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Brit Hogg Dube Syndrome - A Rare Disease Entity with Review of Literature

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Abstract

Introduction: Birt-Hogg-Dubé Syndrome is very uncommon in the North America. Several families have been reported since Birt, Hogg, and Dubé described the original kindred in 1977. Birt-Hogg-Dubé Syndrome (BHDS) is inherited in an autosomal dominant pattern and may be due to inactivation of a tumor-suppressor gene, which results in the various skin lesions such as cutaneous hamartomas and risk of internal malignancies. We report a rare case of Birt-Hogg-Dubé Syndrome who presented with lung sarcoma no skin manifestation which is the usual presentation as seen in literature.

Case Report: A 25-year-old female presented with some vague chest and abdominal symptoms. CT of the chest showed a mass in the left upper lobe and a cyst in the lung. She underwent left side upper lobectomy. Pathology reported low grade sarcoma, but was otherwise nonspecific. She had small lung cysts in lower lobe consistent with a history of Birt-Hogg-Dube syndrome. At 3 years follow up, patient doing very well. Genetic testing confirmed syndrome in family.

Discussion: Mortality and morbidity associated with Birt-Hogg-Dubé syndrome is related to internal manifestations such as pneumothorax or renal cell carcinoma. The morbidity of cutaneous lesions is limited to cosmetic appearance. Surgical removal has provided definitive treatment of solitary perifollicular fibromas. Birt-Hogg-Dubé syndrome patients with a history of smoking appear to have more severe lung disease than those who do not smoke.

Conclusion: Birt-Hogg-Dubé Syndrome (BHDS) cannot be prevented, but associated findings of renal carcinoma, pulmonary cysts and pneumothorax can be monitored. Birt-Hogg-Dubé syndrome patients should be counseled regarding the increased risk of pneumothorax with activities altering ambient pressure, such as scuba diving and air travel, particularly if they have chest pain or shortness of breath. Smoking cessation in BHDS patients should be strongly encouraged.

Introduction

Birt-Hogg-Dubé syndrome is infrequent in the North America. Few families have been reported since Birt, Hogg, and Dubé described the original case in 1977 [1].The cause of this syndrome is largely unknown. Birt-Hogg-Dubé Syndrome (BHDS) is inherited in an autosomal dominant pattern [2]. Several reports suggest Birt-Hogg-Dubé Syndrome may result from the inactivation of a tumor-suppressor gene, which results in the cutaneous hamartomas associated with internal neoplasia [3]. The Birt-Hogg-Dubé Syndrome gene locus has been localized to band 17p11.2 [1]. Expression of the Birt-Hogg-Dubé Syndrome protein has been widespread in a variety of tissues, including the kidneys, lungs and skin. Multiple or bilateral renal carcinomas, particularly chromophobe renal carcinoma, renal oncocytomas, pulmonary cysts and spontaneous pneumothoraces have been reported in association with this syndrome. Other, less commonly associated features include a large nevus, parathyroid adenomas, chorioretinopathy, bullous emphysema, lipomas, angiolipomas, multiple oral mucosal papules, facial angiofibromas and desmoplastic melanoma [4].

We report a rare case of Birt-Hogg-Dubé Syndrome that presented with low grade lung parenchymal sarcoma and associated lung cysts but no cutaneous manifestation.

Case Report

A 25-year-old female who otherwise was in excellent health presented with some vague chest and abdominal symptoms in early 2010. CT scan of the chest showed a mass in the left upper lobe and a cyst in the lower lung and some kind of abnormality in the air cavity (Figure 1). USG of abdomen did not show any visceral pathology. She underwent left sided upper lobectomy and wedge resection of left lower lobe lesion. The tumor was circumscribed in nature predominantly endobronchial neoplasm. The specimen comprised of spindle to ovoid cell, moderate cellularity andatypia with occasional mitotic figures.

