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Case Report

Pulmonary cystic disease associated with integumentary and renal manifestations

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Abstract

A 69-year-old man with multiple skin lesions on his face, neck and upper torso, which first appeared in the 3rd decade of his life, was admitted to our hospital. He had cystic changes in his lungs noted on chest computed tomography (CT) scanning, as well as a left kidney mass. This patient exhibited a rare complex of renal, cutaneous and pulmonary manifestations, eponymously named Birt-Hogg-Dube syndrome, with characteristic skin features (fibrofolliculomas, trichodiscomas and acrochordons). This syndrome is due to an autosomal dominant germ-line mutation of the *folliculin* (*FLCN*) gene located at chromosome 17p11.2. Diagnosis and differentiation from other disease complexes including the skin, kidneys and lungs are important in prognostication and management of potentially life-threatening complications such as renal cell carcinoma and pneumothoraces.

Keywords: pulmonary cystic disease, Birt-Hogg-Dube syndrome, folliculin, mutation

INTRODUCTION

Patients with cutaneous, renal and pulmonary lesions may represent specific syndromes that the following case illustrates.

CASE REPORT

A 69-year-old man with a previous diagnosis of interstitial lung disease (ILD) went to our pulmonary clinic because of abnormal chest imaging. His previous medical history consisted of diabetes mellitus, hypertension, paroxysmal atrial fibrillation, a history of a complete heart block requiring dual-chamber pacemaker insertion, prostate cancer for which he had undergone appropriate radiation therapy, and pulmonary embolism on lifelong warfarin therapy. He was also receiving mycophenolate mofetil, high-dose prednisone and rituximab, for a proteinase-3 positive systemic vasculitis previously manifesting as fever of unknown origin.

He complained of dyspnea on moderate exertion, experiencing breathlessness after walking on a flat surface for 3 blocks. He denied cough or sputum production. He presented with constitutional symptoms, including fatigue, fevers with shaking chills and night sweats. A review of system revealed that he had no chest pain or discomfort, hemoptysis, epistaxis, arthralgias or arthritides, xerophthalmia or xerostomia.

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Papulo-nodular lesions on his face, neck and upper torso that had been present for 40 years were noted.

His home medications included diltiazem, glipizide, aspirin, mycophenolate mofetil, prednisone, omeprazole, tasmsulosin, temazepam, warfarin and rituximab (dosed every 3 months). He denied smoking or a significant travel history. He had lived in Northern California most of his life. He was an office-worker, and denied occupational exposures to asbestos, chemical fumes or organic dusts. His father died of lung cancer, while his mother was still alive but had coronary artery disease and hypertension. He reported that the pulmonary abnormalities which his sister and brother also exhibited were identical to his.

Physical examination revealed that he was a well-built male, with papulo-nodular lesions scattered throughout his face, more so along the malar region, on the bridge of his nose and on his neck (***Fig. 1A***). There were a few larger nodular lesions of about 1.0 cm in size along the lateral aspect of his neck and upper torso (***Fig. 1B***). His heart was regular in rhythm without any murmurs. He had equal chest rise, bilateral resonance on percussion of his posterior thorax and clear breath sounds on auscultation. His abdominal exam was within normal limits. No renal mass was palpable. He did not have peripheral cyanosis, digital clubbing or lower extremity edema. His neurological examination was non-focal and unremarkable.

