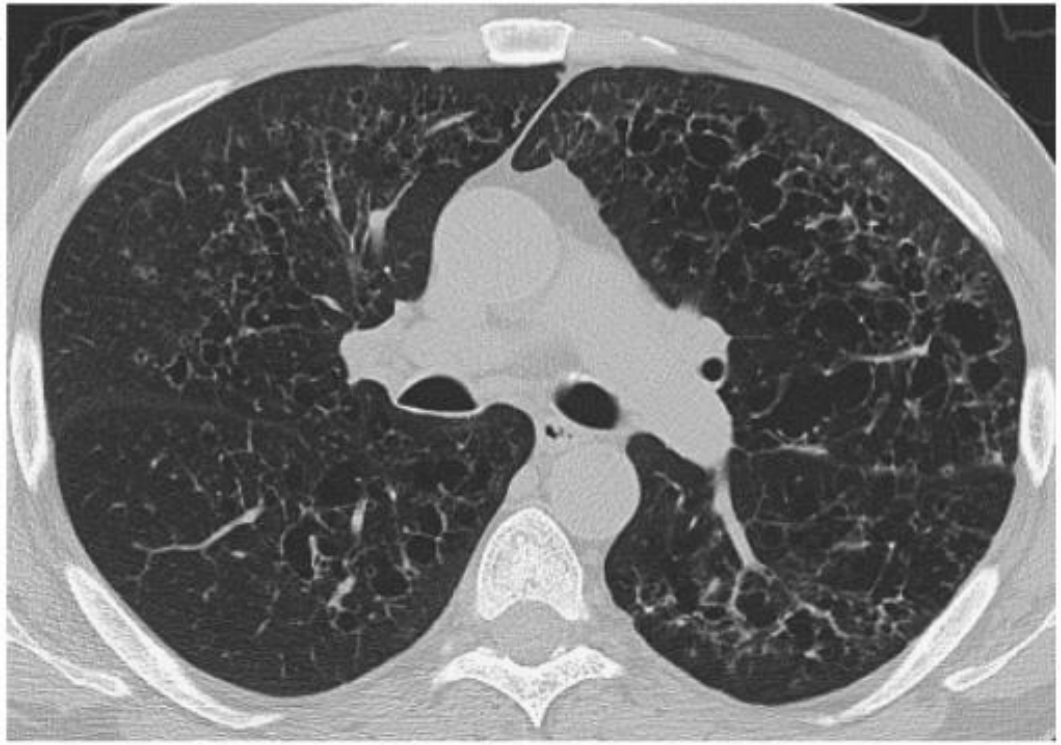
- Irregular cysts and nodules in a smoker
- Upper and middle lobe predominant, sparing costophrenic angles
- Young smokers; M=F



Emile J., Abla O., *et al.* Blood 2016
Beatrice Trotman-Dickenson Er J Rad 2014

Langerhans cell histiocytosis

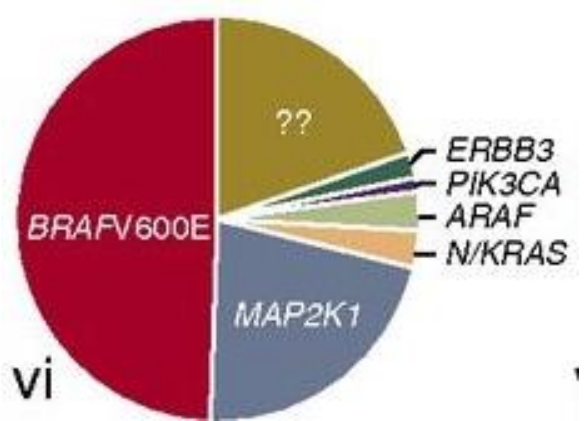
- Can be single organ or multisystem
- Extrapulmonary manifestations can be in any organ but more often include:
- Pituitary-hypothalamic
- Bony lesions
- Skin lesions

