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CLINICAL VIGNETTE

Fear of Flight

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Case Presentation

A 41-year old woman came to our interstitial lung disease clinic with recurrent pneumothoraces (PTX). The patient explained that in 2018 she had two episodes of spontaneous PTX one month apart. After the second PTX she underwent right surgical wedge biopsy and talc pleurodesis. She had a persistent dry cough, but no other symptoms were noted in between episodes of PTX. She is a former 8 pack-year smoker who quit smoking more than 10 years ago. She was fearful of another PTX because her mother had a history of multiple PTX in her thirties and died from lung cancer in her sixties. She also wanted to know if it was dangerous to travel by air due to the possibility of developing a PTX while in flight.

The first available chest x-ray was from the second pneumothorax, prior to the lung surgery, showing a right sided PTX (Figure 1). Subsequent high-resolution CT imaging in 2019 revealed multiple thin walled cystic changes, primarily in the lower lung lobes with various size cysts (Figure 2). The evidence of right lower lobe lung surgery and pleurodesis was also seen on the CT scan.

Cystic Lung Diseases

Cystic lung diseases represent a heterogeneous group of rare lung abnormalities. Lung cysts are thin walled (<2mm) and they are surrounded by healthy lung parenchyma. They can be localized or diffuse. Diffuse lung diseases are generally considered to be a part of a systemic disease, while localized cysts are usually the result of pulmonary infection or trauma. As cystic lung diseases are rare, their overall prevalence is unknown. They are often discovered incidentally, but if found in younger patients under the age of 50 are not considered benign.[1] The most common presentation of cystic lung disease is a spontaneous PTX, which is also the most feared consequence of the disease.

Cyst or Not Cyst

A common difficulty is to distinguish lung cysts from other lung abnormalities with a similar presentation on imaging. Differentials include: 1. Pneumocele, a gas-filled round change in the lung parenchyma that is thin walled. It is the result of chest trauma or previous infection, such as Staphylococcus aureus pneumonia. 2. A bulla is the destruction of the alveolar structure and is mostly seen with pulmonary emphysema. The bulla has no wall and it is usually greater than 1 cm in diameter. 3. Honeycomb changes are multiple layers of small thin walled peripheral lung abnormalities in bronchiectatic areas. They are associated with usual interstitial pneumonia (UIP). 4. Lung cavities are gas-filled areas in a lung consolidation that are surrounded by a thick wall (>2mm). Cavities can be seen with bronchogenic carcinoma and lung infections.

General Evaluation for Cystic Lung Diseases

The medical history is critical in identifying the underlying cause of cystic lung changes. These include age, sex, smoking status, personal and family history of lung disease. High resolution CT scanning of the lung is the most important diagnostic test to distinguish among cystic lung diseases. With good imaging, a lung biopsy is usually unnecessary. Blood laboratory studies ordered are complete blood cell (CBC) count with differential cell count, complete metabolic panel (CMP), HIV and collagen vascular disease serology. In our practice, patients also undergo a 6-minute walk and pulmonary function test even if they are asymptomatic to establish baseline parameters. Additional imaging with contrasted CT or MRI of the abdomen and pelvis may be indicated for some forms of diffuse cystic lung disease associated with a germline mutation.

Differential Diagnosis of Diffuse Cystic Lung Diseases

The location, size, shape and number of the lung cysts provide important clues for diagnosis. As our patient presented with diffuse, rather than localized cystic lung disease, we will focus on its differential diagnosis. Birt-Hogg-Dubé (BHD) syndrome, lympangioleiomyomatosis (LAM), pulmonary Langerhans cell histocytosis (PLCH), pulmonary amyloidosis, light chain deposition disease, desquamative interstitial pneumonia (DIP), lymphocytic interstitial pneumonia (LIP), cystic metastatic disease and pneumocystis pneumonia are the most common considerations (summarized with distinguishing features in Table 1).

