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Case report

A case of bilateral renal oncocytomas in the setting of Birt-Hogg-Dube syndrome ☆☆☆★★

Brian Covello, MD^{a,*}, Sean Kaufman, MD^b, Elizabeth Whittington, MD^b, Orlando Enrizo, MD^a

^aDepartment of Interventional Radiology, Kendall Regional Medical Center, 11750 SW 40th St, Miami, FL 33175, USA

^bDepartment of Pathology, Kendall Regional Medical Center, 11750 SW 40th St, Miami, FL 33175, USA

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ABSTRACT

Birt-Hogg-Dube syndrome is a rare autosomal dominant disorder characterized by pulmonary cysts, renal tumors, and dermal lesions. This syndrome results from a mutation in the gene *folliculin*, located on chromosome 17p11.2. Herein, a case is described in which the presence of bilateral renal oncocytomas led to the diagnosis of Birt-Hogg-Dube syndrome via an interdisciplinary effort by radiology, pathology, and primary care medicine. No radiographic features alone are sufficient to confirm the diagnosis of Birt-Hogg-Dube. A high index of suspicion must be maintained by both the pathologist and radiologist in the appropriate clinical setting.

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Introduction

Birt-Hogg-Dube syndrome (BHD) is a rare autosomal dominant genetic disorder characterized by pulmonary cysts, renal tumors, and dermal lesions [1]. First described in 1977 by Birt, Hogg, and Dube in a family with skin lesions, this condition is due to a germline mutation in the *folliculin* gene located on chromosome 17p11.2 [1]. The actual incidence of BHD is unknown, and this syndrome typically presents in patients over 20 years of age [1,2]. Fibrofolliculomas are benign tumors of the

hair follicle and are the most common skin findings in BHD; they appear as small dome-shaped yellowish-tan papules on the face, neck, and extremities [2].

Pulmonary cysts are an additional hallmark, however, normal chest computed tomography (CT) is reported in up to 12% of patients [3]. Cysts vary in shape, size, and location. Pulmonary cysts may rupture and cause spontaneous pneumothorax [3,4].

Bilateral renal cancer was first associated with BHD in 1993 [5]. A firm association between oncocytomas, chromophobe renal cell carcinoma (RCC), clear cell RCC, and papillary RCC

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* Corresponding author.

E-mail address: brcovello@gmail.com (B. Covello).

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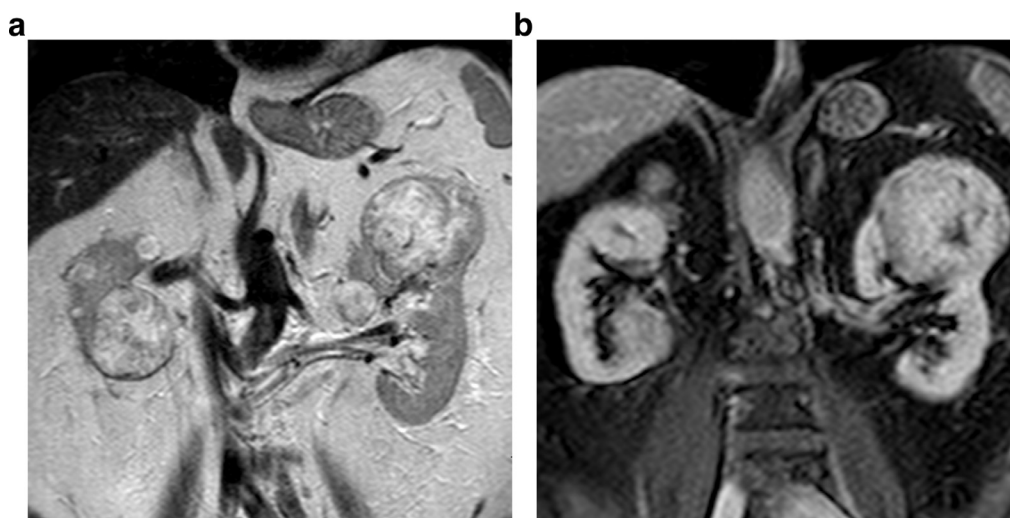


Fig. 1 – (A) T2-Weighted coronal-slice magnetic resonance image shows multiple T2-hyperintense heterogeneous renal masses bilaterally. (B) T1-weighted coronal slice magnetic resonance image shows the largest renal mass in the left upper pole which measures 7.8 × 8.2 × 7.5 cm and contains a hypointense central stellate scar indicative of fibrosis.