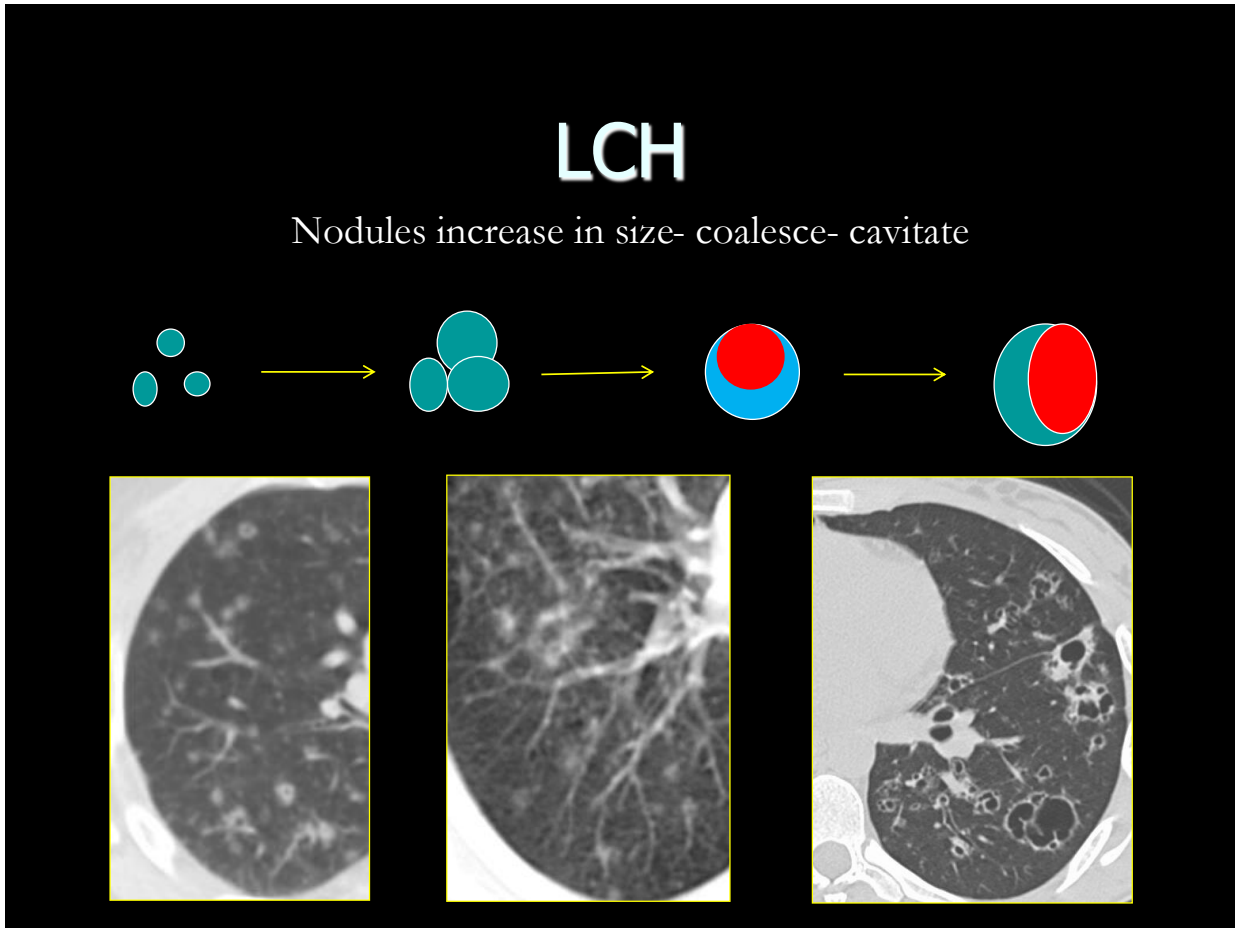


Emile J., Abla O., *et al.* Blood 2016
Beatrice Trotman-Dickenson Er J Rad 2014

Langerhans cell histiocytosis

- Accumulation **CD1a+**, Langerin (**CD207+)** dendritic cells around small airways
- Loosely formed granulomas form
- Granulomas destroy surrounding bronchiolar walls and parenchyma
- Majority of lesions show MAPK activation mutations

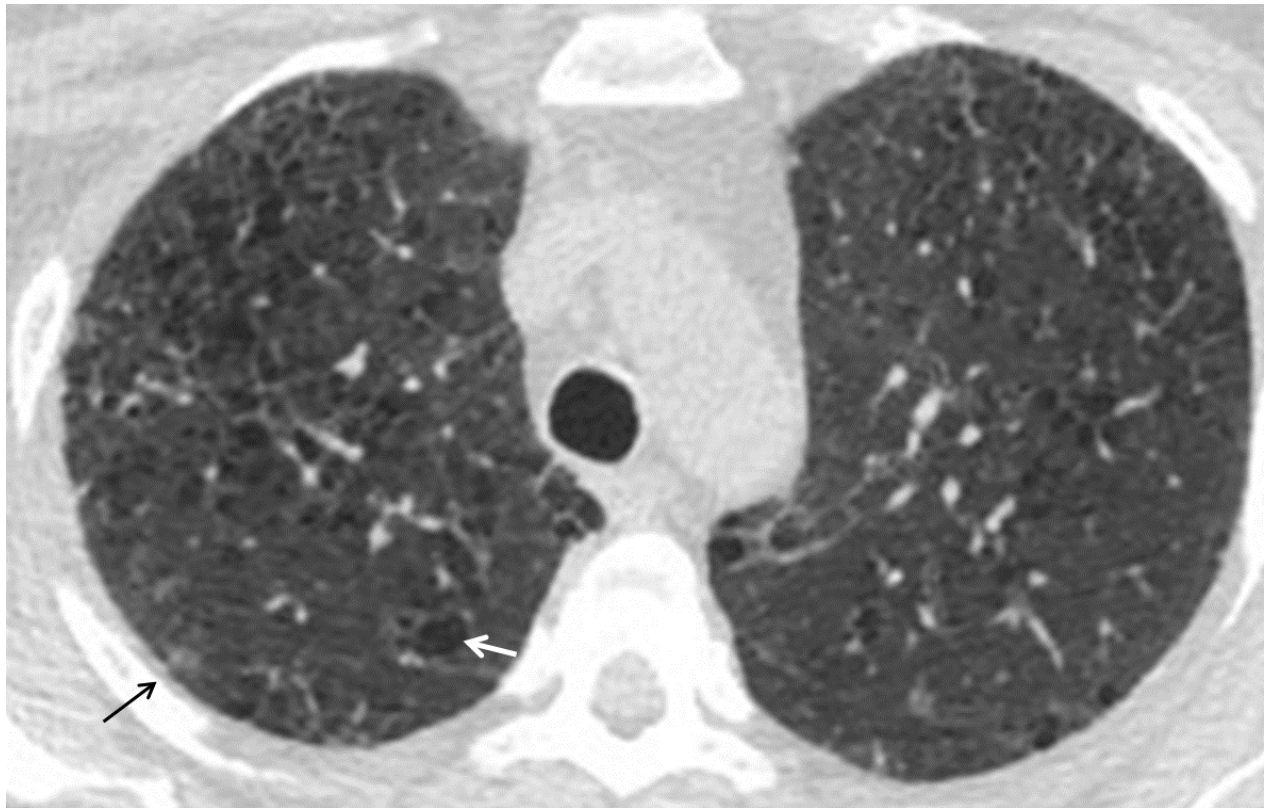




Emile J., Abla O., *et al.* Blood 2016
Beatrice Trotman-Dickenson
Vassallo, Harari, and Tazi Thorax 2017

Langerhans cell histiocytosis

- BAL with >5% CD1a+, CD207+ cells supports diagnosis
- Transbronchial biopsy is diagnostic up to 40% of time
- PFTs most consistently show depressed DLCO
- Smoking cessation
- TKIs (BRAF and MEK inhibitors) on a clinical trial basis



A.

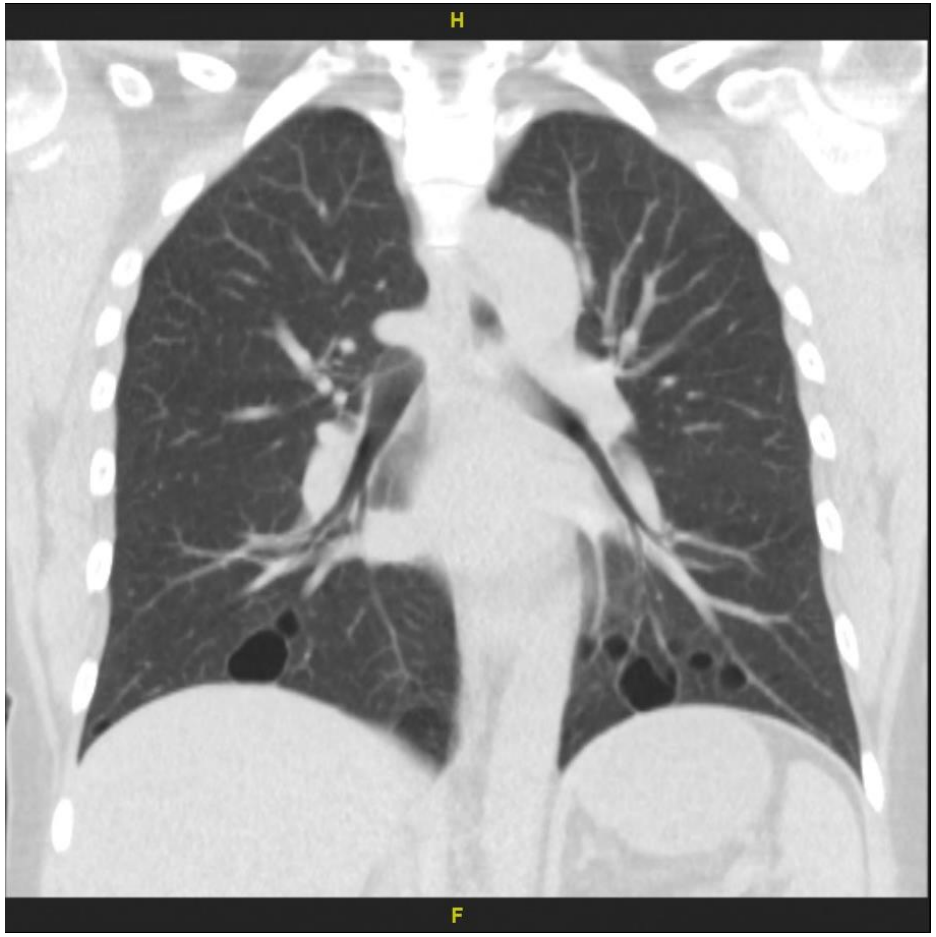
Elia D *et al.* Eur J Intern Med 2015
B. Trotman-Dickenson. Eu J Rad 2015