In this young woman with recurrent spontaneous PTX, family history of PTX, distant smoking history and no other medical

history the differential diagnosis can be further narrowed. Laboratory workup which included CBC, CMP, HIV testing and collagen vascular disease serology were non-revealing. She had a normal lung function test and normal walk test. PLHC, LAM and BHD syndrome remained reasonable possibilities. High resolution chest CT imaging was essential in ruling out PLCH, which presents with numerous bizarre shaped cysts with nodules. Both BHD syndrome and LAM disease present with diffuse cysts and without nodules. However, in LAM, cysts are distributed evenly in the lung and they are uniform in size. In BHD syndrome the cysts are mostly subpleural, can be various in size and predominantly present in the lower lobes. Skin disease is commonly seen in both LAM disease related to tuberous sclerosis complex (TSC-LAM) and in BHD syndrome. In TSC-LAM disease, hypomelanotic macules, angiofibromas, periungual fibromas, shagreen patch and confetti skin lesions can be present.[2] In BHD syndrome facial fibrofolliculomas are common.[3] Recently, VEGF-D serum levels became available for the diagnosis of LAM.[4] VEGF-D level of >800pg/ml is diagnostic for the disease, but low values cannot rule it out. Folliculin (*FLCN*) gene mutation is diagnostic for BHD syndrome and can be observed in nearly 90% of suspected cases.[5] We performed VEGF-D level and *FLCN* gene mutation analysis to help with the final diagnosis. The VEGF-D level was low in our patient and genetic testing showed a previously annotated, pathogenic splice mutation with a single nucleotid change in the *FLCN* confirming BHD syndrome.

Birt-Hogg-Dubé (BHD) Syndrome

BHD syndrome is a rare genetic abnormality of the *FLCN* gene. The exact mechanism of how *FLCN* loss causes BHD syndrome is not known however it has been shown to behave like a classic tumor suppressor gene with a second hit commonly resulting from an additional somatic mutation.[6] It is suspected that *FLCN* regulates the mammalian target of rapamycin (mTOR) pathway. Dysregulation of the mTOR pathway is known to result in cystic lung disease and tumor formation.[7] A *FLCN* germline mutation is inherited in an autosomal dominant fashion and often multiple generations are affected.

The classic clinical presentation of BHD syndrome is spontaneous, recurrent PTX. It is estimated that 30% of patients with BHD syndrome experience PTX.[3] PTX usually presents in the patient's thirties and forties due to the rupture of lung cysts on the pleural surface. In an analysis of 223 patients with the syndrome, Zbar et al. found that after adjusting for age and gender the risk of PTX was 50.3 times higher in BHD syndrome than in healthy individuals.[8] However, lung function remains normal in the majority of the cases. Another classic finding is benign skin tumors called fibrofolliculomas or trichodiscomas, which mostly are located on the face. Renal cell carcinoma is observed in up to 30% of individuals with BHD syndrome and if left untreated can metastasize. In a review of 198 patients by Toro and colleagues at the National Cancer Institute, they found that 93% of patients had fibrofulliculomas, 89% had lung cysts and 23% had kidney tumors.[3]

An expert panel has developed the following diagnostic criteria for BHD syndrome shown below.[9] Patients must fulfill one major or two minor criteria for diagnosis.

Major criteria:

- At least five fibrofolliculomas/trichodiscomas, at least one histologically confirmed, of adult onset.
- Germline *FLCN* pathogenic variant.

Minor criteria:

- Multiple lung cysts: bilateral, basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax.
- Renal cancer: early-onset (age <50 y) or multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology.
- A first-degree relative with BHD syndrome.

Family History

Further investigation into the family history of the patient revealed a strong family heritage of lung disease. The patient's mother had recurrent PTX in her thirties suggesting chronic lung disease. The patient's father had pulmonary fibrosis with UIP pattern (Figure 3). UIP is a lower lobe predominant pulmonary fibrosis affecting primarily the subpleural regions. The fibrosis causes traction of the lung tissue leading to bronchiectasis and honeycomb-like change. Honeycombing can be mistaken for lung cysts, but localized only to the fibrotic areas. It is currently unknown if UIP and BHD syndrome are genetically related.

The patient was interested in pursuing *FLCN* genetic testing her 18 year-old son. The genetic testing showed the familial splice mutation. CT imaging of his chest revealed a large right subpleural lung cyst (Figure 4). There is no evidence of fibrofulliculomas or renal tumors in any member of the family.

Follow Up

The prognosis of BHD syndrome is generally good. In families without renal cancer the death rate is low. Cross-sectional abdominal imaging for renal cancer is recommended lifelong beginning in early adulthood. Experts recommend active surveillance for a small renal cancer with periodic imaging until a tumor reaches 3 cm in size at which time treatment is initiated.[10] The interval of optimal pulmonary follow up is not known, but it is usually symptom driven. Pulmonologists usually monitor patients with pulmonary function testing yearly and with chest imaging as needed.

