Cystic Lung Diseases

- Increased Awareness
- Spontaneous Pneumothorax
- High resolution imaging (HRCT)
- Multidisciplinary approach like interstitial lung disease

CT definition of a lung cyst
- Air filled structure with a distinct wall
  - Emphysema has no wall
- ≤2mm (up to 3mm in thickness)

Differential Diagnosis of Cystic Lung Diseases

- Non-infectious:
  - Neoplastic
    - Pulmonary Langerhans’ cell histiocytosis (PLCH)
    - Lymphangioleiomyomatosis (LAM)
    - Sporadic or associated with Tuberous Sclerosis (TSC)
    - Metastases
    - Birt-Hogg-Dubé Syndrome (BHD)
    - Lymphoid interstitial pneumonia (LIP)
    - Cystic adenomatoid malformation (CAM)
    - Light chain deposition disease
    - Idiopathic pulmonary fibrosis (IPF)
      - Honeycombing ++
  - Infectious:
    - Pneumocystis carinii pneumonia (PCP)
    - Tuberculosis
    - Staphylococcus
  - Mimics:
    - Cystic bronchiectasis
    - Centrilobular emphysema
    - Panlobular emphysema

Important clinical clues
- Sex, Age
- Smoking Hx
- Size of cyst wall
- Distribution on CT thorax

<table>
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<tr>
<th>Disease</th>
<th>Findings</th>
<th>Distribution</th>
<th>Associated Findings</th>
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<tr>
<td>IPF</td>
<td>Honeycomib cysts</td>
<td>Subpleural, basilar predominance</td>
<td>Irregular lines of attenuation, ground-glass</td>
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<tr>
<td>PLCH</td>
<td>Thin-walled cysts</td>
<td>Random, spares bases</td>
<td>Nodules</td>
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<tr>
<td>LAM</td>
<td>Thin-walled cysts</td>
<td>Random, diffuse</td>
<td>Cystic effusion, Angiomyolipoma of kidneys and liver in TSC</td>
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<tr>
<td>LIP</td>
<td>Thin-walled cysts</td>
<td>Basilar predominance</td>
<td>Renal masses, skin lesions</td>
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<td>BHD</td>
<td>Thin-walled cysts</td>
<td>Basilar predominance</td>
<td>Ground-glass attenuation</td>
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<tr>
<td>Unidentified</td>
<td>Cystic structures</td>
<td>Contiguous with bronchial tree</td>
<td>Sigmoid sign each cystic space has an adjacent vessel</td>
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<tr>
<td>Centrilobular Emphysema</td>
<td>Cystic airspaces</td>
<td>Upper lobe predominant</td>
<td>Vessels present within cystic airspace</td>
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<tr>
<td>Panlobular Emphysema</td>
<td>Cystic airspaces without discernible wall</td>
<td>Upper lobe predominant</td>
<td>Vessels present within cystic airspace</td>
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St. Vincent's University Hospital
Lymphangioleiomyomatosis - LAM

- Uncommon diffuse cystic lung disease
- Sporadic (essentially women) or in association with tuberous sclerosis complex (TSC - 30% in women, 15% in men)
- TSC-LAM: mutations of TSC1 (hamartin) or TSC2 (tuberin)
- Sporadic LAM: mutation of TSC2
- Increased VEGF-C and VEGF-D levels in blood and by IHC
- mTOR inhibitors for treatment

37 y o lady non smoker: incidental finding in lung bases on CT abdomen

Transbronchial biopsy right lower lobe

Reported yield of TB BX in LAM: >60%

Other findings in LAM

- β-catenin and demonstrated high specificity with overall immunoreactivity superior to HMB45, ER-α, and PR (Flavin RJ et al, Am J Clin Pathol. 2011;135(6):776-82)
- PR>ER (Gao L et al Virchows Arch. 2014;464(4):495-503)
- mTOR pathway upregulated by hamartin/tuberin- rapamycin as treatment
- Recur after Tx (LAM cells circulate and metastasize)
- Candidate organ of origin for LAM cells: uterus, kidney, GU, lymphatic system
Pulmonary Langerhans Cell Histiocytosis- PLCH

- Diffuse cystic lung disease in young smokers
- Peribronchial accumulation of Langerhans cells and other immune cells (cigarette smoke induced cytokines- osteopontin)
- BRAF (V600E) and MAP2K1 mutations in PLCH (50%) and systemic LCH
- Bronchiocentric distribution of CD1a+ Langerhans Cells
- Pericatricial cyst/airspace enlargement

IHC of PLCH

- >30 CD1a+/Langerin+ cells per HPF in the appropriate histologic context are diagnostic of pulmonary or extrapulmonary LCH.
- Langerin (CD207) and CD1a have equivalent sensitivity and specificity for pulmonary and extrapulmonary LCH
  - improved specificity for LCH over S100
  - S100 : increased expression in non-LCH pathologies (sarcoidosis and infectious processes)
  - S100 expressed in nerves, myoepithelial cells, and interdigitating dendritic cells within pulmonary lymphoid aggregates.