Gupta DCLD Classification

Genetic

Birt-Hogg-Dubé (Lung manifestation)

- Lower lobe predominant, subpleural and paramediastinal cysts
- Most penetrant aspect of syndrome (~80%)
- Typically “occurs” in the 4th decade. Case reports earlier
- 30% of patients with PTX and ~85% recurrence w/o intervention
- Lung function is mostly preserved throughout the lifespan

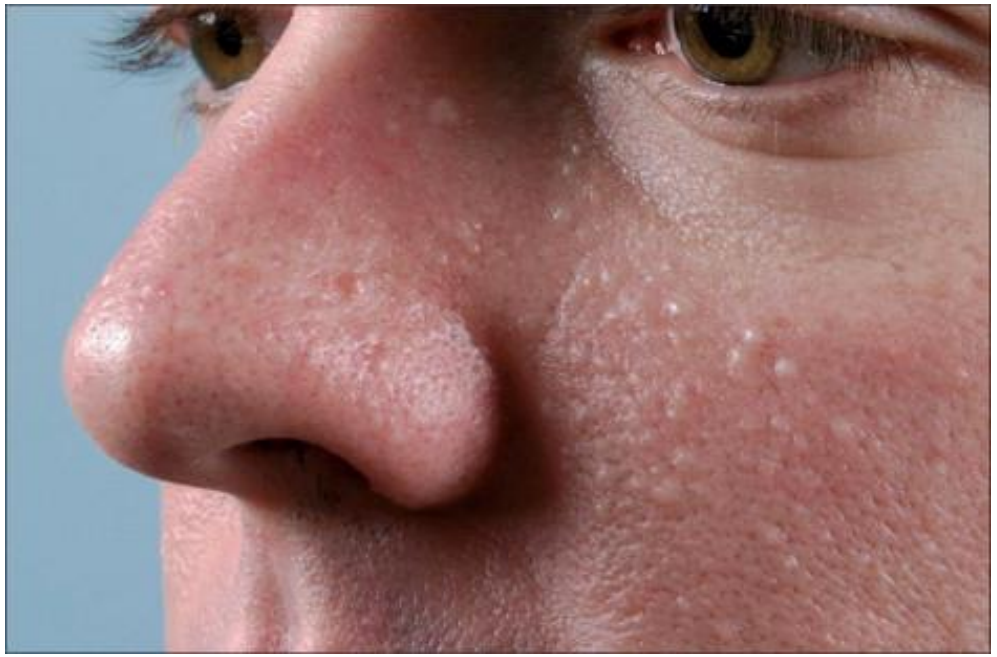


K.

Kennedy J.C. *et al.* Semin Respir Crit Care Med 2020

Birt-Hogg-Dubé (Skin manifestation)

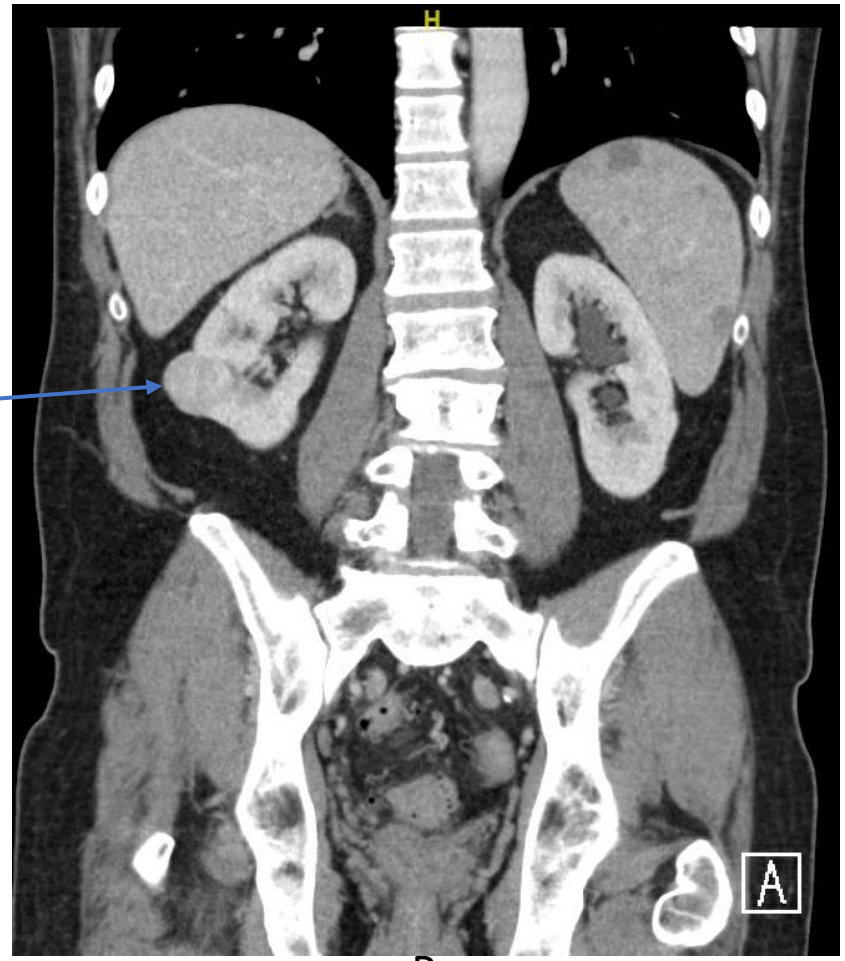
- **Fibrofolliculomas;** Abnormal growth of hair follicles



Menko *et al.* Lancet Oncology 2009

Birt-Hogg-Dubé (Renal manifestations)

- Multiple, frequently bilateral, renal tumors
- Most frequently Chromophobe RCC, and Oncocytic hybrid RCC
- Mean age of onset in the early 50s

