

Birt Hogg Dubè Syndrome: A Case Report

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Abstract

Background: Here we present a case of 56 year old female who presented with mild shortness of breath and right side pain. Chest tomography indicated bilateral bullous pulmonary lesions as the causal of the patient's discomfort and pain. The patient had familial history of cancer and pneumothorax, and had undergone surgery on the left lung due to bullous lesion and pneumothorax. The patient has been operated in our clinic due to right lung bullous lesions; resected bullous tissue has been evaluated histologically in a further center.

Objectives: Birt Hogg Dubè (BHD) syndrome is an inherited genodermatosis. Spontaneous pneumothorax and pulmonary bullous lesions, renal cyst or tumor has a triad with lesions on the skin. We aimed to evaluate the patients presenting recurrent primary spontaneous pneumothorax with family history of pneumothorax and with having atypical bullae localization for BHD syndrome.

Conclusions: Patients with BHD syndrome must be subject to routine cancer screening and watchful waiting due to the fact that lung, gastrointestinal, ovarian, breast and pancreatic cancer and especially renal cancer risk is very high when compared to the society.

Keywords: Birt Hogg Dubè syndrome; Cancer predisposition

Introduction

Birt-Hogg-Dubè syndrome (BHDS) is a rare genetic disorder. In recent years, renal and pulmonary cyst, kidney cancer and non-cancerous fibrofolliculomas have been linked with BHDS. This hereditary autosomal dominant syndrome is known to be caused by the mutation in the gene of localized folliculin in 17p11.2 chromosome [1]. The cases have been mostly reported from America, Italy and Ireland. Although the exact incidence of this disease is yet to be known, 200 families with BHDS were affected to be reported with this condition [2].

On clinical examination, patients with BHDS show benign dermatologic lesions on upper body, nucha, neck and face named fibrofolliculoma, trichodiscoma or acrochordon, and these patients are at the increased risk of developing renal cyst or tumor, pulmonary bullous lesion and recurrent spontaneous pneumothorax attacks [3]. It is matter of great concern that this syndrome has been found to increase the predispositions of certain types of cancer such as lung, gastrointestinal, ovarian, breast, pancreatic cancers, and especially the renal cancer [4]. Therefore, it is necessary to check the family history for patients with pulmonary cysts and/or spontaneous pneumothorax. If occurrences of BHD syndrome have been found in family history, a close follow up is recommended due to increased cancer risk in renal or other systems. We present here a case of 56 year old female suspected for BHD syndrome.

Case Presentation

A 56-year-old female patient with the complaints of mild shortness of breath and right side pain was evaluated by thoracic Computerized Tomography (CT). Thin-walled bullous lesion 13 cm in diameter was observed in the lower lobe of the right lung in the thoracic computerized tomography (Figure 1A and B). The patient, although without a history of chronic systemic disease, had been operated on bulla resection 20 years ago as the patient was diagnosed with bullous lesion with left spontaneous pneumothorax. Upon checking the family history, we found that the sister, brother and nephew of the patient had a history

of pneumothorax. The patient was examined genealogically for the evidence of familial cancer and pneumothorax (Figure 2).

The patient was mild dyspneic on the physical examination; the oxygen saturation was 96% in room air. Fibrofolliculoma and acrochordon lesions were observed on the face, around the nose and especially on the neck (Figure 3). The patient was evaluated with abdominal CT and USG because of hematuria detection in the preoperative urine samples performed before the surgery. In the left renal, 7 cm cyst and 2 mm calculus were reported (Figure 4). It was followed after urologic consultation.

Thyroid function tests were within normal limits, and these were being followed after thyroid biopsy due to multinodular goiter.

Left hemithorax volume was decreased due to the earlier surgery that the patient had. In pulmonary function test, FEV1 (forced expiratory volume in one second) and FVC (forced vital capacity) were found to be 88% and 92%, respectively. Respiratory sound was not heard from the lower lobe of right lung in the respiratory system auscultation. Other system examinations were evaluated as normal.

Thin-walled bullous lesion of 13*10 cm diameter was explored in the lower lobe of the right lung with right thoracotomy operation (Figure 5). Bulla was resected using a 3, 5*60 mm tissue supported endoGIA stapler. As the patient did not develop any postoperative complication,

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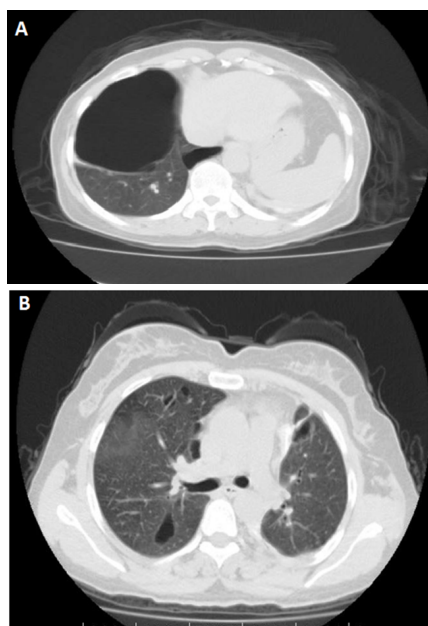


Figure 1: Bullous lesion localized in the lower lobe of the right lung and bilateral lung parenchyma.



