FLCN-NEGATIVE BIRT-HOGG-DUBÉ SYNDROME

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Introduction

- Birt-Hogg-Dubé syndrome is a rare, complex genetic disorder inherited in an autosomal dominant fashion, involving benign skin tumors, lung cysts, and various renal tumors.
- The unusual clinical finding in our case is that the patient tested negative for known mutations in the hallmark FLCN (folliculin) gene, while having the characteristic clinical findings and pathology report suggestive of the disease – this indicates there may be other variant mutations in this gene

Patient Presentation

History of Present Illness:
- 50-year-old Haitian female with past medical history of benign bone tumor s/p left fibular osteotomy and residual left foot drop and uterine fibroids presents to the orthopedic clinic for mid to low back pain and left leg pain due to prior surgery
- She was incidentally found to have a cystic lung lesion on thoracic x-ray (Figure A)
- Besides her MSK and neuropathic pain in her left foot, she denied any symptoms of shortness of breath, hemoptysis, cough, fevers, chills, unintentional weight loss, night sweats, chest pain, recent respiratory infections, or prior history of tuberculosis. The rest of the review of symptoms was negative

Family History:
- Multiple brothers with "lung problems/asthma" with 1 deceased due disease at age of 69 years old
- Father deceased due to same "lung problems"

Social History:
- No history of tobacco use, alcohol use, or drug use
- No known history of toxic or chemical exposure

Medications:
- Gabapentin

Laboratory Data:
- CBC: normal
- CMP: normal
- PT/INR, PTT, and D-Dimer: normal
- ESR elevated at 50 (upper limit of normal 20)
- Autoimmune workup – Lupus panel: negative

Imaging:
- Lumbar Dorsal Spine X-Ray: thin walled smooth rounded likely cavitary lesion in left hemithorax
- CT chest w/ Contrast: Large left upper lobe air filled cyst measuring 7.4 x 6.3 x 7.5cm demonstrate moderately thin smooth wall without evidence of solid or liquid content
- CT chest w/o Contrast: Unremarkable non-contrast CT chest
- Renal U/S: Unremarkable renal sonogram

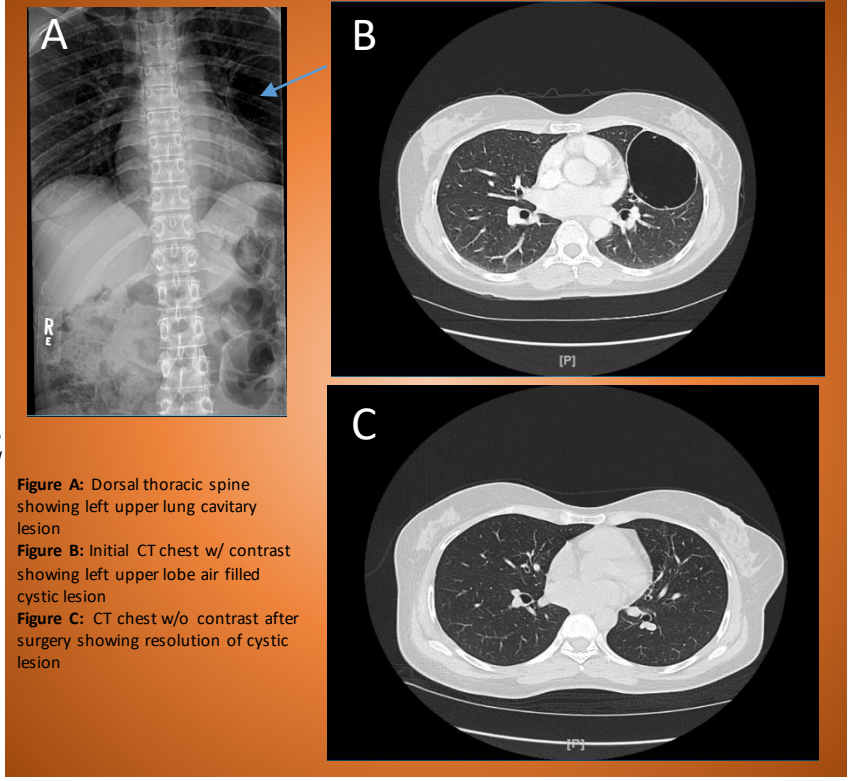

Figure A: Dorsal thoracic spine showing left upper lung cavitary lesion
Figure B: Initial CT chest w/ contrast showing left upper lobe air filled cystic lesion
Figure C: CT chest w/o contrast after surgery showing resolution of cystic lesion

Clinical Course

- Patient had CT chest without contrast which showed large left upper lobe air-filled cyst as well as two additional smaller cysts in the left lung suggestive for Birt-Hogg-Dubé syndrome (Figure B)
- She was promptly referred to cardiothoracic surgeon due to risk of pneumothorax
- She underwent VATs with pneumolysis, lingualectomy, and hilar lymphadenectomy
- Special pathology was sought from Johns Hopkins and was found to be consistent with Birt-Hogg-Dubè
- Genetic evaluation of folliculin (FLCN) gene was negative
- Repeat CT w/o contrast showed well healing lung tissue and resolution of lung cyst (Figure C).
- Due to known risk with renal tumors and cysts, renal US was performed, which was unremarkable

Discussion

- BHD is inherited in an autosomal dominant pattern and the incidence of BHD worldwide is unknown; however, approximately 200 families have been identified worldwide
- The typical presentation are either cutaneous lesions, pulmonary manifestations (cysts/pneumothorax) and/ or cancer/cysts of the kidney.
- The differential diagnosis of this is broad with fibrous papules of the nose, sebaceous hyperplasia, tuberous sclerosis complex being the most notable dermatologic differentials. While Emphysema and Pulmonary Langerhans cell Histiocytosis being common pulmonary differentials. In terms of renal, VHL, Hereditary leiomyomatosis with renal cell cancer, and sporadic tumors are noted.
- In cutaneous lesions, fibrofolliculomas are the earliest and most frequent manifestation of BHD syndrome and are typically 1 to 4 mm in size and the midface is usually most common location. Treatment of this is usually shave biopsy and electrodesiccation if needed.
- Pulmonary manifestations include bilateral pulmonary cysts (70 to 80 percent of BHD patient) and about 30 percent of patients with pulmonary cysts develop into spontaneous pneumothorax.
- Patients with this should be educated on smoking cessation, and high air pressure situations such as air travel and scuba diving avoidance.
- The most serious complications is renal cancer occurring in ~12-34% of patients with BHD with the average age at time of diagnosis around 50 years old. The prognosis and outlook of patients with BHD depends entirely on the penetrance of renal cancer
- Routine surveillance for renal cell carcinoma is advised, which significantly reduces its mortality rate
- The absence of folliculin mutation in our case suggests the possibility of a variant mutation not detected in current testing, or a de-novo gene mutation involved in the pathology.
- Folliculin is thought to be a tumor suppressor, and its role in the development of the disease continues to be an area of study.
- Management currently involves early pleurodesis to prevent pneumothorax, and periodic monitoring for renal cancers. This case shows the importance of early detection via pathological diagnosis.
- Osteopathically, this case is an example of the third tenet, i.e., structure and function are reciprocally related.
- The patient's lung cysts changed the structure of the lung and surrounding thoracic cage, which in turn compromised the function of the neighboring ribs and spine, contributing to thoracic back pain.
- Changes in the lung structure also manifested themselves as viscerosomatic reflexes along the T2 through T7 levels, contributing to their altered structure.

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