There is no randomized clinical trial that studied the relationship between flying and development of a PTX in cystic lung diseases. In theory, pressure change can instigate the rupture of cysts. Expert opinion advises against extreme sports like scuba diving or parachuting.[11] However passenger air flight with cabin pressure optimized to 8000 feet height is not contraindicated in patients without an active PTX.

Genetic testing is recommended for first degree relatives of patients with BHD syndrome starting at age 18 to allowed proper informed consent.[9] If a genetic abnormality is found, lung, abdominal and pelvis imaging is recommended. At UCLA, BHD syndrome patients are also enrolled in a registry and followed prospectively. Our patients have no current evidence of symptoms. They are followed by pulmonary medicine and urology at UCLA. Individuals with bothersome skin manifestations are also sent to dermatology for management.

Conclusion

BHD syndrome is a rare genetic disorder, which usually presents with lung cysts and spontaneous PTX. Detailed history and imaging can provide important clues to the identification of the disease. The management of the disease depends on the presence of skin, lung and renal manifestation, but usually requires a multidisciplinary approach from pulmonary medicine and urology. Passenger air flight is not contraindicated without ongoing PTX.

Table 1. Diffuse Cystic Lung Diseases

	Lung Change	Risk of PTX	Extrapulmonary Manifestations	Association
Birt-Hogg-Dubé syndrome	numerous, lower lobe predominant, subpleural, various size cysts	high	renal tumors, skin fibrofolliculomas	*FLCN* gene mutation
lymphangioleimyomatosis	numerous, diffuse, parenchymal uniform cysts	high	kidney angiomyolipomas, skin angifibromas and shagreen patch (with TSC)	*TSC1,2* gene mutation, present almost exclusively in women and in tuberous sclerosis
pulmonary Langerhans cell histiocytosis	numerous, diffuse, bizarre shaped, various size cysts and nodules with apicobasal gradient	high	brain, bone, gastrointestinal tract, spleen	tobacco smoking
pulmonary amyloidosis	few, diffuse subpleural small cysts	low	trachea, small airways, lymphnodes	Sjögren disease
light chain deposition disease	numerous, diffuse, small parenchymal cysts with nodules	low	kidney, heart, liver	hematological malignancies
desquamative interstitial pneumonia	few, diffuse parenchymal cysts with GGO	low	N/A	smoking
lymphocytic interstitial pneumonia	few, diffuse peribronchovascular and subpleural various size cysts with GGO	low	connective tissue disease	connective tissue disease (primarily Sjögren), lymphoma
cystic metastatic disease	few, basal predominant, small cysts with fluid niveau	high	sarcoma	metastatic squamous cell ca and sarcoma
pneumocystis pneumonia	numerous, diffuse, intraparenchymal cysts with GGO	high	N/A	HIV infection

PTX-pneumothorax, FLCN- folliculin, TSC-tuberous sclerosis complex, GGO-ground glass opacity, HIV-human immunodeficiency virus

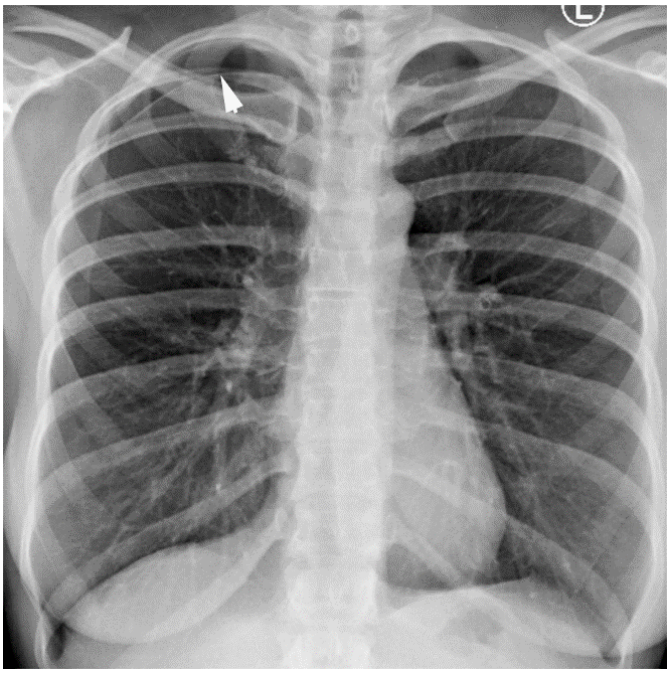

Figure 1. Our patient with right sided apical pneumothorax 2 years prior to her visit at our clinic. Arrow points at ruptured pleural line.