Figure 3: Skin lesions localized in the face.



Figure 4: Left renal cyst (7 cm) in the abdominal tomography.

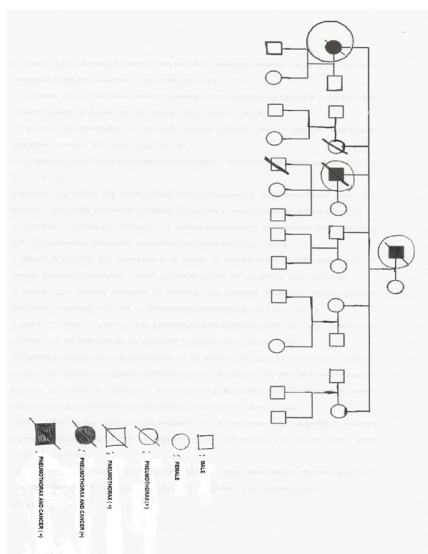


Figure 2: Family tree of the case.

she was discharged from the hospital in the first week. The skin lesions biopsy of the patient revealed the lesions as acrochordon (Figure 6). The lesion was very small (3mm in diameter) with a polypoid appearance. It was fixed in 10% formalin, sampled in a cassette and after the routine tissue processing, it was embedded in paraffin. The block was sectioned in 5 µm thickness and stained with Hematoxylin-eosin. The slides were examined with the light-microscope. Some sections of the lesion were covered with a normal epidermis surrounding a core of fibrovascular tissue with dense collagen fibers (Figure 6).

Pathological specimen of the patient with a history of familial pneumothorax was forwarded to an external pathology clinic for the advanced histochemical evaluation. Histological examination of patient's lung bullae showed typical emphysematous changes. However,

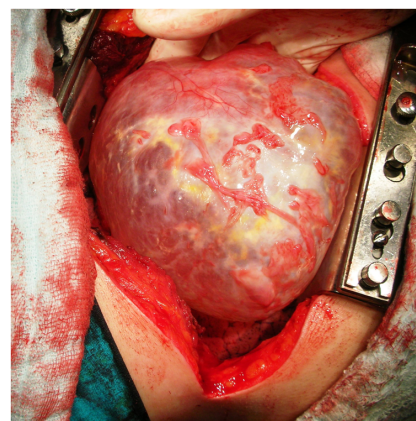


Figure 5: Intraoperative view of the bullous lesion localized in the lower lobe of the right lung.

unlike other causes of spontaneous pneumothorax, bullae located basilar (right lower lobe).

The patient was screened and followed-up closely for three years in terms of renal and other system cancers.

Discussion

BHD syndrome identified in 1977, is an autosomal dominant inherited genodermatosis. It has a clinical triad comprising of skin lesions, renal tumor/cyst, pulmonary bullous lesions or spontaneous pneumothorax attacks. The reasons for the development of cysts and pneumothorax in the lung cannot be fully explained. Folliculin gene

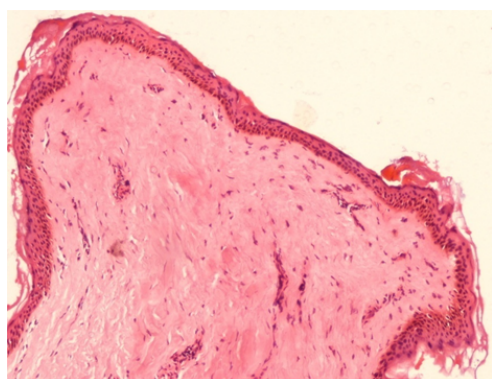


Figure 6: Histological sections from which acrochordons of the skin lesions were observed. Acrochordon (fibroepithelial polyp) consists of connective tissue covered by squamous epithelium). Hematoxylin-eosin (HE) x 200.

has a strong effect on lung fibroblasts and macrophages [5]. Pulmonary structure depends on the interaction of the collagen and elastin fibers in the extracellular matrix forming the structure of alveolus wall [5]. The proteases and cytokines, which were caused by matrix destruction as a result of the inflammatory processes and restructure, have been known to cause mutation of folliculin gene [6].