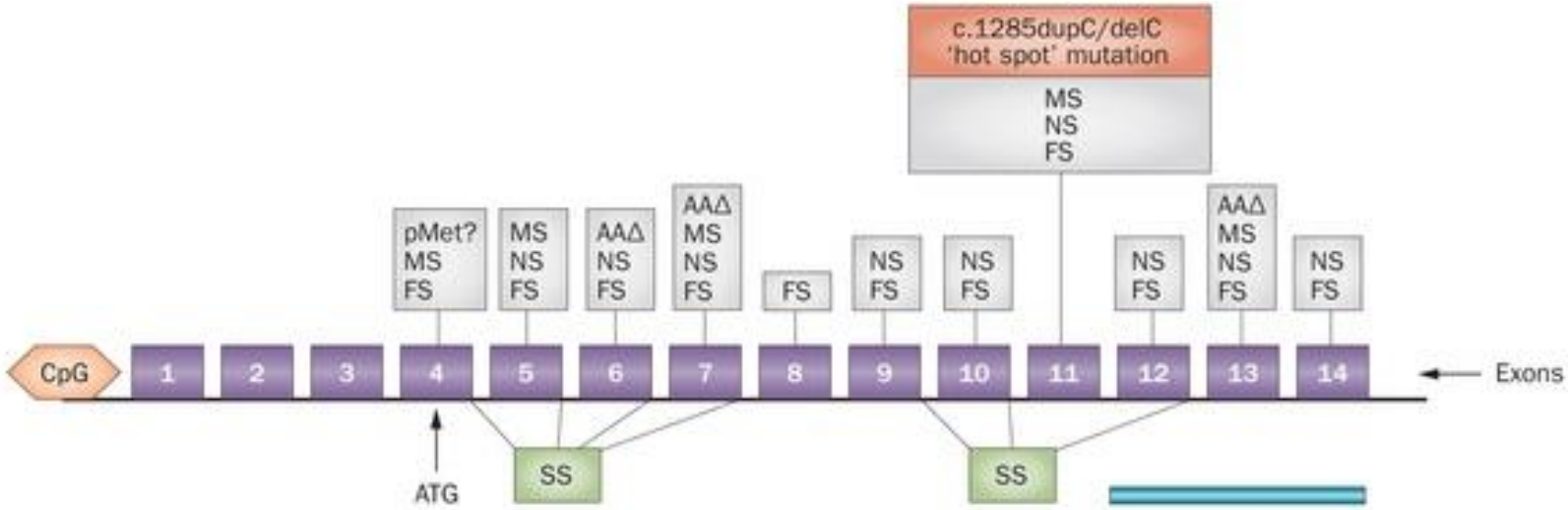


P.

Kennedy J.C. *et al.* Semin Respir Crit Care Med 2020

BHD is caused by loss of function mutations in the *FLCN* gene

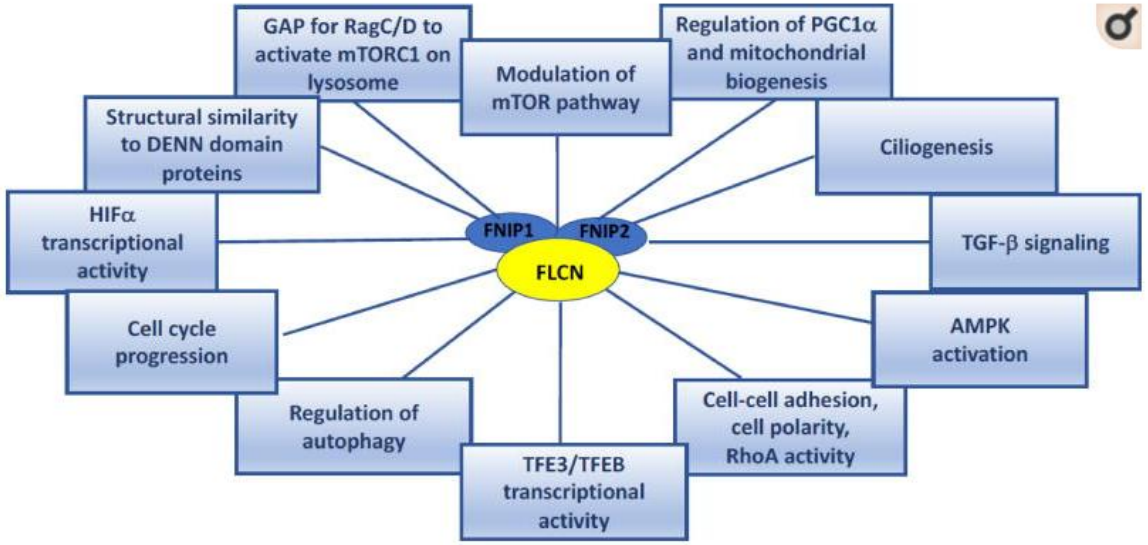
- Encodes a 579 AA protein predicted to weigh 64kDa
- Located physically on 17p11
- 14 exons with mutations distributed in most exons
- C-terminal domain functions as a guanine nucleotide exchange factor (GEF)