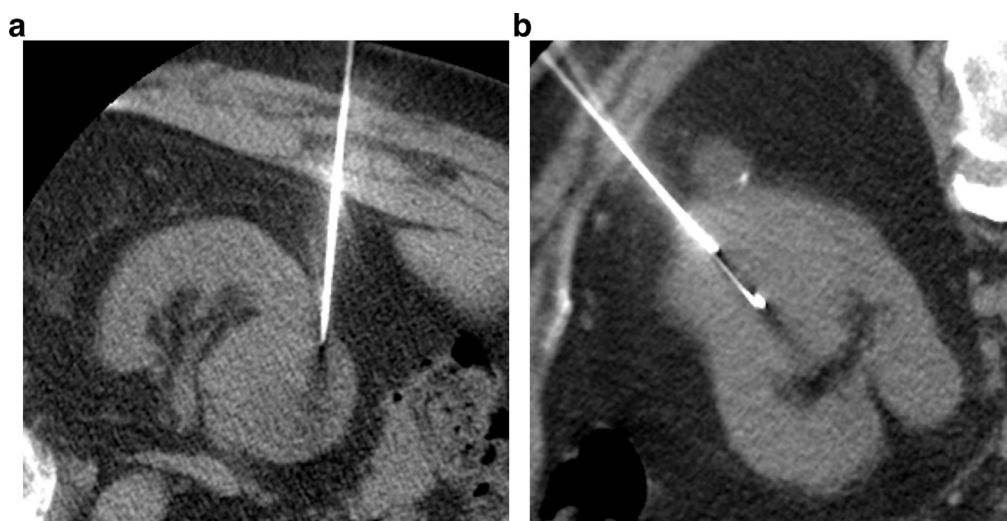


Fig. 2 – Axial-slice computed tomography through the (A) left and (B) right kidneys show the appropriate placement of the coaxial needle system immediately before the percutaneous renal biopsy.

has since been established [4]. Renal tumors are seen in 14–34% of BHD cases, and oncocytomas comprise 5% of the renal masses seen in this syndrome [4].

Herein, a case is described in which the presence of bilateral renal oncocytomas led to the diagnosis of Birt-Hogg-Dube syndrome via an interdisciplinary effort by radiology, pathology, and primary care medicine.

Case presentation

A 72-year-old gentleman with a past medical history of uncontrolled hypertension, hyperlipidemia, glaucoma, and chronic obstructive pulmonary disease presented to his primary care

physician (PCP) for back pain and uncontrolled hypertension. The patient's PCP ordered a magnetic resonance angiogram (MRA) abdomen, which revealed multiple heterogeneous T2 hyperintense, T1 hypointense renal masses with heterogeneous arterial enhancement (Fig.1A). The largest renal mass in the left upper pole measured 7.8 × 8.2 × 7.5 cm and contained a hypointense central stellate scar indicative of fibrosis (Fig.B). There was one additional mass with similar imaging characteristics in the left kidney. The right kidney contained a 4.7 × 5.2 × 5.1 cm T2 hyperintense, T1 hypointense heterogeneous mass with a hypointense central stellate scar. There were four additional lesions within the mid and upper pole of the right kidney. The patient was referred to interventional radiology for bilateral percutaneous renal biopsy (Fig.2).