For BHD syndrome, the final diagnosis based on the detection of mutation in folliculin gene in DNA analysis. Following diagnostic criteria, both major and minor criteria were considered [7]. Major criteria include the presence of fibrofolliculoma, trichodiscoma or acrochordon, confirmed histologically on at least 5 cervical or facial areas, and the detection of mutation in folliculin gene as confirmed by the DNA analysis [8]. Minor criteria include the multiple lung cysts localized in the basals that may develop or may not develop primary spontaneous pneumothorax and of which underlying reasons cannot be detected. History of renal cancer and diagnosis of BHD syndrome in the first degree relatives are also considered as minor criteria. Diagnosis is confirmed if one of major criteria or two of minor criteria occur. Development of bullous lesions localized in the bilateral lower lobe on patient without history of smoking and the existence of familial history led to screening for multiple cystic lung diseases. Our patient did not have history of smoking.

It is difficult to diagnose BHD syndrome from symptoms alone, because hereditary renal cancers, pneumothorax, and cutaneous tumors may also occur with other syndromes for example, hereditary recurrent pneumothorax or pulmonary cysts are associated with Marfan syndrome, while Tuberous Sclerosis Complex (TSC), alpha1-antitrypsin deficiency, and cystic fibrosis are found to be associated with Ehlers-Danlos syndrome. On the other hand, non-hereditary recurrent pneumothorax and/or pulmonary cysts may occur with Langerhans cell histiocytosis and lymphangioleiomyomatosis. Definitive diagnosis of TSC is important as similar symptoms such as angiofibroma on the face, lung cysts and pneumothorax, renal cysts and tumor are associated with other syndromes, especially with BHD. Occurrence of TSC, especially in female patients, is associated with central nervous system symptoms and diffuse distribution of the lung cysts, and these show distinctive features from BHD [9].

Although fibrofolliculomas are unique to BHD, they may exist with an unclear appearance, and must be confirmed histologically. Other diseases can appear the dermatologic manifestations of BHD including TSC, Cowden syndrome, familial trichoepitheliomas, and multiple endocrine neoplasia type 1 [3].

Hereditary bilateral, multifocal kidney tumors like to those seen in BHD may also consist of with von Hippel-Lindau disease, hereditary papillary renal cancer, and hereditary leiomyomatosis and renal cell cancer syndrome. However, they can be differentiated with examination of the tumors' histology [3].

We confirmed the diagnosis of our patient as BHDS on the basis of fulfilling one major (presence of fibrofolliculoma or trichodiscoma confirmed histologically) and one minor (presence of multiple lung cysts localized in the basals) criteria.

Folliculin gene plays an active role in renal distal nephrons, lung type 1 pneumocytes and stromal cells; epithelial canal of the breast, pancreatic acinar cells, and in the serous glands of parathyroid and ovary [4]. Therefore, the mutation of folliculin gene takes a part in the development of tumors associated with these tissues. Renal cancer risk for the patients especially with BHD syndrome is nine times higher [10].

Thyroid nodules have been associated with the BHD syndrome [11]. Due to multi-nodular goiter our patient is followed after thyroid biopsy. In literature, a connection between BHD and thyroid cancer has not yet been proved. Other diseases such as multinodular goiter, medullary thyroid carcinoma, parotid oncocytoma, connective tissue nevus, lipomas, angiolipomas, parathyroid adenomas, neurothekeoma, meningiomas, angiofibromas of the face, trichoblastomas, cutaneous focal mucinosis, cutaneous leiomyoma, breast cancer, tonsillar cancer, colorectal cancer, sarcoma of the leg, lung cancer, melanoma, dermatofibrosarcoma protuberans, basal cell carcinoma, cutaneous leiomyosarcoma, and squamous cell carcinoma have been reported to be associated with the BHD syndrome [6].

In the literature, no specific treatment for BHD syndrome is mentioned. The fibrofolliculomas can be resected surgically. The renal and pulmonary symptoms are followed. CT scans, ultrasounds, or MRIs of the kidneys are suggested regularly, and family members are recommended not to smoke [11]. Due to MRI does not carry the same risk of radiation complications as CT scans and is more sensitive than ultrasounds, it is the preferred method for observation of the kidneys in patient with BHD. In patient with BHD syndrome, for kidney cancer is approached with total or partial nephrectomy [3].

Patients with recurrent primary spontaneous pneumothorax along with familial history of pneumothorax and with having atypical bullae localization must be evaluated clinically, radiologically and histologically in detail in terms of BDH syndrome, and they must be followed regularly in terms of cancer predisposition.

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