CASE REPORT

Birt-Hogg-Dubé syndrome: spontaneous pneumothorax as a first symptom

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SUMMARY

Birt-Hogg-Dubé syndrome (BHDS) is a rare hereditary autosomal dominant condition characterised by benign cutaneous lesions, lung cysts, increased risk of spontaneous pneumothorax and renal cancer. It shows great heterogenous presentation within and between affected families. We report a case of a Danish female patient with recurrent pneumothoraces as the first symptom of BHDS. Over the years, she developed skin changes, and a family history of skin changes, pneumothoraces and renal cancer was discovered. BHDS was suspected, a genetic analysis was performed and a pathogenic variation c.1285delC in *FLCN* gene was detected in the patient. As we stated the diagnosis BHDS, we discovered several undiagnosed family members all of them now entering a lifelong follow-up programme with abdominal imaging because of the increased risk of developing renal cancer. BHDS should be known to oncologists, dermatologists and pulmonologists as the patients most often present to these medical disciplines.

BACKGROUND

Birt-Hogg-Dubé syndrome (BHDS) is a hereditary condition first described in 1977¹ and is characterised by benign cutaneous lesions, lung cysts, increased risk of spontaneous pneumothorax and renal cancer.^{2–4} The penetrance of cutaneous lesions, lung cysts, spontaneous pneumothorax and renal neoplasms varies within and between families.^{2–4–6}

Skin lesions are found in 82%–92% of individuals with BHDS and are localised on head, neck and upper part of the trunk. Fibrofolliculomas are the most common phenotypic symptom in BHDS, but other skin lesions such as trichodiscomas/

angiofibromas, acrochordons and epidermal cysts can also be part of the BHDS phenotype.^{7–9}

Lung cysts are present in up to 89% of the individuals with BHDS and are usually multiple and bilateral.⁷ The cysts are often irregularly shaped and located in the basal parts of the lungs.¹⁰ Approximately 30% of individuals with BHDS will experience one or more episodes of spontaneous pneumothorax.^{2–7} The lung parenchyma is most often not affected and despite the multiple cysts, lung function is not affected or just mild obstructive.⁹

BHDS-associated renal neoplasms are often bilateral and multifocal with large histological variability. The most frequent neoplasms are oncocytic, chromophobe or hybrid chromophobe-oncocytic tumours. Renal cancers develop in 16%–29% with a median age range at 20–75 years.^{4–6–8–11} Other tumours that have been reported in individuals with BHDS are oral papules,⁸ desmoplastic melanomas,¹² parotid gland oncocytomas^{5–7} and single cases of thyroid cancer, colon cancer, squamous cell carcinoma, Hodgkin's disease, uterine cancer, prostate cancer and breast cancer.⁷

Genetics

BHDS is characterised by heterozygous germline mutation within the *FLCN* (Folliculin) gene (OMIM 607273), which is located on a short arm of chromosome 17, position 11.2.^{13–14} The *FLCN* gene has 14 coding exons, encodes 579 amino acids and provides instructions for making protein Folliculin.¹⁵

The Folliculin protein is present in many of the human tissues including skin, lung, kidney, pancreas, breast, parotid gland, brain, prostate and ovary.¹⁶ The exact function of the Folliculin protein is still not fully elucidated. Several studies have reported that the Folliculin protein is involved in 5' adenosine monophosphate-activated protein kinase and the mammalian target of rapamycin signalling pathways, indicating that the Folliculin protein functions as a tumour suppressor.^{17–20}

Great variety of pathogenic variations has been identified in individuals with BHDS (insertions, deletions, non-sense missense, frameshift, splice-site mutations and single-nucleotide polymorphism variants). The majority of the pathogenic variants are associated with truncation of the Folliculin protein resulting in the loss of protein function.^{2–21} The most common pathogenic variants are c.1285dupC and c.1285delC, which duplicate or delete a single C nucleotide in a polycytosine

Figure 1 Picture of skin changes.

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Figure 2 Pedigree.

tract in exon 11 suggesting the hypermutable site of the FLCN gene.⁵ Until now (November 2016), 152 unique DNA variants in FLCN gene have been reported.²²

BHDS is inherited in autosomal dominant manner and the offspring of an individual with a pathogenic variant in FLCN gene have a 50% risk of inheriting the pathogenic variant and thus BHDS.

