A case report of recurrent pneumothoraces as a presentation of Birt Hogg Dube syndrome

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ABSTRACT
Birt Hogg Dube (BHD) syndrome, also called as Hornstein Knickenburg syndrome is a rare syndrome caused by germline mutation in the folliculin (FLCN) gene and transmitted via autosomal dominant pattern. Different phenotypes with different manifestations have been reported including, skin manifestations as fibrofolliculoma, lung manifestations as pulmonary cysts and spontaneous pneumothorax, renal manifestations as renal neoplasia and rarely colon polyps and colon cancer. We presented a case of 35-year-old female with Birt-Hogg-Dube Syndrome.

1. Introduction
Birt Hogg Dube (BHD) syndrome, also called as Hornstein Knickenburg syndrome is a rare syndrome caused by germline mutation in the folliculin (FLCN) gene and transmitted via autosomal dominant pattern [1]. Different phenotypes with different manifestations have been reported including, skin manifestations as fibrofolliculoma, lung manifestations as pulmonary cysts and spontaneous pneumothorax, renal manifestations as renal neoplasia and rarely colon polyps and colon cancer [2,4–6].

We presented a case of 35-year-old female with Birt-Hogg-Dube Syndrome.

2. Case
35-old female was referred to the pulmonary office for recurrent bilateral pneumothoraces which were treated eventually with VATS (Video Assisted Thoracoscopic Surgery) and mechanical pleurodesis. Patient initially had symptoms 5 years prior to referral with sudden onset shortness of breath and chest pain localized to the left after a recent air travel. Patient was evaluated in the emergency department (ED); imaging evaluation diagnosed a left pneumothorax with mid-line deviation (Fig. 1). Patient underwent a left VATS with excision of apical bleb and mechanical pleurodesis. Biopsy performed at the time of the surgery revealed sub-pleural fibrosis with reactive changes.

Patient was discharged home following an uneventful post-operative course. Three months after the surgery patient developed sudden onset of shortness of breath with chest pain that was not precipitated by any trauma or activity. Evaluation in the ED revealed a right sided pneumothorax (Fig. 2). Patient was managed conservatively with supplemental oxygen resulting in the resolution of the pneumothorax.

Patient had a Pulmonary Function Test (PFT) showing mild obstructive ventilatory defect (FEV1/FVC of 68% and FEV1 of 85%). Trans-thoracic echocardiogram was performed which showed no intracardiac shunt and the left ventricular ejection fraction was more than 65%. Alpha-1 antitrypsin genetic analysis was negative for any abnormal mutation and screening test for cystic fibrosis came back negative.

6 months prior to being seen in the pulmonary office, patient presented to the ED for shortness of breath. Chest X-ray and CT (Computed Tomography) scan of the chest revealed right sided pneumothorax and multiple parenchymal cysts of the lung (Figs. 3–5). Patient underwent a right VATS and pleurodesis.

On evaluation in the pulmonary office, patient was found to have follicular skin lesion in the cheek bilaterally, also reported multiple family members being diagnosed with spontaneous pneumothorax. She did not endorse any other medical history or surgical history. After detailed discussion with the patient, a decision was made to perform a VEGF (Vascular Endothelial Growth Factor) level and Folliculin gene mutation analysis to rule out LAM (Lymphangiomyomatosis) and BHD syndrome respectively.

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Patient was found to have a normal VEGF level and mutation in the folliculin gene. This confirmed the diagnosis of BHD syndrome.

Patient underwent CT abdomen and pelvis (MRI was not approved by the insurance) to rule out any renal tumor which is associated with BHD syndrome. The CT scan failed to identify any suspicious lesion.

3. Discussion

BHD syndrome is an inherited autosomal dominant disorder caused by mutation in short arm of chromosome #17 (17 p11.2) which codes for folliculin gene. This mutated genetic locus is proposed to be responsible for developing lung cysts, renal cancers and skin lesions [1].

It was first described in 1977 by 3 Canadian scientists Birt, Hogg and Dube in the form of grayish while skin papules with histology showing fibrofolliculoma, trichodiscoma and acrochordons [7].

According to the BHD foundation, there has been total of 663 families reported so far [8]. Symptoms include cutaneous lesion with fibrofolliculomas seen in almost 90%, pulmonary manifestation in the form of multiple pulmonary cysts in about 70–80% and approximately 30% of which developed single or multiple episodes of spontaneous...
pneumothorax, 12–34% of patient developed renal neoplasm and rarely colon polyposis and colorectal carcinoma [4–6].

According to guidelines published by European BHDS consortium diagnosis of BHDS requires 1 major or 2 minor criteria [3].

3.1. Major criteria

1. Five or more fibrofolliculomas or Trichodiscomas with at least one of them is histologically proven
2. Genetic study with FLCN gene mutation

3.2. Minor criteria

1. First degree relative with BHDS
2. Multiple bilateral basal pulmonary cysts with or without spontaneous with no other apparent causes
3. Renal tumor diagnosed before 50 years of age
4. Bilateral multiple renal cancer
5. Renal cancer with mixed chromophobe and oncocytotic histology

For the pulmonary manifestations like that of our patient, other differential diagnosis includes Lymphangioleiomyomatosis, Pulmonary Langerhans cell histiocytosis and Lymphoid interstitial pneumonia. It is very important to distinguish and rule out other closely related clinical conditions before we proceed with management [11,12]. Infectious etiology for diffuse cystic lung disease should be ruled out if it is associated with Constitutional symptoms like fever or chills.

Chronic cysts with minimal or no constitutional symptoms should be evaluated by the characteristics of cysts seen in the High-Resolution Computed Tomography (HRCT) scan followed by subsequent diagnostic tests. Results of the PFT depends on the histology of the lung tissue.

Management of BHD syndrome depends upon the clinical manifestation of the phenotype. Skin lesions are particularly benign and usually not treated except for cosmetic reason [9]. Treatment of pulmonary manifestation is same as that of general population. Though mTOR pathway could be targeted, asymptomatic pulmonary cysts are monitored with follow up imaging and would not warrant any further intervention. Phenotypes with renal neoplasia will need surgical intervention with nephron sparing surgery whenever possible, depending upon the location and size of the tumor with tumor greater than 3 cm in diameter needing surgical removal and less than 3 cm being monitored with imaging studies every 3 years [10–12].

After demonstration of folliculin gene mutation in a proband, all first-degree relatives should be counseled for genetic testing starting at the age of 20 years. All the carriers of mutation should be offered renal cancer screening [13].

There has been a study reported about the existence of the genotype-phenotype correlation with respect to the intragenic position of mutation, which can be pivotal in the risk stratification for the renal cancer [14]. Prognosis depends upon the occurrence of histologic type of renal cancer. Majority of death results from metastatic diseases due to clear cell carcinoma [10].

4. Conclusion

BHD syndrome can present with myriad of manifestations. Because of rarity of the condition, there is neither consensus nor any established guidelines for the surveillance. The management has become more challenging due to unpredictable correlation between the genotype and the phenotypes.

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