PLCH

- Identification of either BRAF (V600E) or MAP2K1 mutations in most cases of LCH provides additional evidence of the neoplastic nature of the disease
- Important implications for potential risk stratification and treatment.
- Inhibitors of BRAF and MEK may prove to be effective options in treatment of LCH.
- MAP2K1 have been associated with resistance to BRAF inhibition.
- Inhibitors of MEK, combined with BRAF inhibitors, may prove to be an effective treatment option in LCH

68 y.o. lady presented with pneumothorax.
Cystic Metastatic Sarcoma

- Endometrial sarcoma
- Angiosarcoma
- Epithelioid sarcoma
- Leiomyosarcoma
- Osteosarcoma
- Cystic renal cell carcinoma
- Benign leiomyoma/meningioma
- Cellular fibrohistiocytoma

Birt Hogg Dubé Syndrome -BHD

- A rare syndrome
  - 1/200,000
- Autosomal dominant
- Fibrofolliculomas, renal tumours, pulmonary cysts & pneumothorax
- Germline mutations of gene coding for folliculin (FLCN)
  - chromosome 17p11.2
  - non sense / frameshift mutations=> FLCN truncated
  - mTOR signaling pathway
Histological clues suggestive of BHD

- Can be subtle and overlooked
- Cystic spaces away from pleura
  - can be both subpleural and peribronchial deep within parenchyma
  - lined by pneumocytes, not hyperplastic
- Punch out aspect
  - no inflammatory changes
- No / minimal bronchiolar disease
  - unless concomitant smoking!
- Respiratory bronchiolitis, mucus retention
- Lack of subpleural fibroelastotic scar
  - as commonly seen in smokers

Importance of Multidisciplinary Meeting

- Rare diseases / genetic syndromes
- Expertise required
- Multiple organ involvement (skin+++)
  - age of presentation varies / prognosis: renal malignancy
- Previous history of pneumothorax
  - especially if non smoker
- CT appearances differ from emphysema in most cases
  - multiple, irregular-shaped cysts of various sizes, round or oval
  - lower/ medial lung zone predominance
  - abutting or including the proximal portions of lower pulmonary arteries or veins
- Smoking history
- PFTs (decreased DLCO?)

BHD in women/non smokers

- Pathologists should remain vigilant when assessing ruptured pulmonary bulla/bleb and bear in mind the possibility of BHD especially in a non-smoking woman.
  - Spontaneous pneumothorax in the general hospital more commonly affects men (reported annual incidence of 16–28 per 100 000 in males and 1.2–6.0 per 100 000 in females)
  - Overall, women smoke less
  - the differential diagnosis is wider for the causes of pneumothorax in women (LAM, endometriosis)
30yo male smoker. Presented with pneumothorax. Very fit. No family history. Alpha-1 AT negative.

Lung involvement in MCTD
- B cell non-Hodgkin’s lymphoma, extranodal marginal zone lymphoma, MALT-type
- Follicular bronchiolitis (hyperplasia of BALT)
- Lymphoid interstitial pneumonia (LIP)
Congenital Cystic Adenomatoid Malformation (CCAM), type 4. No blastematous features.

CCAM of the lung

A spectrum of abnormalities ranging from those thought to be related to disordered airway development (types 0, 1, and 2),

A Rarer type-4 lesion appears to be more of an abnormality in the development of alveolar parenchyma.

A Usually present before the age of 2 years

1. Can present in adulthood

Congenital cystic adenomatoid malformation classification based on presumed site of development of the malformation:

0 = tracheobronchial,
1 = bronchial/bronchiolar,
2 = bronchiolar/interstitial,
3 = bronchiolar/alveolar,
4 = distal acinar.

**CCAM in adults**

- Type-4 CCAMs are rare overall, accounting for ≤15% of all CCAMs
- Opinion is divided over the extent to which type-4 CCAMs overlap with purely cystic type-1 pleuropulmonary blastomas
- In the present case, no significant cellularity or cytological atypia despite widespread sampling - preferred diagnosis of type-4 CCAM.

**Cystic Lung Diseases**

- Increased Awareness
- Spontaneous Pneumothorax
  - Blebs/bullectomies
  - Women/lower lobe/cellularly
- High resolution imaging (HRCT)
- Multidisciplinary approach like interstitial lung disease
  - Smoking, molecular/genetics, etc...