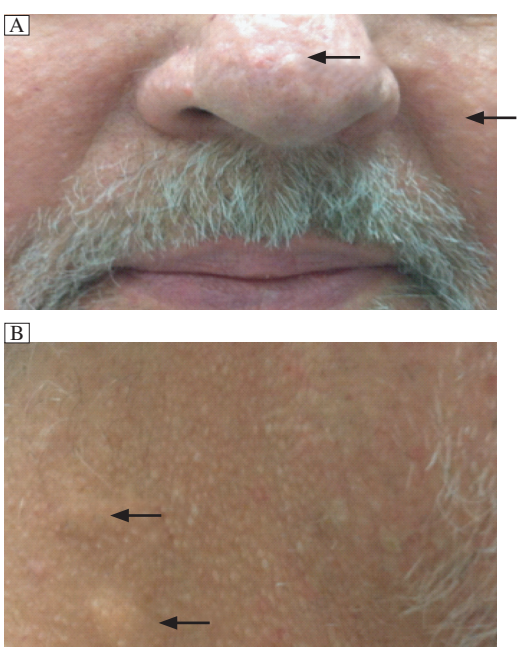

Fig. 1 **Skin lesions of a 69-year-old patient with Birt-Hog–gDube syndrome.** A: Papulo-nodular lesions (arrows) scattered over the malar region and nose. They are rounded, and opaque, sporadically appearing when the patient was in the 2rd decade of his life. B: Larger, nodular lesions (arrows) on the lateral aspect of his neck interspersed with the smaller, opaque papular skin changes.

Laboratory studies showed that his serine protei–nase-3 (PR3) titer had been elevated to 114 AU/mL (normal range 0-19 AU/mL), but was now normal on current therapy. Serology of typhoid fever, lyme disease, tuberculosis, malaria and HIV was within normal limits. His total complement activity was low at 44 (normal range 66-144) and C-reactive protein level was elevated at 2.9 mg/dL (normal range 0-0.8 mg/dL). Asymmetric, thin-walled cysts predominantly at the bases of both lungs were noted on his chest computed tomography (CT) scan (***Fig. 2A*** and ***2B***). No significant hilar or mediastinal lymphad–enopathy was noted. Limited abdominal cuts from a chest CT scan revealed that a left renal lesion was described to be complex and cystic on a subsequent

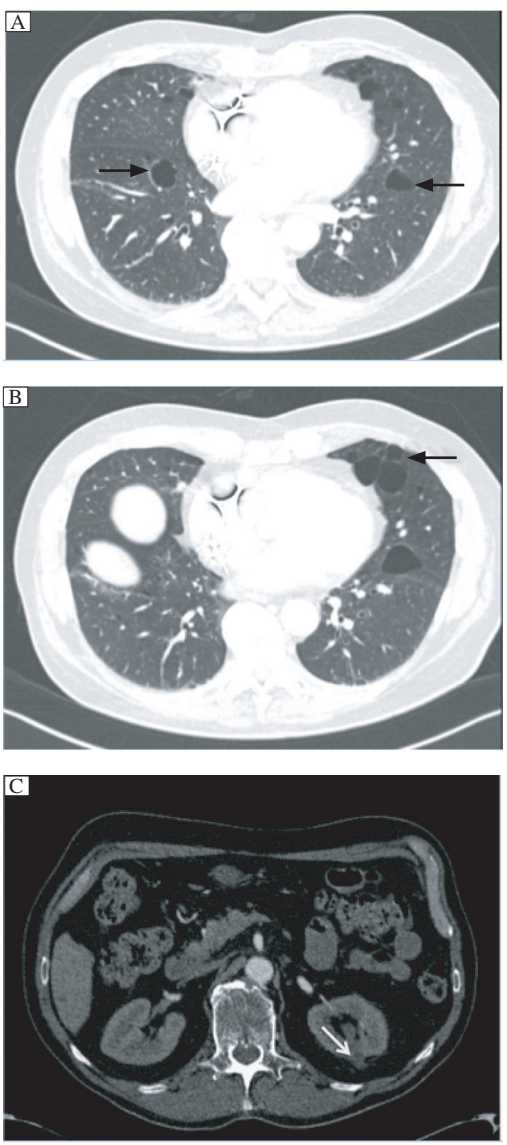

Fig. 2 **CT results of the case.** A: Asymmetric, thin-walled cysts (indicated by arrows) on both bases of the patient´s lungs. B: Some of the cysts (arrow) are sub-pleural. C: A left renal cyst is noted on an ab–dominal CT scan (arrow).

abdominal sonogram (***Fig. 2C***). There was no abdominal lymphadenopathy.

