

Resection and Re-resection for a Clear Cell Renal Carcinoma with Sarcomatoid Features in a Patient with Birt-Hogg-Dubé Syndrome

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Abstract

Background: Birt-Hogg-Dubé syndrome (BHDS) is a rare monogenic autosomal dominant disorder which is, among other disease manifestations, associated with an increased life-time risk of developing renal cell carcinoma (RCC). Sarcomatoid RCC (sRCC) is a subtype of RCC associated with poor prognosis, high recurrence rates, and a significant resistance to a variety of systemic treatments.

Case Report: Here, it is reported that the first case of a sRCC with local recurrence in a 62-year-old female patient with BHDS. This patient was successfully treated with a partial robotic nephrectomy and a re-resection of the tumor recurrence resulting in good short-term oncological outcomes.

Conclusions: Robotic partial nephrectomy for sRCC, and robotic re-resection for locally recurrent sRCC in BHDS patients is a feasible treatment strategy associated with good short-term oncological outcomes. Due to the high risk of local and distant recurrences in sRCC cases, a lifelong follow-up with regular imaging is recommended.

Abbreviations: BHD: Birt-Hogg-Dubé; FLCN: Folliculin; MRI: Magnetic Resonance Imaging; GIST: Gastro-Intestinal Stromal Tumor; (s)RCC: (Sarcomatoid) Renal Clear Cell Carcinoma.

Keywords: Birt-Hogg-Dubé; Renal clear cell carcinoma; Kidneys; Lesion; Sarcomatoid; Nephrectomy; Metastasis.

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Introduction

Birt-Hogg-Dubé syndrome (BHDS) is a rare autosomal dominant disorder caused by constitutional mutations in the folliculin (FLCN) gene. The FLCN gene is a tumor suppressor gene that encodes for the FLCN protein. BHDS is usually diagnosed during the third decade of life.

The typical clinical manifestation of BHDS consists of multiple fibrofolliculomas (benign hair follicle tumor), trichodiscomas, and acrochordons (skin tags). Furthermore, patients with BHDS are more prone to developing renal clear cell carcinoma (RCC), lung cysts, and spontaneous pneumothorax [1-3]. Notably, Menko proposed a set of diagnostic criteria for BHDS that, among other things, includes the development of kidney cancer before the age of 50 [4]. Typically, this tumor is either multifocal or bilateral, and contains the characteristic and the unique mixed pattern of chromophobe cancer as well as an oncocytoma.

Due to the increased risk of kidney cancer, annual follow-up with magnetic resonance imaging (MRI) and ultrasound, or abdominal CT-scan every three to five years is recommended as of the age of 20 in patients diagnosed with BHDS.

Case report

A 62-year-old female patient, previously diagnosed with BHDS, was diagnosed with a mass on the right kidney in 2019 for which a partial robotic nephrectomy was performed. Histopathological analysis of the resected specimen confirmed the diagnosis of a

sarcomatoid renal clear-cell carcinoma (sRCC), pT3aN0Mo, Fuhrman grade 4. After resection no adjuvant treatment was necessary, and a strict follow-up regimen was initiated. During a follow-up abdominal CT-scan two years after surgery, a 12-mm solid tissue nodule was discovered in the lower posterior pole of the right kidney. In retrospect, this lesion was already visualized on previous imaging as a small cortical irregularity.

The left kidney showed no abnormalities on imaging, and no locoregional adenopathy's, nor lung, bone, or adrenal lesions suspect for metastasis were identified. Furthermore, a suspect nodule originating from the small intestine was visualized, which increased in diameter from approximately 15 mm to 20 mm compared to previous imaging. Considering these findings, a right robot-assisted partial nephrectomy was scheduled, combined with an exploratory laparoscopy to re-sect the intestinal lesion.