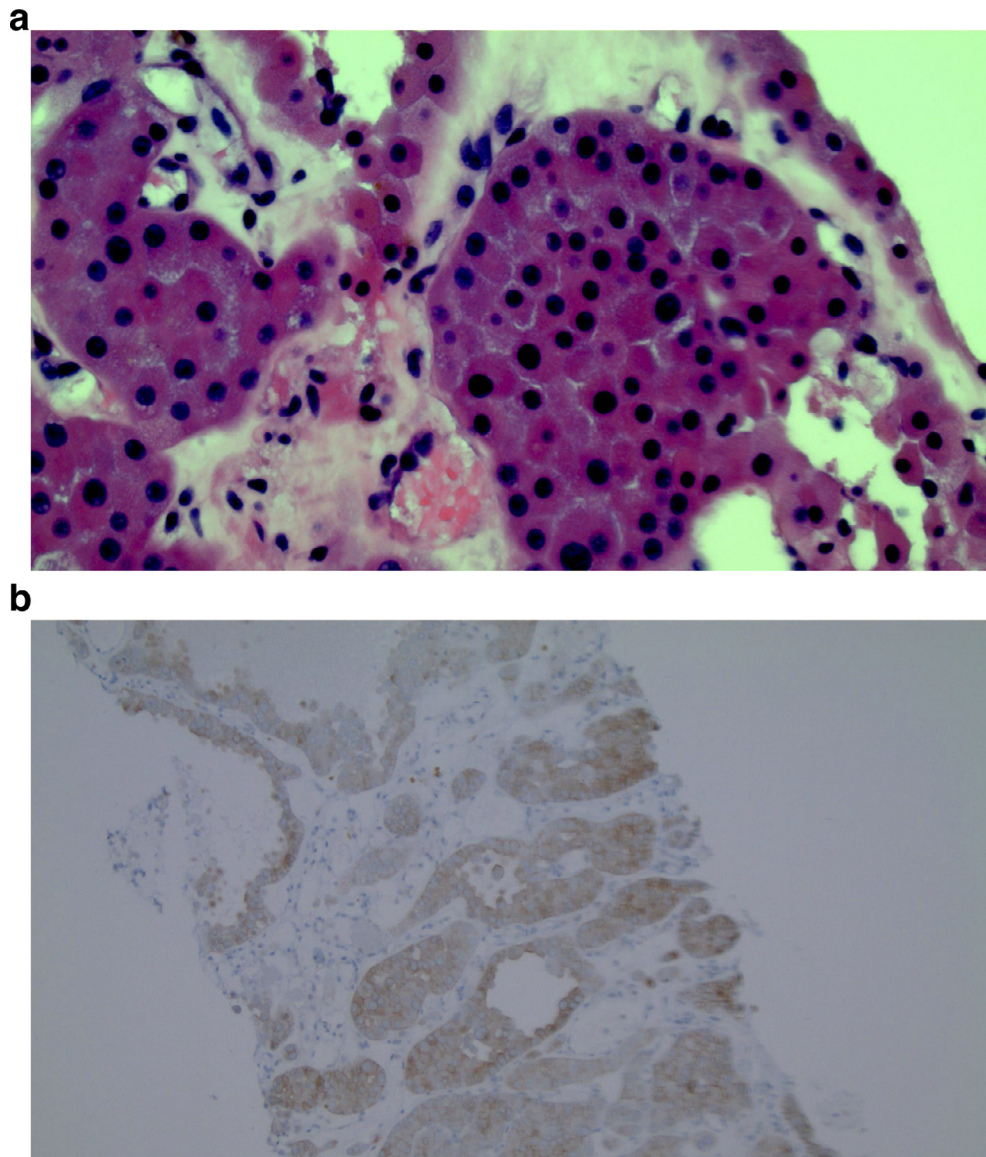


Fig.3 – (A) 20x magnification histological slide showing densely eosinophilic cytoplasm with round, regular nuclei in a fibrotic background. (B) 10x magnification histological slide with CD117 positive staining. Together, these findings are consistent with oncocytoma.

Biopsy revealed tumors with densely eosinophilic cytoplasm with round, regular nuclei in a fibrotic background (Fig.3A). Colloidal iron and CK7 stains were negative. CD117 was positive (Fig. 3B). Pathology confirmed the diagnosis of bilateral renal oncocytomas.

Given the peculiar finding of bilateral renal oncocytomas, pathology initiated discussions with radiology over the possibility of BHD. A retrospective chart review showed that the patient had a prior hospital admission for pneumonia. The patient had no history of pneumothorax. Upon review of prior chest CT, a thin-walled pulmonary cyst was discovered in the left upper lobe (Fig. 4A). A follow-up thin slice axial chest CT was ordered for further characterization of pulmonary cysts. A second smaller sub-centimeter pulmonary cyst was found in the left upper lobe (Fig. 4B).

After further discussion with the patient's PCP, the patient was noted to have dome-shaped tan papules on his neck and chest (Fig.5). Pathology confirmed fibrofolliculomas on microscopy (Fig. 6). The patient was subsequently diagnosed with BHD and referred to an outside center for genetic testing and counseling. The patient was not aware of any relevant family history.

