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**CASE REPORT**

# Multiple chromophobe and clear cell renal cancer in a patient affected by Birt-Hogg-Dubè syndrome: a case report

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**ABSTRACT**

**Objectives:** Birt-Hogg-Dubé syndrome (BHDS) is a rare autosomal dominant characterized by the presence of fibrofolliculomas and/or trichodiscomas, pulmonary cysts, spontaneous pneumothorax, and renal tumors. The syndrome is linked to mutations in the *FLCN* gene, which is preferentially expressed in the skin, kidney, and lung. The aim of our paper is to describe a case of multiple bilateral renal cancer in a patient affected by BHDS.

**Case presentation:** Patient subjected to enucleoresection seven kidney tumors discovered right after ultrasound performed for other reasons. Definitive histologic examination were as follows: multifocal type chromophobe renal cell carcinoma and clear cell. After 1 month, the patient was readmitted for spontaneous pneumothorax. After about a year, the patient was again subjected to resection of multiple renal tumors left. Histological examination proved that it was multifocal renal cell carcinoma, clear cell varieties. The genome analysis highlighted positive for mutation c. 1379_1380 of *FLCN* gene, *BHDS* gene. Currently, the patient is under close follow-up. After 1 year, the chest computed tomography (CT) confirmed the presence of minute air bubbles scattered on both sides. Instead, the abdominal CT was positive for a small round lesion 6 mm exophytic.

**Conclusions:** The BHDS is a rare syndrome whose management is extremely complex both in terms of oncological and functional. Kidney tumors associated with BHDS usually have a favorable clinical course. Present evidence suggests a close follow-up of the carriers of the genetic mutation patients whether or not they have expressed the lesions of disease given the high rate of recurrence of renal lesions.

**Keywords:** Birt-Hodd-Dubè syndrome, BHDS, Renal tumors, Spontaneous pneumothorax

## Introduction

Birt-Hogg-Dubé syndrome (BHDS) is a rare autosomal dominant genodermatosis that is characterized by the presence of fibrofolliculomas and/or trichodiscomas, pulmonary cysts, spontaneous pneumothorax, and renal tumors.

The syndrome is linked to mutations in the *FLCN* gene (1), which encodes folliculin and is preferentially expressed in the skin, kidney, and lung.

In 1977, Birt, Hogg, and Dubé investigated several members of the same family with thyroid cancer and fibrofolliculoma occurring in an inherited autosomal dominant fashion (2). Hornstein and Knickenberg described a distinct entity, 2 years earlier, in two brother with perifollicular fibromas, multiple acrochordons, and intestinal polyps. Their father was affected by renal and bilateral lung cysts. This condition was named Hornstein-Knickenberg syndrome; however, some investigators consider these two syndromes as the same entity (1). In 1993, bilateral renal cancer was first described in a patient with BHDS by Roth and colleagues, and now the association between increased risk of renal cancer and BHDS is well known (3). In 2001, a BHD-associated gene locus was localized to chromosome 17p11.2 by linkage analysis. Subsequently, *FLCN* (BHD) gene, coding for a protein called folliculin, was identified (3). Transmission is dominant. FLCN is a tumor suppressor gene, its inactivation follows the "two hit" model; interesting and not completely understood is how a germline mutation can cause such different clinical manifestations (4). FLCN germline mutation testing is positive in over 96% of BHD families (5). While not all patients with BHD syndrome will develop renal cell