The right robot-assisted partial nephrectomy was performed first, with an operative (console) time of 120 minutes. A standard robotic configuration [5,6] was utilized, with four robotic arms and a 12-mm assistant trocar. Estimated blood loss was 50 ml, and no intraoperative complications were reported. The surgical technique of choice was tumor enucleation, and no ischemia was used during surgery. After the robotic partial nephrectomy, an exploratory laparoscopy was performed, revealing a suspect lesion on the terminal ileum and cecal floor. Both lesions were resected simultaneously by a laparoscopic right hemicolectomy.

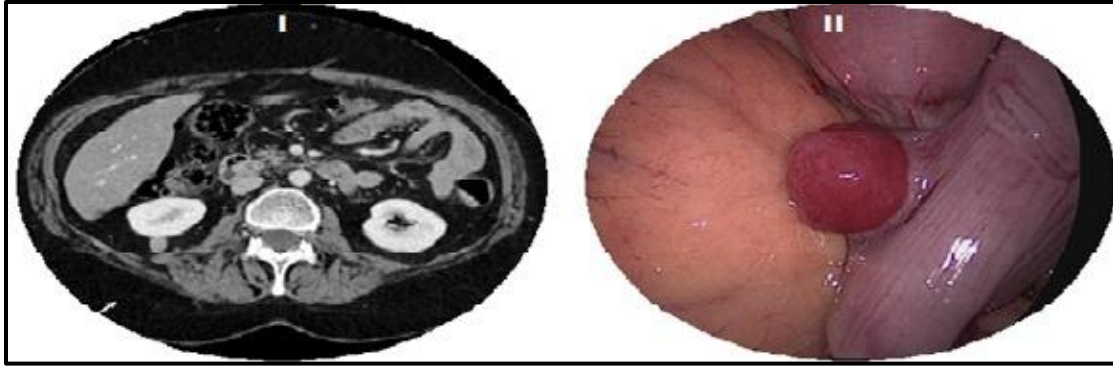


Figure A: Abdominal CT scan 2years after the initial partial nephrectomy showing a new mass of 12mm in the lower posterior pole of the right kidney suspect for a local recurrence.

Figure B: A suspect nodule in the small intestine on exploratory laparoscopy.

Histopathological examination of the right partial nephrectomy specimen revealed a RCC of 2.3 cm, extending into the peri-renal fatty tissue, with negative surgical margins. The tumor was surprisingly cellular, with scattered groups of large cells and a clear to slightly eosinophilic cytoplasm and centrally located enlarged nuclei. Spindle-shaped tumor cells, as well as monstrous cells with strongly enlarged and irregular nuclei, were observed. These atypical cells were positive for melan-A and caldesmon staining, as well as EMA immunohistochemistry. These histopathological findings are consistent with an sRCC, Fuhrman grade 4, pT3aN0M0. The histopathological examination was similar to that of the sRCC described in 2019, as such this can be considered a recurrence of the previously resected sRCC. The histopathology report of the right hemicolectomy revealed a small diverticulum on the cecal floor which showed no signs of malignancy, whereas the lesion resected from the small intestine was a gastro intestinal stromal tumor (GIST) of 2.2 cm. The spindle-shaped cells infiltrated the muscularis propria of the intestinal wall and reached up to the serosal surface without

breaching it. Additional immuno-histochemical examination showed that the spindle-shaped cells were CD34, CD117 and DOG-1 positive. Due to its small size and limited mitotic activity (less than 1 mitosis per 50 high magnification fields), it was consistent with a GIST of low malignant potential. Postoperatively, the patient developed pneumonia which responded well to iv-antibiotics (Clavien-Dindo 2 complication). The patient was discharged home on post-operative day five. One month after surgery, blood tests revealed a serum creatinine level of 0.70 mg/dl, corresponding to an eGFR of 85 ml/min/1.73 m². Genetic counselling and frequent follow-up visits were scheduled.

During the last follow up, visit six months after surgery, the patient had a normal renal function, and no evidence for local or systemic recurrence was found on imaging.