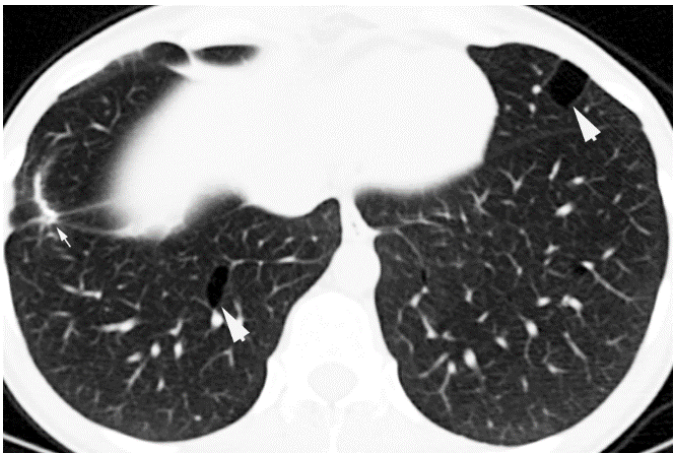

Figure 2. Lung CT scan performed following pulmonary consultation with us showing bilateral cystic changes. Cysts are various size, primarily localized in the lower lobe in the subpleural region. Large arrows are pointing cysts. The small arrow is pointing at lung resection surgery scar from 2 years before.

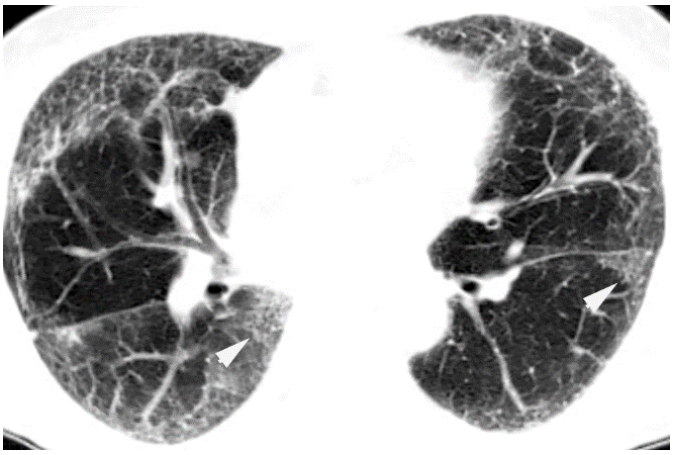

Figure 3. CT image of the patient's father demonstrating peripheral lower lobe predominant pulmonary fibrosis. The fibrosis is usual interstitial pneumonia with traction bronchiectasis and honeycombing. Arrows are pointing at honeycombing, which can mimic cystic changes.

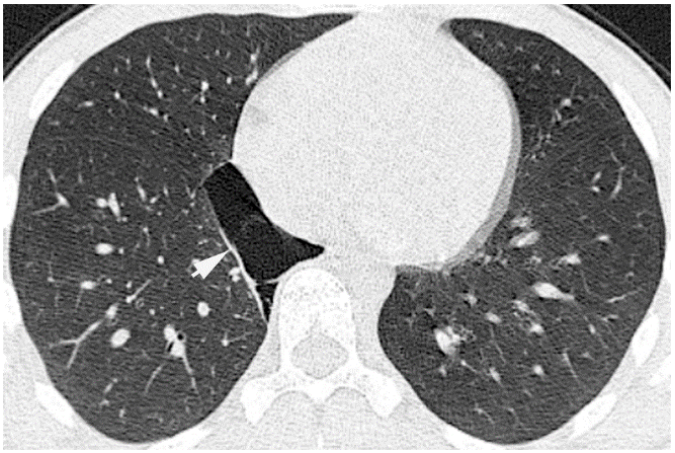

Figure 4. Ct image of the patient's son. Imaging revealed a large lung cyst. The arrow is pointing at subpleurally localized cyst close to the mediastinum.

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