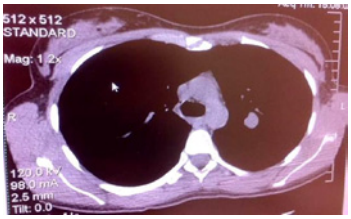

Figure 1: CT scan of chest showing left upper lobe mass. No meditational nodes seen.

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The cytoplasm was eosinophilic and wispy. Perivascular epithelial cell tumor was initially suspected among other possibilities but immunostains did not support a specific diagnosis. Stains showed that the cells were reactive with antibodies to vimentin and CD10 (cluster of differentiation) (Figure 2). It was negative for smooth muscle, actin, CD35, tyrosine, CD21, S100, CD34, epithelial membrane antigen, CD45, cytokeratin, lysozyme fascin, CD68, ER (estrogen receptors), CD117, CD45 and renal cell carcinoma antigen. These findings offered no strong support for a specific direction of any differentiation. . The case was subsequently referred to the specialized cancer clinic for second opinion. After extensive work-up it was considered to be low grade sarcoma although a more specific diagnosis could not be made. The lower lobe wedge resection showed collapsed and complex cystic spaces. Adjacent lung parenchyma was unremarkable. There was no evidence of emphysema or abnormal infiltrate. The final report confirmed tumor 1.7 × 1.7 × 1.7 cm. It was overall undetermined but consistent with low grade spindle cell sarcoma confined to the lung. Margins were negative. Hilar lymph nodes sampling was negative. With an additional pathology finding of a small lung cyst in lower lobe wedge resection, it was consistent with a history of Birt-Hogg-Dube Syndrome. In the postoperative period, the patient did quite well. The genetic testing was done which confirmed FLCN mutations (Folliculin-tumor-suppressorprotein) detected by sequencing located on the short arm of chromosome 17 (17p11.2). Patient had deletion for exons 2-13 of the FLCN gene. She was heterozygous for partial deletion of the FLCN gene that includes exons 2-1 by array based comparative genomic hybridization using Exon Array Dx. Probe sequences were based on Genome Reference Consortium build 37. Results were confirmed by quantitative PCR (polymerase chain reaction) with a probe in intron 2 of FLCN gene. This was confirmed in her sibling and mother as well. At 2 and 3 years follow-up patient is radiologically (Figure 3 and 4) free of disease locally and distantly.

Discussion

The cutaneous manifestations of BHD were originally described as abnormal growth of a hair follicle or lesions with a hair follicle at the periphery, often found on the face, and skin tags. Cutaneous manifestations are often confirmed by pathology [5]. Many patients (90%) have multiple cysts in both lungs, and 25% have one or more episodes of pneumothorax. The cysts are usually detected by chest imaging. Renal tumors can manifest as renal cell carcinoma or some subtypes [6]. Although the original syndrome was discovered on the basis of cutaneous findings, it is now recognized that individuals with BHD may only manifest the pulmonary and/or renal findings, without any skin lesions as seen in our patient.

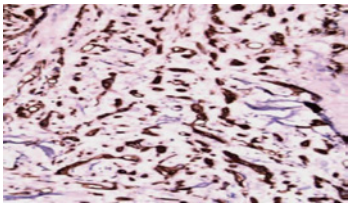

Figure 2: Strong and diffuse CD10 expression in a cytoplasmic staining pattern. (Original magnification 200).

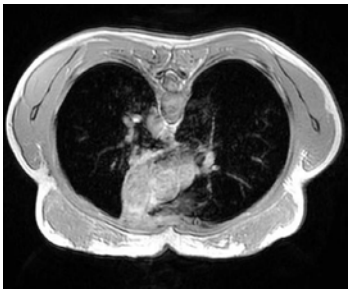

Figure 3: Follow up MRI of chest at 24 months shows no recurrence.