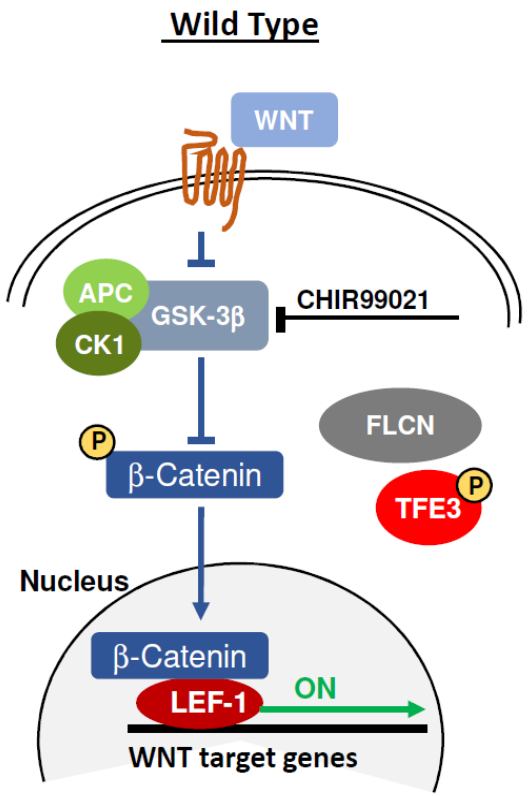


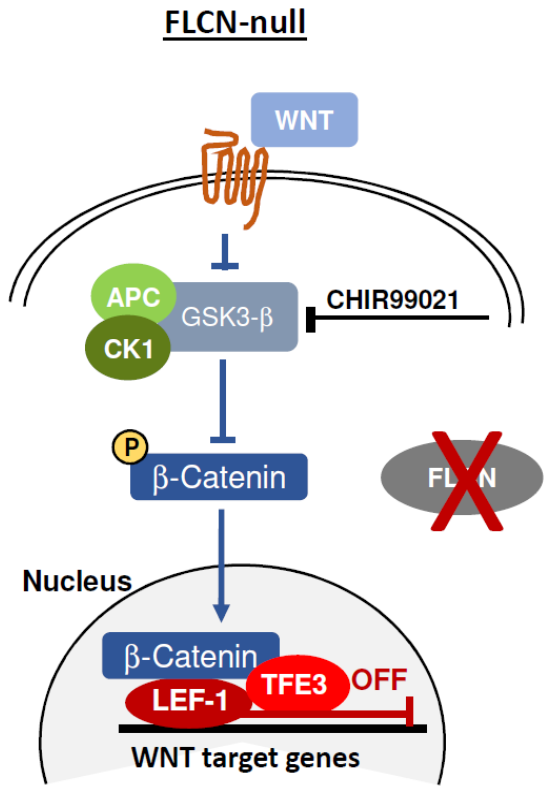
Schmidt and Linehan Nat Rev Urol 2015

Folliculin protein plays a role in many cellular processes

- Mechanism of lung cyst pathogenesis is incompletely understood



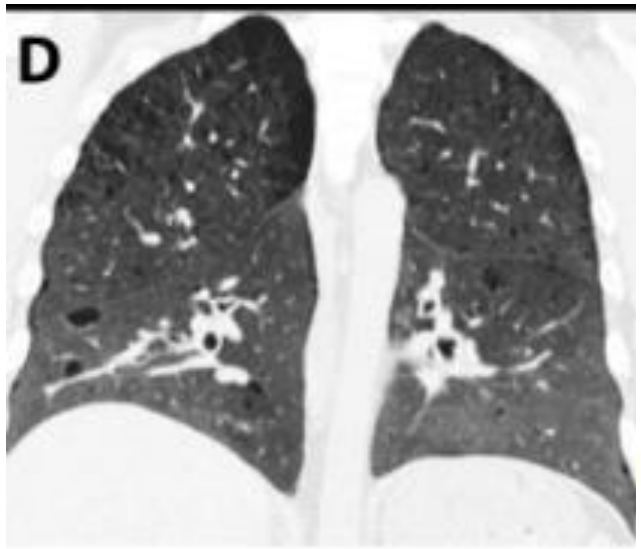




Kennedy JC, Khabibullin D *et al.* Hum Mol Genet 2019
Schmidt and Linehan Gene 2018

Diffuse lung disease associated with mutations in *NF-1* **(NF-DLD)**

- Upper lobe predominant, subpleural, very thin walled cysts
- Bullae, dense GGOs and subpleural fibrosis that spares the bases
- Present in 15-25% of patients with NF1
- Has been reported in children as young as three (“presents in adulthood”)



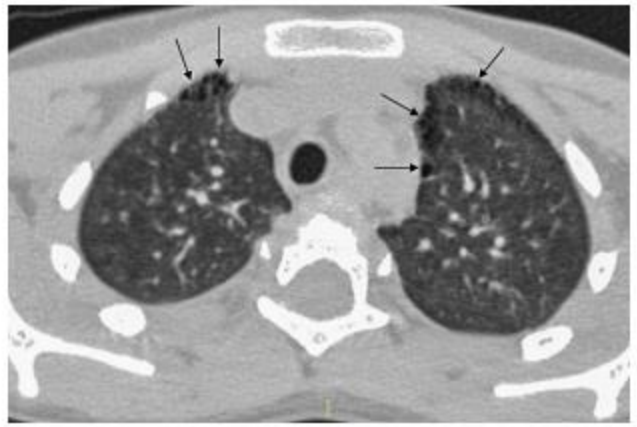
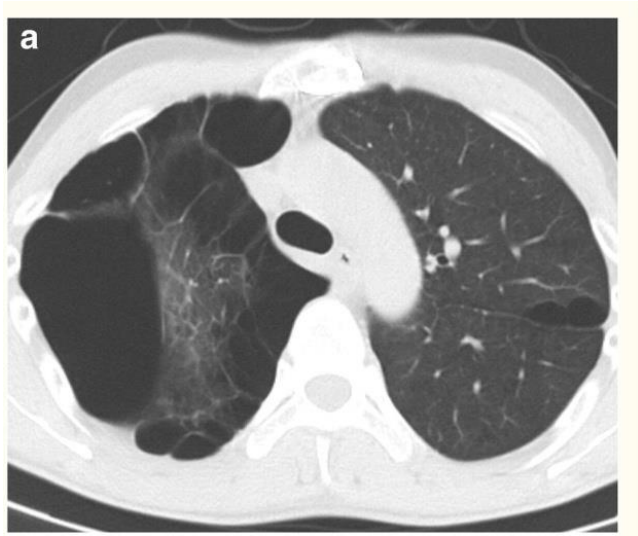


FIGURE 1 The axial CT image in a 4-year-old boy shows multiple rows of small (<1 cm) subpleural cysts at the upper lobes (arrows). CT, computed tomography

Shino MY *et al.* Semin Respir Crit Care Med 2012
Spinnato P *et al*. Pediatric Pulmonology 2019
Junior S. *et al.* Respiratory Medicine 2019
Green D.B. *et al.* Current Problems in Diagnostic Radiology 2022

Marfan associated cystic lung disease

- Cysts, bullae/blebs appear to have an apical predominance
- Pneumothorax can be a presenting feature (Ghent II criteria)
- Lung manifestations are seen in ~10% of patients with Marfan

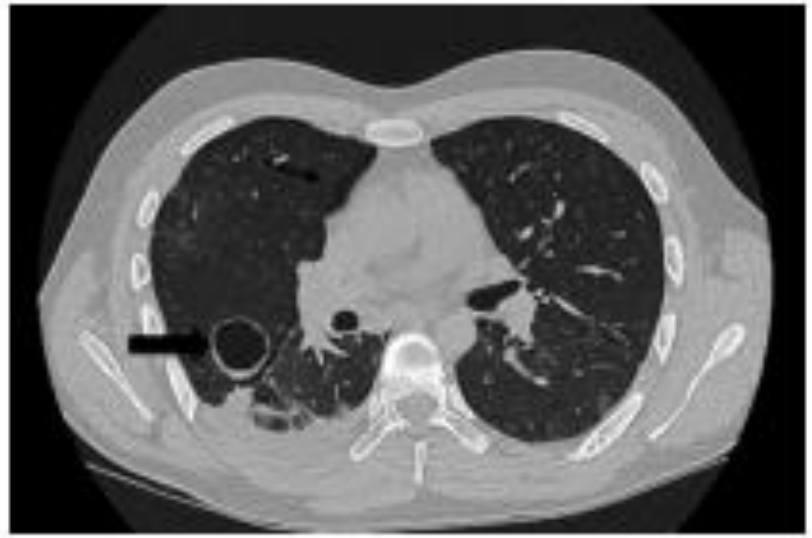


Heterozygous mutations in *FBN1*
FBN2/TGFBR1/TGFBR2

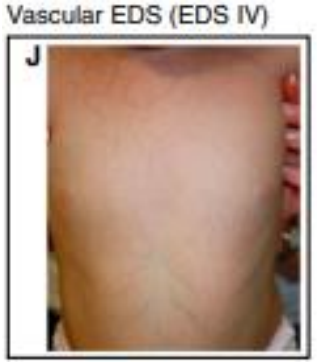
Milewicz DM *et al.* Nat Rev Dis Primers 2022
Yabuuchi Y *et al.* BMC Pulm Med 2020
Boone PM. *et al*. Am J Respir Crit Care Med 2019