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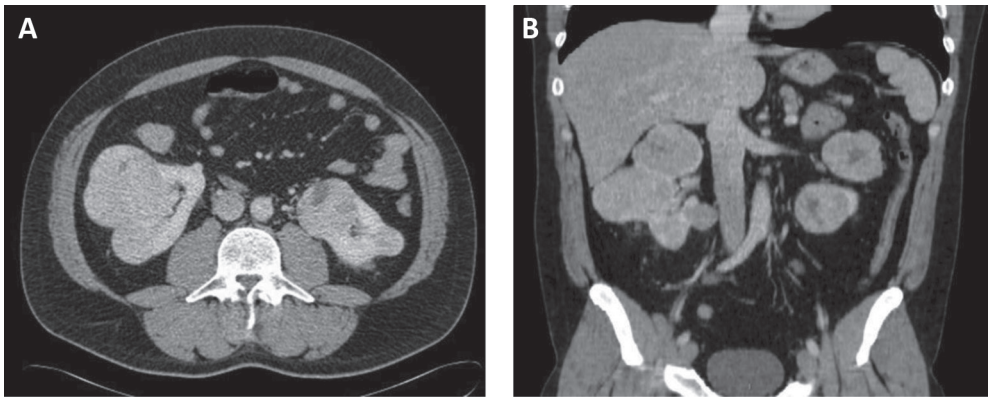


**Fig. 1 -** CT abdominal enhanced axial scan in venous phase (**A**) and MPR coronal reconstruction (**B**). Bilateral renal masses with heterogeneous enhancement; enhancing masses with a central scar in left kidney are depicted.

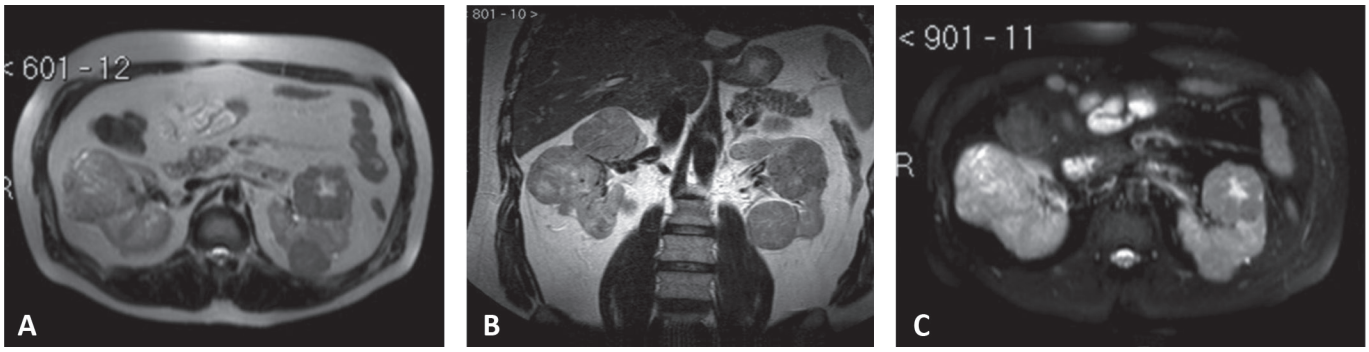


**Fig. 2 -** T2-weighted SE axial (**A**) and coronal (**B**) images. Bilateral heterogeneous masses with internal hyperintense foci on right kidney and hyperintense central scar on the left, with no signal intensity degree on T2-weighted SE axial scan with fat saturation (**C**).

carcinoma (RCC), Stamatakis et al (5) suggest that the risk does not decrease with advancing age, and thus, lifelong screening is recommended. Nevertheless, renal tumor prognosis is quite good because of the low malignant histological pattern of lesions and the low clinical stage at diagnosis (6). Management of these patients is absolutely challenging and not easy to asses.

The aim of our paper is to describe a case of multiple renal cancer in a patient affected by BHDS.

## Case presentation

Our patient was a 38-year-old Caucasian man. The patient had no relevant medical history. He was nonsmoker and he only underwent tonsillectomy at an early age.

The patient presented incidental multiple renal masses in abdominal ultrasound performed for other reasons at our hospital in early 2008.

Subsequently, abdominal computed tomography (CT) was taken for better characterization of renal lesions. Kidneys showed an increase in their size due to the presence of rounded-exophytic multiple bilateral tumors with a diameter between 18 and 70 mm. The first suspected diagnosis was compatible with multiple oncocytomas. This diagnosis was confirmed by magnetic resonance imaging (MRI) (Figs. 1-3).