What is the autosomal dominant, cystic, pulmonary disease that manifests with skin and renal manifestations?

DISCUSSION

In 1977, Arthur Birt, Georgina Hogg and James Dube reported a case series in the Archives of Dermatology describing 70 kindred patients who had numerous papular lesions that were a type of pilar hamartoma called fibrofolliculoma[1]. They also had trichodiscomas (tumors of the hair discs) and acrochordons (skin tags). These lesions surfaced after the age of 25 years old, and were scattered on the face, neck and upper torso. Inheritance of these lesions was found to be in an autosomal dominant pattern. Further characterization of the population of this patient showed an associated occurrence of renal neoplasia, lung cysts and spontaneous pneumothoraces. The family of our patient was part of the original cohort of patients in North America that were found to have such abnormalities. He was diagnosed by participating in a National Institute of Health study approximately 7 years ago[2].

By using genetic linkage analysis, Schmidt et al. localized the genetic abnormality in what has been known as Birt-Hogg-Dube (BHD) syndrome at the peri-centromeric region of chromosome 17p11.2[3]. This region encodes a protein of unknown function called folliculin, and is therefore called the *folliculin* (*FLCN*) gene locus[4]. Germ-line mutations in this region resulted in truncation of the protein. In an analysis of BHD mutation spectrum and phenotype, families with identifiable BHD mutation all had members with classic dermatologic manifestations, 85% of them were found to have lung cysts, 32% had a previous history of spontaneous pneumothorax, while 20% developed renal tumors[2]. In another cohort of patients, about 10% of those with identified FLCN mutation did not manifest with typical skin symptoms[5]. It is estimated that about 200 families with FLCN mutations have BHD syndrome in the worldwide[5-9]. However, as its clinical heterogeneity and variable expression, BHD is thought to be under-diagnosed.

The skin lesions are described as multiple, pale-yellow, slightly raised, dome-shaped papules at 2-4 mm in diameter and has an opaque appearance[1]. These lesions are usually scattered over the face, neck and upper torso, and intermingled with acrochordon-like papilloma and trichodiscomas. Our patient had fibrofolliculomas that was first noted when he was in his 3rd decade of life. Histologically, fibrofolliculomas, the disease-defining lesion in BHD, appears as an anastomosing complex of sub-epithelial connective tissue surrounding a hair follicle. A skin biopsy performed on this patient while enrolled in the National Institutes of Health (NIH) study 7 years ago revealed findings that were consistent with fibrofolliculomas. Other skin lesions have been identified in BHD, including facial angiofibromas[10] and oral papules[11].

In 2 large cohort studies involving more than 100 families with mutations in the *BHD* gene locus (*FLCN*), 45% to 49% of the families had members with renal tumors[2,5]. Pavlovich et al.[12] conducted a retrospective analysis of renal neoplasms that occur in patients with BHD. They found that the average age of tumor onset was 50.7 years, with about 60% of patients developing bilateral tumors and 77% presenting with multiple renal tumor types[12]. Recently, a left complex, cystic renal lesion measuring 1.0×1.5 cm was identified in our patient. A sub-specialist´s decision was made to follow this lesion by using serial sonogram every 3-6 months, with biopsy of the lesion if any change is noted.

The most common identified renal tumor in BHD is a hybrid of renal oncocytoma and chromophobe renal cell carcinoma followed by simple chromophobe renal cell carcinoma, oncocytoma and papillary renal cell carcinoma. It is believed that these tumors could become potential precursors of the classic clear cell renal carcinoma. With the paucity of data, the biologic behavior of BHD-associated renal cancer has not been fully elucidated, and await the result of larger prospective studies[5].