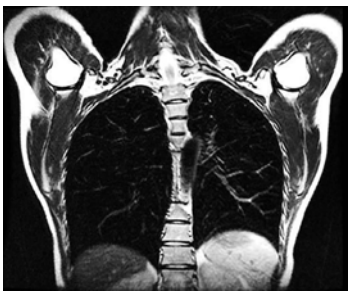

Figure 4: Sagittal section on MRI chest at 36 months shows clear lung parenchyma. No local or nodal recurrence.

Mortality and morbidity associated with Birt-Hogg-Dubé Syndrome is directly associated to internal manifestations of disease process such as pneumothorax or renal cell carcinoma [7]. Birt-Hogg-Dubé Syndrome patients with a history of smoking appear to have more severe lung disease than those who do not smoke [8]. Otherwise, the morbidity of cutaneous lesions is limited to cosmetic appearance. No racial predilection is reported in Birt-Hogg-Dubé Syndrome [9]. Perifollicular fibromas may represent a part of the spectrum of lesions in Birt-Hogg-Dubé Syndrome and are reported only in white and light-skinned persons. No sexual predilection is reported in Birt-Hogg-Dubé Syndrome. No specific medical treatment exists for Birt-Hogg-Dubé Syndrome (BHDS). Patients with the cutaneous lesions should undergo surgical resection [2]. Surgical removal has provided definitive treatment of solitary perifollicular fibromas in many case reports. Electrodessication and dermabrasion has been suggested as a treatment option. However, lesions may recur. There are few successful outcomes with carbon dioxide and YAG laser skin resurfacing [10].

Nickerson et al. confirmed mutation found in BHD on *FLCN*gene, which consists of 14 coding exons spanning approximately 20 kb of genomic DNA. Of the nine BHD families screened, eight had frame shift or termination mutations within the 14 exons of *FLCN*. Five of these families had mutations in exon 11. Screening of an additional 53 BHD families found 22 had exon 11 mutations, suggesting a mutation hotspot [5]. In 2005 Schmidt et al. screened a further 30 families and after combining the mutational data, found that 53% of the *FLCN* mutations involved either a cytosine insertion or deletion in the mononucleotide tract of eight cytosine's (C8) in exon 11 [11]. It is not yet clear that the truncated FLCN is targeted for degradation, or remains in the cell with an altered function. Two FLCN germline mutations in exon 11 (c.1733insC and c.1733delC) were identified in three of four BHD families, as well as two of four sporadic cases of BHD syndrome [12]. It seems that the majority of hereditary cancer syndrome genes follow the paradigm of a tumour suppressor gene or Knudson's two hit theory [13]. Tumors usually carry a copy of an inactivating germline

mutation and lose the other copy via Loss of Heterozygosity (LOH), methylation, or somatic mutation. LOH is most commonly found in hereditary tumors, but in BHD only 17% of hereditary renal tumour showed LOH. The somatic mutation represents the second hit of Knudson's theory, and should be screened for BHD related tumors without LOH [14].

Menko et al. proposed diagnostic criteria for BHDS (patients should meet 1 major or 2 minor criteria for diagnosis). In major criteria at least 5 fibrofolliculomas or richodiscomas, at least 1 histological confirmed and adult onset *FLCN* germline mutation. In minor criteria there are multiple lung cysts - Bilateral basally located lung cysts (with no other apparent cause), renal cancer - Early onset (<50 y) or multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology and or first-degree relative with BHDS [15].

Conclusion

Birt-Hogg-Dubé Syndrome (BHDS) cannot be prevented, but associated findings of renal carcinoma; pulmonary cysts and pneumothoraces can be closely monitored and treated in timely fashion to reduce mortality and morbidity. Birt-Hogg-Dubé Syndrome patients should be counseled and educated especially about the potential risk of pneumothorax with activities altering ambient pressure such as scuba diving and air travel, particularly if they have chest pain or shortness of breath. Smoking cessation in BHDS patients should be strongly encouraged.

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