Ehlers-Danlos type IV (vEDS)

- Pneumothorax, cavitary lesions, cysts and bullae can be seen
- Presenting symptom can be arterial aneurysm, dissection, rupture of colon or gravid uterus
- Thin, almost translucent skin can be present



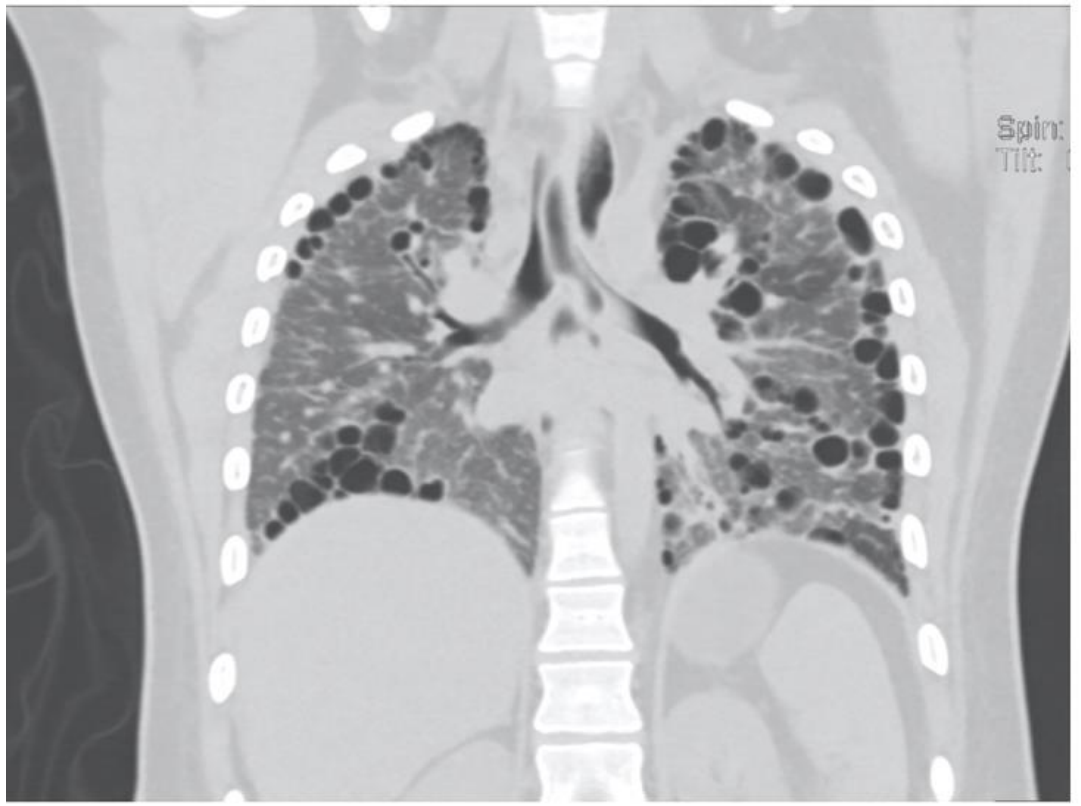
Heterozygous mutations in *COL3A1*



Lim R. *et al.* Ann Am Thorac Soc 2018
Boone PM. *et al*. Am J Respir Crit Care Med 2019
Green D.B. *et al.* Current Problems in Diagnostic Radiology 2022

Down Syndrome (Trisomy 21)

- The most prevalent chromosomal abnormality worldwide (1:700 births)
- ~22-74% of individuals with DS have pulmonary cysts.
- Present from the first few months of life.



L.

Danopoulos S. *et al.* AJP Lung Cell and Mol Phys 2021
Gyves-Ray K. *et al*. Ped Rad 1994
Green D.B. *et al.* Current Problems in Diagnostic Radiology 2022

Gupta DCLD Classification

Associated with lymphoproliferative disorders

Follicular bronchiolitis: lymphoproliferative disorders

- Lymphoid follicular hyperplasia with an airway centric distribution
- Associated with Sjögren, RA, HIV, CVID
- Also associated with COPA syndrome.

(MIM:616414, Autosomal dominant, interferonopathy)

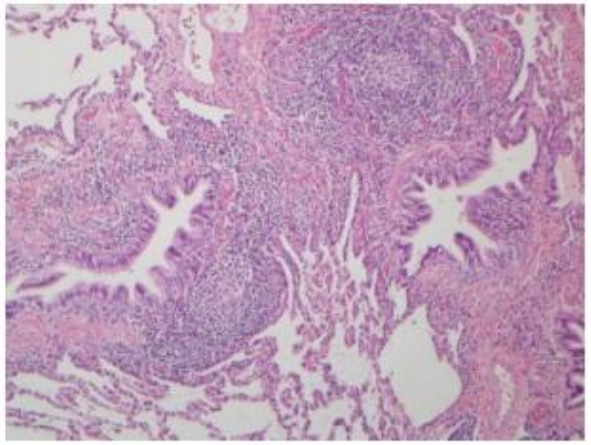
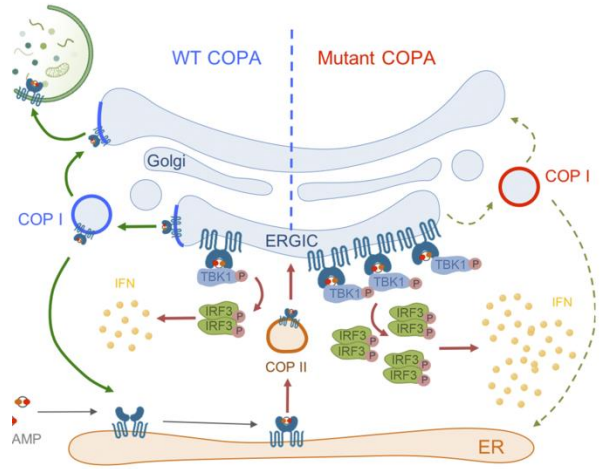
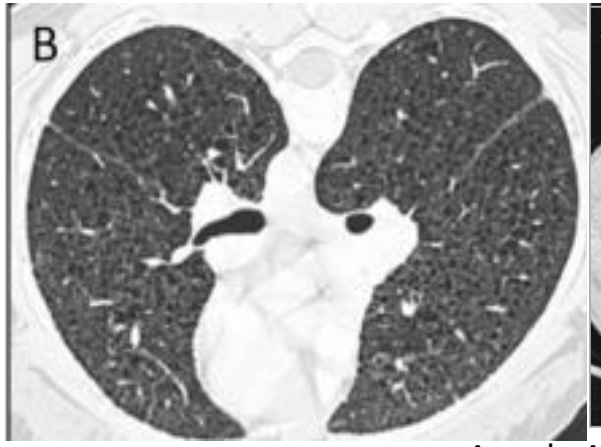
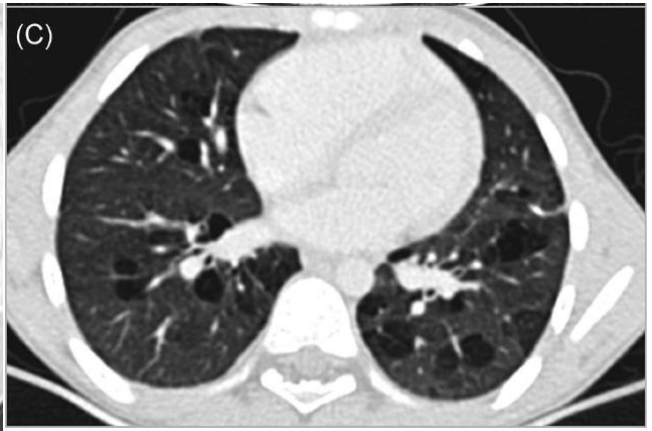