Discussion

Pulmonary cysts, renal tumors, and skin lesions are the hallmarks of BHD [1]. Given the rarity and wide clinical variability of BHD, this syndrome likely remains underdiagnosed. Skin

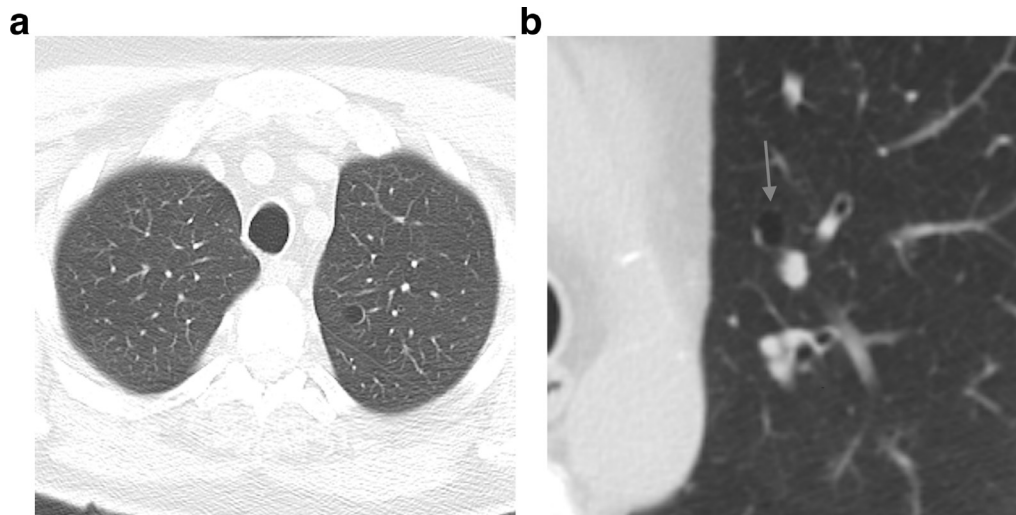


Fig.4 – (A) Axial-slice computed tomography in lung windows show a sub-centimeter pulmonary cyst in the left upper lobe. (B) Follow-up axial thin-slice computed tomography in lung windows shows an additional sub-centimeter pulmonary cyst in the left upper lobe. No other interstitial or pulmonary abnormalities are present.



Fig.5 – Clinical image showing dome-shaped tan papules covering the lateral dermis of the patient's neck.

manifestations and fibrofolliculomas may go initially unnoticed by the clinician, as evidenced by the current case [3]. As described, pathological confirmation of bilateral oncocytomas led to interdisciplinary discussions which allowed for retrospective review of patient images and the discovery of pulmonary cysts. After raising the possibility of BHD with the patient's PCP, the patient's skin findings were clinically identified. The appearance of fibrofolliculomas on the chest, neck, and abdomen, in particular, may be easily missed. Thus, radiologists and pathologists must maintain a high index of suspicion for this syndrome in the appropriate clinical setting.

From a radiological perspective, multiple unchanging pulmonary cysts with recurrent spontaneous pneumothorax may be the initial presentation of a patient [3]. Spontaneous pneumothorax is thought to occur secondary to cyst rupture [3]. Pulmonary cysts are found in over 85% of patients with BHD [4]. Several radiology studies have attempted to characterize the lung cysts found in BHD and differentiate them from lymphangioleiomyomatosis (LAM), pulmonary Langerhans's cell histiocytosis (LCH), and lymphocytic interstitial pneumonia (LIP) [2]. In contradistinction to these other entities, the pulmonary cysts of BHD do not progress over time and the lungs lack other interstitial changes [2]. Cysts vary in shape, size, and location, and they show no central or peripheral predominance [3]. In one study, thoracic CT was normal in 2 out of 17 patients [3]. The currently described patient had no history of spontaneous pneumothorax, although two small sub-centimeter pulmonary cysts were visualized on chest CT in the left upper lobe. Agarwal et al (2010) reported 47% of their patients had fewer than ten cysts [3]. While pulmonary cysts may aid in the diagnosis, they lack the specificity required for diagnostic confirmation. Small pulmonary cysts may be overlooked or considered benign on initial radiological reports. In the current case, a retrospective review of patient imaging after the diagnosis of bilateral renal oncocytomas revealed the patient's pulmonary cysts.

Both malignant and benign renal tumors may occur in BHD, and renal malignancy develops in 15-30% of patients [1,4,6]. Studies show that renal tumors in BHD occurred at an average age of 50.4 years [7,8]. Bilateral renal cancer in BHD was first described in 1993 [5]. Various types of RCC, including chromophobe, mixed, clear cell, and papillary subtypes have since been associated with BHD [4]. Oncocytomas account for 5% of the renal tumors in BHD [4]. Bilateral oncocytomas are a peculiar finding in patients, and this finding was the first indication to pathology that an underlying syndrome may be present. BHD is caused by mutations in the follicular gene (FLCN) located on chromosome 17p11.2 [9,10].