To complete characterization of lesions, positron emission tomography (PET-TC) was performed. It showed moderate bilateral accumulation of the tracer at the level of multiple tumors in both kidneys.

Therefore, we performed his first surgery at early February 2009: enucleation and resection of seven right kidney tumors. The patient was discharged after 6 days of hospitalization.

Histopathological examination showed multifocal chromophobe RCC (90%) and clear-cell RCC (10%), grade II Fuhrman, and stage pT3a (2009 TNM classification) in all specimens.

One month after the operation, the patient visited our hospital again complaining of chest pain and dyspnea, due to a complete right-sided pneumothorax, that was treated with placement of right pleural drainage.

During follow-up, a second renal scintigraphy was performed that revealed decreased right renal function. Function of left kidney and right kidney was 61% and 31%, respectively.

In May 2009, the patient underwent another nephron-sparing surgery, in order to enucleate multiple left renal lesions in cold ischemia. In this occasion, the result of histological examination was multifocal clear-cell RCC, Fuhrman grade II, and stage pt2 (2009 TNM classification).

Due to the characteristics of renal tumors and the presence of an episode of spontaneous pneumothorax, a genomic analysis that revealed a positive result for a c. 1379_1380 gene FLCN state of heterozygosity mutation was performed.

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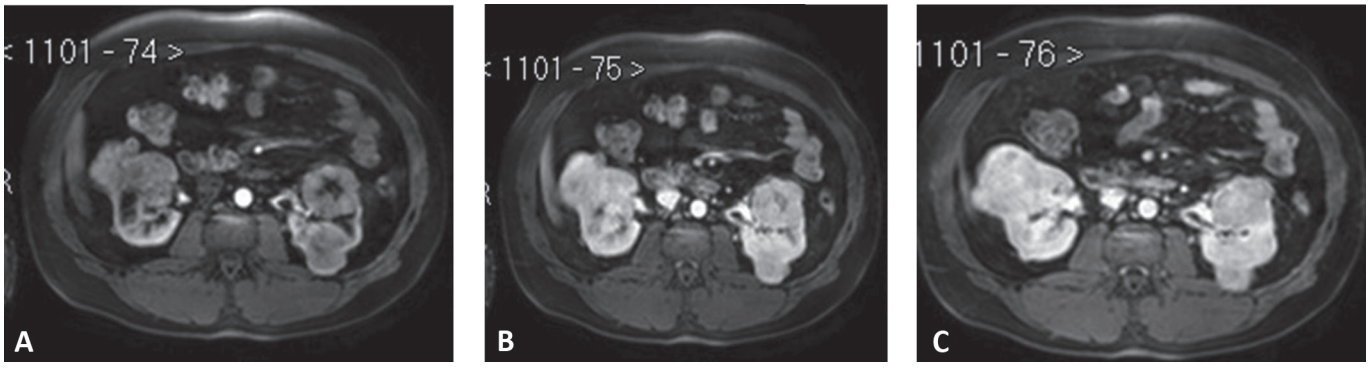


**Fig. 3 -** Enhanced axial T1 fs-weighted scans in arterial (**A**), venous (**B**), and late (**C**) phase. Renal bilateral masses with intense heterogeneous enhancement; central scar remains dark in arterial and venous phase, with late enhancement.