CASE PRESENTATION

An 18-year-old woman was admitted to the hospital with shortness of breath and pleuritic chest pain. Her medical history was notable for asthma treated with inhaled corticosteroids, and she was otherwise healthy and non-smoking. X-ray revealed spontaneous pneumothorax, which was successfully treated with chest tube insertion. Because of recurrent bilateral pneumothoraces, a chest CT was performed showing bilateral cysts in the lungs primarily in the basal parts. After several pneumothoraces treated with chest tubes, the patient underwent right-sided video-assisted thoracic surgery bullectomy and pleurodesis. The surgery was successful and prevented pneumothorax for 6 years. Meanwhile in her 20s, the patient developed skin-coloured papules in her face (figure 1), neck and trunk. Biopsy from the face was not performed but the lesions were not incompatible with fibrofolliculomas as evaluated by a dermatologist. Cysts in the liver were found, and in addition she had an ovarian cyst removed which turned out to be a mucinous cystadenoma. Six years after surgery, the pneumothoraces reoccurred on the left side. A thorough interview revealed that the brother of the patient had skin lesions and he also had a single episode of

spontaneous pneumothorax. The father of the patient died of renal cell adenocarcinoma at the age of 33 years. The brother of the father had several pneumothoraces and was treated successfully with pleurodesis. He is also diagnosed with kidney cysts and progressive skin changes. The grandmother had pneumothorax, skin lesions and died at 59 years of age. Shortly before she died, she had undergone surgery for a brain tumour. The histological examination of the tumour revealed a metastasis of malignant lymphoma. The brother of the grandmother as well as his daughter also had skin changes. The great grandmother of the patient had skin changes and breathing difficulties. The pedigree shows a typical autosomal disorder (figure 2).

INVESTIGATIONS

Due to the recurrent episodes of spontaneous pneumothoraces, skin lesions and the family history, BHDS was suspected. The molecular genetic analysis (next generation sequencing and multiplex ligation-dependent probe amplification analysis) was performed and a pathogenic variation c.1285delC (formerly known as c.1733delC) in FLCN gene was detected in the patient.

OUTCOME AND FOLLOW-UP

The screening recommendation of the National Institutes of Health suggests abdominal imaging every 36 month after the initial screening. MRI is preferable over CT, considering the cumulative radiation dose whereas ultrasonography often fails to identify BHDS-associated lesions.³ The renal neoplasms in individuals with BHDS appear usually earlier than in sporadic cases

of renal neoplasms. The median age of renal neoplasm diagnosis in individual with BHDS is 46 years (20–83)⁶ emphasising the importance of lifelong follow-up.

DISCUSSION

The phenotypes of BHDS-affected families are heterogeneous. Not all patients with BHDS present the classical triad of spontaneous pneumothorax/lung cysts, skin lesions and renal neoplasms. If the patients present as isolated phenotypes with either only renal involvement, pulmonary involvement or skin changes, BHDS can be difficult to diagnose.

It has been suggested that there is a genotype–phenotype correlation among families with BHDS, but it still remains to be clarified. One large study including 219 individuals from 53 families, found significantly fewer renal cancers among patients with the folliculin (FLCN) mutation located in the exon 11 having C-deletion than those with C-insertion.⁵ On the contrary, other studies did not find this association.^{4,23}

This case underlines the importance of diagnosing BHDS. The diagnosis is important in managing the patient, and in addition it has had great impact for the family, as we found several undiagnosed family members. Furthermore, three family members are under current genetic investigation. One of them is having bilateral kidney changes on abdominal imaging and is waiting for surgery. Several were asymptomatic. All of them are now entering a follow-up programme. BHDS should be known to oncologists, dermatologists and pulmonologists as the patients most often present to these medical disciplines.

Learning points

- Birt-Hogg-Dubé syndrome (BHDS) should be suspected in patients with lung cysts and recurrent pneumothoraces.
- BHDS is inherited in autosomal dominant manner and the offspring of an individual with a pathogenic variant in FLCN gene have a 50% risk of inheriting the pathogenic variant and thus BHDS.
- The phenotypes of BHDS-affected families are highly heterogeneous.
- BHDS is characterised by heterozygous germline mutation within the FLCN gene (OMIM 607273), which is located on a short arm of chromosome 17, position 11.2.
- BHDS is important to diagnose to reveal and find undiagnosed family members.

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