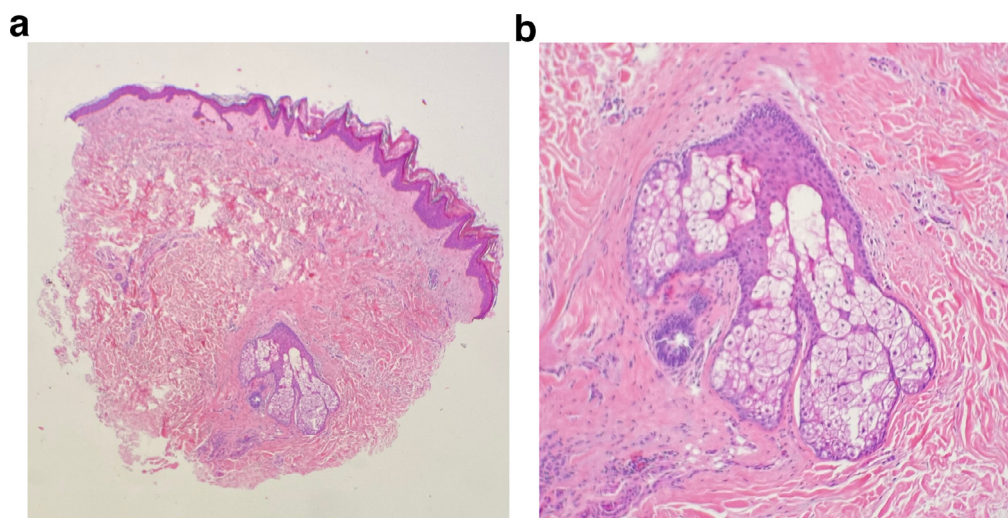


Fig.6 – (A) 4x and (B) 10x magnification hematoxylin and eosin stain of dome-shaped papules reveal pathological confirmation of fibrofolliculoma.

Folliculin acts as a tumor suppressor via the mTOR signaling pathway [1]. Mutations in folliculin cause a loss of folliculin protein and promote kidney tumorigenesis [1]. All patients with BHD should undergo genetic testing with a DNA panel and receive genetic counseling [1]. Given the autosomal dominant nature of the disease, when a mutation is detected, genetic testing and counseling for at-risk family members is also indicated [1]. Folliculin-mutations may occur in carrier patients without presentation of skin lesions. Genetic testing remains especially important in lieu of this syndromic variability and potential for incomplete penetrance [1]. The lack of family history in the current case may be attributable to patient unawareness, incomplete penetrance of folliculin mutations in family members, or full penetrance in family members who had yet to be diagnosed. The patient was referred for genetic testing and possible testing of his at-risk family members. The prevalence of incomplete penetrance is not currently known, and further genetic prospective studies are needed to investigate folliculin mutation penetrance and variability [1].

Surveillance for renal malignancy is indicated for patients and at-risk relatives, although no standardized guidelines currently exist [1]. Studies have investigated both CT and MRI for surveillance [11]. MRI is thought to be superior to CT, as annual CT surveillance would impart high radiation doses to the patient [1]. Ultrasound is too insensitive for appropriate detection and surveillance [1].

Treatment of BHD depends on the pathology of renal masses present. If renal malignancy is diagnosed, nephron-sparing surgery is typically the first-line treatment [1]. Other nephron-sparing techniques such as radiofrequency ablation may be considered given lesion size smaller than 3 cm, and interventional radiology may play a bigger role in the treatment of BHD-related renal cancers in the future [1,12]. The current patient required no treatment given the benignity of oncocytomas.

In summary, a case of BHD in a 72-year-old male has been presented. Interdisciplinary communication between pathol-

ogy and radiology was critical for this diagnosis. While the hallmarks of BHD include skin lesions, pulmonary cysts, and renal tumors, some of these findings may be easily overlooked. This fact places an additional burden upon radiologists and pathologists to have a high degree of suspicion for this entity in the appropriate clinical setting. When a patient presents with recurrent spontaneous pneumothorax with pulmonary cysts on imaging, BHD should be included in the differential. In the described case, the peculiarity of bilateral renal oncocytomas as noted by pathology ultimately led the radiologist to discover pulmonary cysts, the clinician to discover skin lesions, and the interdisciplinary team to arrive at the correct diagnosis.

Patient consent statement

Informed Consent: Written informed consent was obtained from all individual participants in this study. Written consent for publication was obtained for every individual's data included in this study

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