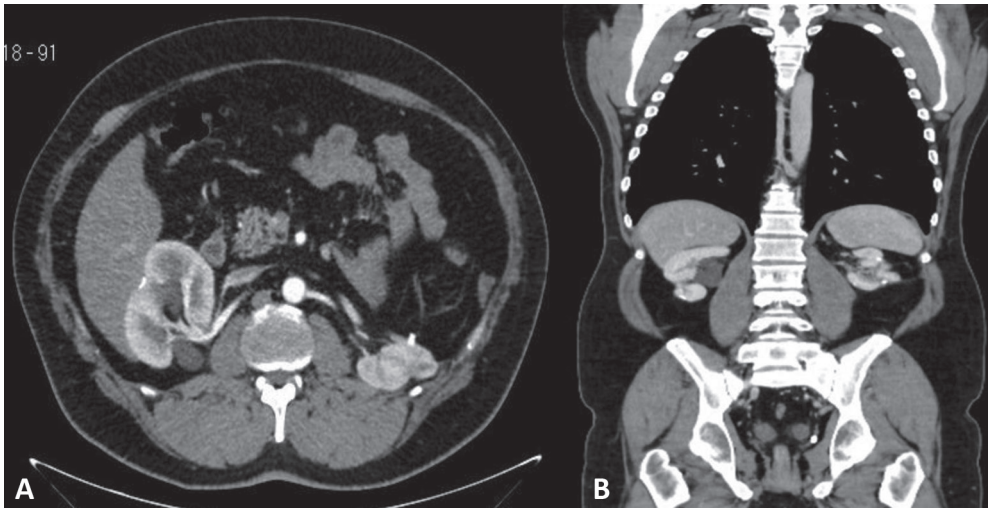


**Fig. 4 -** Axial CT scan in portal venous phase (**A**) and coronal MPR reconstruction: (**B**) after surgical enucleation of bilateral renal solid lesions, no evidence of local disease.

His mother, his older brother, and his daughter showed FLCN mutation; however, they have so far shown no phenotypic features of the disease. In fact, diagnosis was made through genetic test.

During 5-year follow-up, with abdominal ultrasound, CT scan and MRI (Fig. 4), the patient was free for renal lesions. In May 2014, total-body CT scan was performed, which showed the presence of tiny scattered bubbles of centrilobular emphysema in both lungs, although kidneys had not detectable solid tumoral lesions. A new CT scan performed 1 year later confirmed the presence of tiny scattered bubbles of centrilobular emphysema in both lungs, unchanged from the previous examination. But abdominal CT scan showed a small rounded exophytic lesion of 6 mm in diameter at the upper pole of the right kidney with vascularization in the arterial phase. Since then, the patient has chosen a close monitoring of renal lesion.

## Discussion

BHDS is a rare autosomal dominant disorder associated with the germinal mutation of *FLCN* gene. *FLCN* gene is a novel tumor suppressor responsible for this syndrome. While Stamatakis reported FLCN germline mutation testing positive in over 96% of BHD families (5), Kuroda et al estimated germline *FLCN* gene mutation rates from 84% to 88% of BHD (6). Various types of mutation were reported in literature: Toro et al. in their article described 50 families series 23 different germline mutations were identified, of these, 13 were novel; specifically, they were four splice sites, two insertions, three deletions, one missense mutation, one deletion/insertion, and two insertions (7). So far, no apparent genotype-phenotype correlations have been recognized (6). Genetic studies using knockout mice for this gene have shown its role in metabolism; in kidney-targeted FLCN, knockout mice developed polycystic kidneys with elevated mechanistic target of rapamycin complex 1 (mTORC1) activity and augmented mitochondrial biogenesis through upregulated peroxisome proliferator activated receptor gamma coactivator 1-alpha (Ppargc1a) (8). In a recent paper Hasumi et al focused their work to define the role of two proteins, folliculin (FLCN)-interacting proteins 1 and 2 (FNIP1 and FNIP2). They concluded that Fnip1 and Fnip2 complex has an essential role for tumor suppressive function and will be a possible target for kidney cancer (8). Menko et al proposed diagnostic criteria on the basis of clinical manifestations and the outcome of DNA testing. The diagnostic criteria are as follows: Major criteria: (1) At least five fibrofolliculomas or trichodiscomas, at least one