Approximately 80% of patients with BHD have pulmonary cysts on chest imaging (CT) and about 40% of those with the *BHD* gene locus mutations will develop pneumothoraces[5]. The cysts are thin-walled, variable in size and shape, predominantly basilar and sub-pleural in distribution[13]. A Japanese study histologically described the cysts as having walls that were partially incorporated into the interstitial stroma of the interlobular septum, visceral pleura or broncho-vascular bundle, and were lined by cells that are differentiated pneumocytes[6]. These cysts are thought to be histologically distinct from those found in emphysematous and non-specific blebs or bullae. A retrospective study by Ayo et al. revealed that cystic lung disease in BHD seemed to be more extensive in smokers[14]. It is possible that the relatively low number of pulmonary cysts in our patient may be due to the fact that he was a never-smoker.

Zbar et al.[13] examined the clinical characteristics of 98 BHD patients that the risk for developing a pneumothorax was found to be 50.3 times greater than

that of an unaffected patient. Episodes of pneumothorax occurred in relation to the presence of lung cysts were more recurrent rather than isolated, and manifested at a median age of 38 years[13]. Our patient has not developed a pneumothorax yet. We again believe that the relatively low number of cystic lesions in his lungs, and his non-smoking status may have ameliorated the likelihood of such an event from occurring.

The BHD syndrome has been defined based on the presence of fibrofolliculomas. At least 5 to 10 lesions with at least 1 papule which are histologically diagnosed are required[2]. It has been suggested that diagnostic criteria be applied to its diagnosis as the multitude of ways that BHD presents - with various permutations of integumentary, renal and pulmonary manifestations. It has been suggested that employing diagnostic criteria would help in the identification of these patients[15]. Proposed major criteria include 5 or more adult-onset fibrofolliculomas or trichodiscomas with at least 1 histologically confirmed, and a confirmed pathogenic FLCN germ-line mutation. Typical lung cysts on imaging with or without accompanying pneumothoraces, renal cancer (early onset, multifocal, bilateral, mixed chromophobe or oncocytic histology) and a first degree relative with BHD are the proposed minor criteria. These diagnostic criteria have not been prospectively validated.

The diagnosis and differentiation of BHD syndrome from other syndromes that manifest in a similar fashion are essential. An example would be tuberous sclerosis complex with lymphangioleiomyomatosis (LAM). Both diseases share clinical characteristics, including lung, skin and renal involvement. However, prognosis and management are significantly different[16]. Our patient fits the syndrome of BHD as he fulfills the set criteria, with skin lesions that are bioptically proven to be fibrofolliculomas - a skin finding that is fairly specific to BHD.

Expectant therapy and preventative measures are integral parts of managing this rare disease complex. Surveillance screening for renal tumors via imaging (magnetic resonance imaging, CT) should be an annual endeavor. Our patient was scheduled to undergo surveillance scans for the left renal lesion that was recently identified. Once renal cancer is diagnosed, the usual steps in appropriately staging the malignancy and corresponding therapy (surgery, with or without adjuvant chemotherapy to prevent metastatic disease) should commence. Patients with cystic lung disease are advised to seek a pulmonologist´s expertise and care. Although there has been no direct correlation with the development of renal cell cancer and cystic lung disease with pneumothoraces in those with BHD syndrome, smoking cessation should still be encouraged as smoking is an independent risk factor for renal cell cancer and for spontaneous pneumothoraces[5,13]. Pneumothoraces are conventionally managed. The skin lesions associated with BHD syndrome may cause some cosmetic concerns to some BHD patients. There have been several approaches employed to eradicate these skin tumors, including curettage, shave and cautery therapies and laser treatments[15].

The current presenting symptoms of our patient are not classic manifestations of Birt-Hogg-Dube syndrome. They are thought to be complicated by the simultaneous presence of a separate disease entity (a vasculitis). Nevertheless, his risk for renal carcinoma, and to a lesser extent, his risk for developing pneumothoraces is still remain. Though there are no defined guidelines for the therapy of this rare heritable syndrome, we will have his pulmonary status followed closely. A multi-disciplinary approach has been adopted, together with ongoing consultations with urology and rheumatology in his management for optimal care.

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