Fig. 2 Histopathology of follicular bronchiolitis. Follicular bronchiolitis characterized by lymphoid follicular hyperplasia with germinal centers and adjacent lymphocytic infiltrates (hematoxylin and eosin stain, ×200).







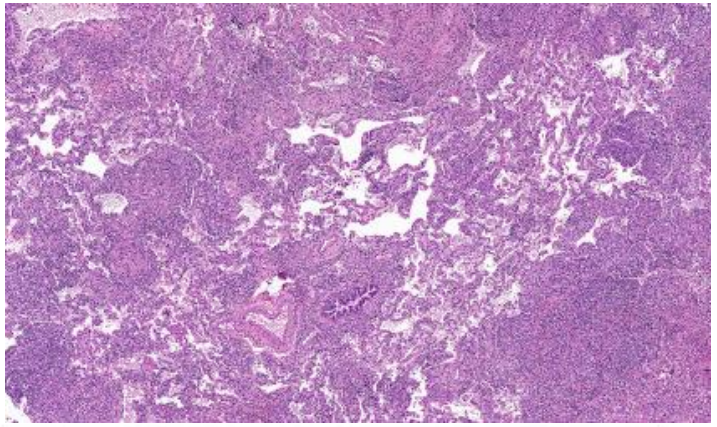
Arcadu A *et al.* Semin Respir Crit Care Med 2016
Taveira-DaSilva AM *et al*. J Med Genet 2019
Lepelley *et al.* J Exp Med 2020
Prenzel *et al.* Pediatr Pulmonol 2020

Lymphocytic Interstitial Pneumonia (LIP): lymphoproliferative disorders

- Path similar to FB with dense interstitial lymphocytic infiltrates, plasma cell and histiocytes. T-cells prominent in the interstitium

- Associated with Sjögren, RA, HIV, EBV, CVID

- Increased risk of lymphoma in these patients



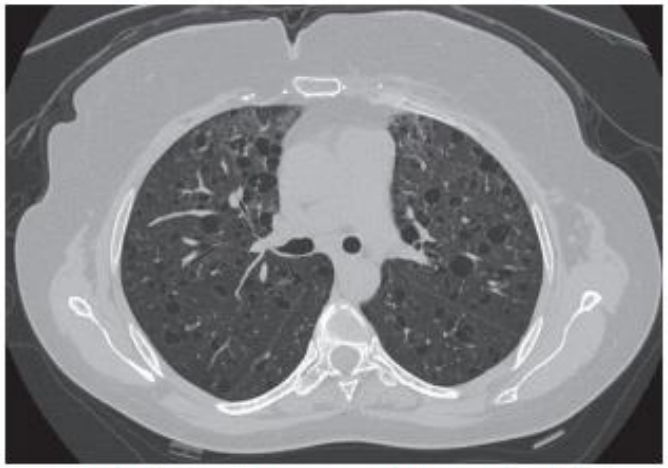


Fig. 7. Lymphoid interstitial pneumonia (LIP) in a patient with Sjögren syndrome. Cysts in LIP usually have diffuse random distribution,

Panchabhai TS *et al.* Clin Chest Med 2016
Obaidat *et al.* Respir Care 2020

Amyloid-associated cystic lung disease: lymphoproliferative disorders

- Typically results from clonal proliferation of plasma cells with deposition of immunoglobulin light chains (lambda or kappa) forming type AL amyloid
- Cysts are numerous and sub-pleural
- Associated with nodular lesions, often calcified

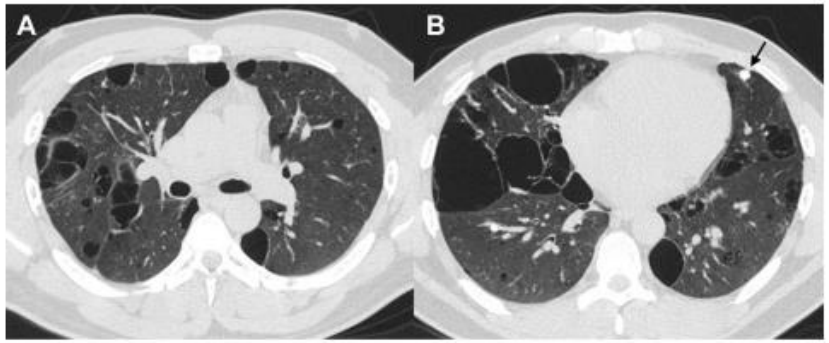
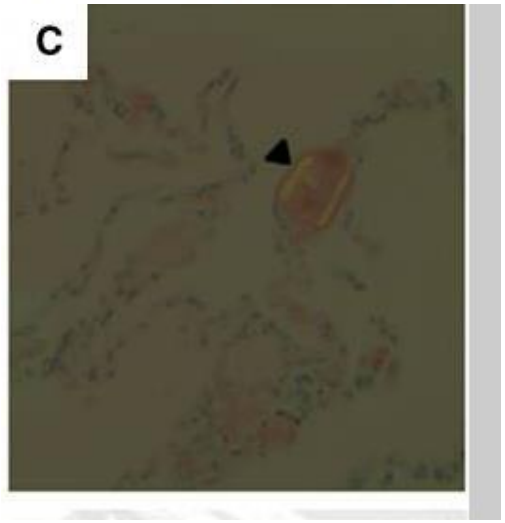


Figure 1 – *Axial high-resolution CT images (A, B) obtained in a 26-year-old man with localized pulmonary parenchymal amyloidosis demonstrating multiple bilateral peripheral-predominant thin-walled rounded cysts of varying sizes. Many of the cysts are subpleural in distribution. A calcified nodule (arrow) is present in the lingula.*