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of them confirmed histologically, occurring in adult onset, (2) Pathogenic FLCN germline mutation; Minor criteria: (1) Multiple lung cysts, bilateral basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax, (2) Renal cancer, early onset (<50 years) or multifocal or bilateral renal cancer, or renal tumor composed of mixed chromophobe and oncocytic morphology, (3) A first-degree relative with BHDS. When patients fulfill one major or two minor criteria, the diagnosis of BHDS is feasible (3, 6). Renal tumors associated with BHDS usually have a favorable outcome, probably because the clinical behavior of hybrid oncocytic tumor, chromophobe RCC, and oncocytoma is usually associated with the low clinical stage at the diagnosis (6). The most typical manifestation of BHD syndrome are the cutaneous fibrofolliculoma that appear as pale yellow to white papules, dome-shaped, and not painful or pruritic 2-4 mm in diameter. They appear on the face, neck, and upper torso after puberty, singly or in a plaque of more than 100 lesions. Histologically, they consist of epithelial strands extending out from a central hair follicle into specialized fibrous tissue, often accompanied by trichodiscomas and acrochordons (9). Zbar et al identified risk factors for renal tumors and spontaneous pneumothorax in 98 patients affected with the BHD syndrome, in 13 BHD haplotype carriers, and in 112 unaffected family members, showing that the odds ratio for pneumothorax in BHD-affected individuals, adjusted for age, was 50.3 and about 32 times higher adjusting for the other risk variables (10). As in our case, it is well known in literature that, unlike other inherited renal cancer syndromes that present with a single histologic tumor, BHD patients develop bilateral multifocal renal tumors with a wide spectrum of histologies. Hybrid oncocytic tumors with features of chromophobe renal cancer and renal oncocytoma are not only the most frequent renal tumors in BHD patients (50%) but also present with chromophobe renal carcinoma, clear cell renal carcinoma, and renal oncocytoma. Multiple tumors with different histologies can also develop in a single kidney of BHD patient (11). Patient's management is challenging and a unique answer is not available in literature. In the case of renal tumors, it is recommended for BHD family members to undergo baseline surveillance by abdominal MRI with intravenous contrast or CT scan. The use of ultrasonography is not recommended for routine screening; however, it may be helpful for surgical planning (5). For preserve the maximum renal function nephron-sparing surgical management is recommended. This kind of approach is the first choice due to the risk to develop multiple bilateral tumors during patients lifetime and needing of multiple surgeries. During a surgical procedure, removal of all detectable renal lesions is undertaken and can be facilitated by intraoperative renal ultrasound to detect small endophytic tumors. Despite metastasis of BHD renal tumors are possible, leading to patient mortality, usually BHD patients have excellent prognosis when managed conservatively if tumors reach 3 cm. This because BHD-associated renal tumors tend to be indolent (9). Actually, the only therapy for cutaneous lesions is surgery, with or without the use of laser (9). Once the diagnosis of BHD syndrome has been made, chest CT scan is recommended to identify the presence of pulmonary cysts and/or evidence of pneumothoraces. Periodic chest imaging is not routinely recommended in asymptomatic patients without history of pneumothoraces. Numerous approaches were used to treat patients who develop pneumothoraces. These approaches depend on the severity of patients symptoms, including simple observation or tube thoracostomy to evacuate the pleural space and reinflate the compressed lung, with or without chemical pleurodesis. When lung bullae or blebs are present or if pneumothoraces are recurrent, surgical intervention (i.e., thoracotomy) with mechanical pleurodesis and resection of bullae may be recommended (9). Currently, the only therapeutic option for BHD-associated renal tumors is the surgical intervention. However, some studies have demonstrated that loss of FLCN function leads to mTOR activation; mTOR inactivation under FLCN deficiency has also been reported. Rapamycn treatment has been shown to partially reverse the cystic kidney phenotype in the kidney-targeted FLCN knockout mouse models (9).

## Conclusion

The BHD syndrome is a rare cancer susceptibility syndrome characterized by clinical features of skin lesions, pulmonary lesions, and renal tumors. BHD-associated renal cancer shares general features with other types of hereditary renal tumors: early age at diagnosis and multifocal or bilateral disease. Surgical management of multiple bilateral kidney tumors is not easy but feasible. Knowledge of the causes of emergence of multiple bilateral renal tumors, as in some syndromes, is of fundamental importance for a correct assessment and management of these patients.

## Disclosures

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Conflict of interest: The authors declare that there are no conflicts of interest.

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