Zamora *et al.* Chest 2016

Gupta N *et al.* Am J Respir Crit Care Med 2015

Light-chain deposition disease: lymphoproliferative disorders

- Systemic accumulation of immunoglobulin light chains
- Non-fibrillary; does not form β-pleated sheets; does not bind congo red
- Path shows dense lymphoid infiltrates with amorphous eosinophilic material
- CT with irregular cysts and nodules that do not favor any area

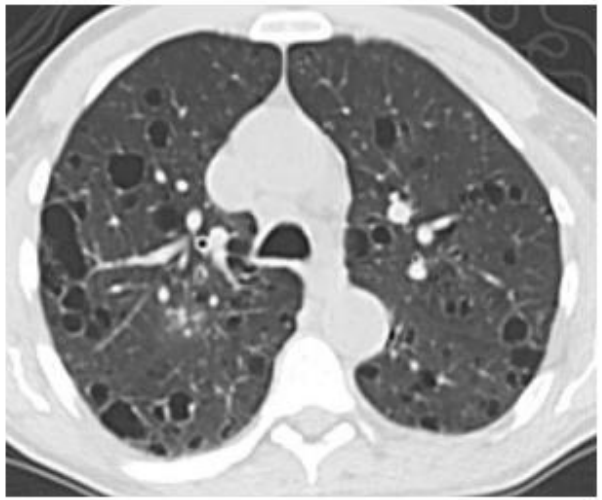
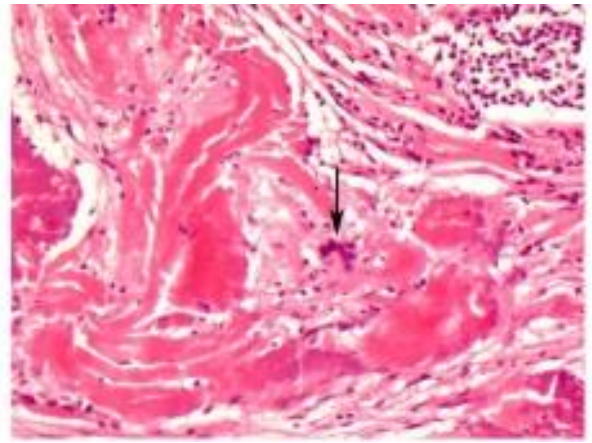


Fig. 6 CT scan of a 57-year-old man, ex-smoker, with light chain deposition disease. Cystic lesions are present bilaterally with some coalescing into irregular shapes (peripheral right lung). There are also scattered small nodules in both lungs as well as clustered nodules in the right lung posteromedially. This patient presented with progressive renal insufficiency related to light chain deposition disease involving the kidneys.



Ryu *et al.* Front. Med. 2013
Sheard S. *et al.* Clinical Radiology 2015

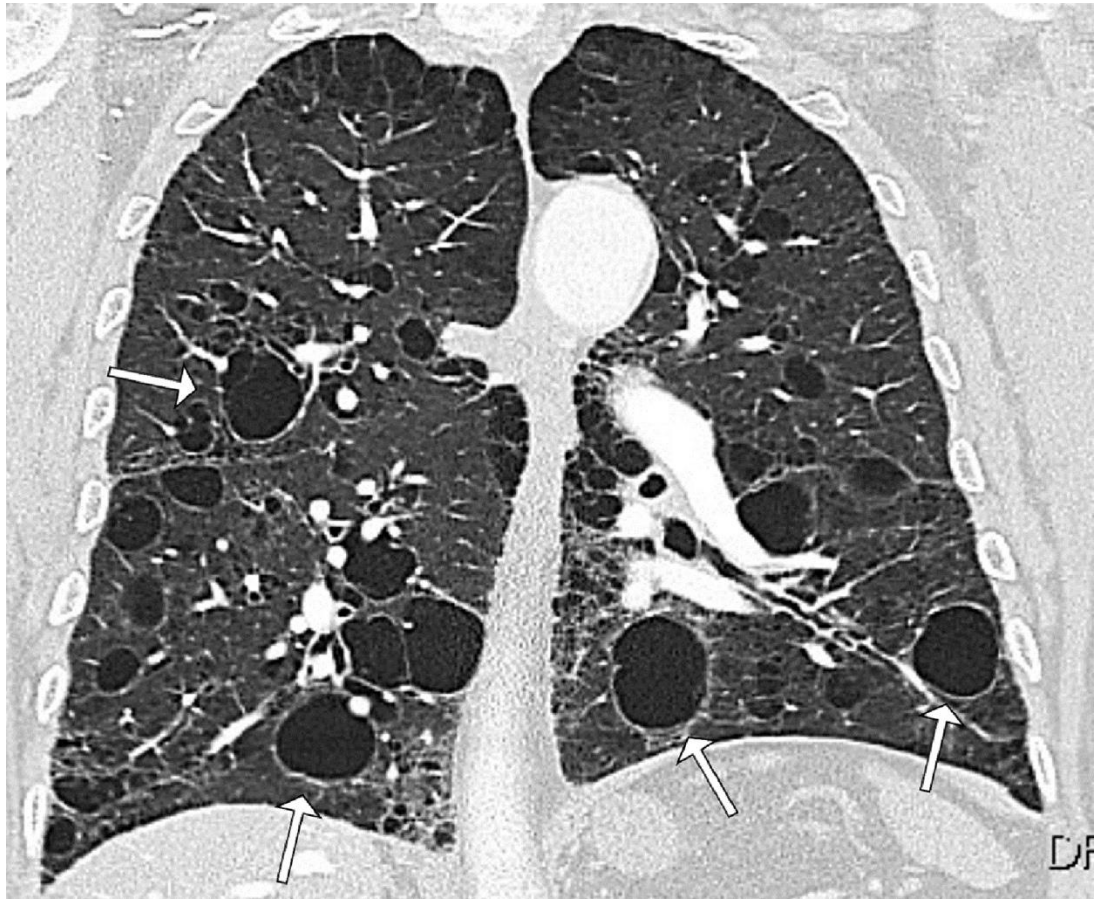
Gupta DCLD Classification

Other/Miscellaneous

Hydrocarbon Pneumonitis/Fire-eater's Disease

- Inhalation or aspiration of hydrocarbon containing vapors or solutions can lead to pneumonitis.

- Cyst formation is hypothesized to be due to solubilization of alveolar surfactants and resulting necrotizing pneumonitis.



Green D.B. *et al.* Current Problems in Diagnostic Radiology 2022
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Recap

- **Neoplastic DCLDs:**

I. Lymphangioleiomyomatosis
II. Langerhans cell histiocytosis

- **Genetic DCLDs:**

I. Birt-Hogg-Dubé
II. Neurofibromatosis type 1 associated
III. Marfan
IV. Vascular Ehlers-Danlos
V. Down Syndrome

- **Lymphoproliferative disorder associated DCLDs:**

I. Follicular bronchiolitis (COPA)
II. Lymphocytic interstitial pneumonia
III. Amyloid-associated
IV. Light chain deposition disease

- **Miscellaneous/Other**

I. Hydrocarbon Pneumonitis/Fire-eater's Lung

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