Discussion and literature review

Overall, RCC is the most common malignant epithelial tumor originating from the kidney in adults [7]. The three major subtypes of RCC

are clear cell RCC, papillary RCC, and chromophobic RCC, accounting for 75%, 15%, and 5% of all renal neoplasm, respectively [7]. sRCC is now recognized as a form of differentiation that can occur with any histologic RCC subtype, but the pathogenesis of sarcomatoid clones is not yet completely understood [7-9].

sRCC is mainly characterized by spindle-shaped mesenchymal cells on histopathological analysis. The frequency of sarcomatoid transformation in RCC's is approximately 1-13%. Although sarcomatoid transformations are rare, their presence is important because of the association with a poorer prognosis, higher local and distant recurrence rates, shorter overall survival, and a relative resistance to various systemic treatments. Patients presenting with primary and localized sRCC have a 2-year and 5-year survival rate of only 25-40% and 14-22%, respectively. Patients with metastatic sRCC have a very poor prognosis, with a median overall survival of four to nine months after diagnosis [7-12].

The clinico-pathological features of 7 patients with an RCC and a sarcomatoid component found in recent medical literature are described in Table 1. There were no reports found on sRCC in patients with BHDS. The median age of patients with a sRCC was 64 years (range 59, 82), and 86% (n=6) of patients were female. The most common site of metastasis of a sRCC is the lung (29%), whereas other reported sites were the iliac fossa, lymph nodes, skull, liver, and small intestine. The most commonly used treatment strategy for a sRCC is radical nephrectomy. Although patients with sRCC

usually have a poor response to systemic treatment [13], recent data shows a potential benefit from immune-checkpoint inhibitors [14,15].

It is reported that the use of sunitinib (25 mg orally, once daily for 2 weeks on and 1 week off) or axitinib (5 mg, twice daily) was unsuccessful in metastatic sRCC, but treatment with nivolumab (240 mg, IV once every 2 weeks) might be beneficial, with some patients achieving complete response to therapy [16]. There has been a report of the successful use of cabozantinib after sunitinib failure in recurrent metastatic sRCC [17]. A stable disease in a diffuse metastatic sRCC case with the mammalian target of rapamycin (mTOR) inhibitor everolimus (10mg/day) was achieved [18].

This is to the best of one's knowledge, the only documented case of (recurrent) sRCC in a patient with BHDS, and the only case successfully treated with a robotic partial nephrectomy and robotic re-resection.

Conclusion

In this case report we present the successful treatment of a sRCC and a sRCC recurrence in a 62-year-old patient with BHDS.

The findings confirm that partial robotic nephrectomy, and robotic re-resection of recurrent sRCC is a feasible treatment strategy for sRCC and locally recurrent sRCC with favorable short-term oncological outcomes. This case also underlines the importance of lifelong follow-up with regular imaging in sRCC cases because of the high risk for recurrences and metastasis, and the importance of early re-intervention.

Author	Age year/sex	Greatest dimension (cm)	Fuhrman nuclear grade	Primary treatment	Sarcomatoid component	Site of metastasis	Follow-up
Boustany, et al.	59/F	7	4	Laparoscopic radical nephrectomy	Atypical spindle cell	Right ilica fossa and subcutaneous Excision	Alive 3 years after diagnosis.
Gupta, et al.	64/F	15.5	NA	Radical nephrectomy, right	Pleomorphic cells, irregular nuclei, moderate pale cytoplasm with spindle cells	Supraclavicular lymph node	Development of Paraneoplastic Pemphigus
			Fuhrman grade 4			Mature adrenal galioneuroma with myelolipoma	
Tomioka, et al.	82/M	6.3	NA	Laparoscopic radical nephrectomy, right	Spindle cell component	3 months after surgery: Bilateral Lung Metastasis	ANED after 20 months
Yaegashi, et al.	62/F	13	pT3bpN2cM1	Radical nephrectomy, left	NA	Lung, skull and liver. Local recurrence	Alive after 71 months
Liao, et al.	65/F	NA	pT3aN1	Radical nephrectomy, left	Spindle cell	Small intestine	Death due to rapid disease progression 19months after surgery
Present case	62/F	2.3	pT3aNxMx	Robotic partial nephrectomy, right	Spindle cells	None, local recurrence	ANED after 10 months

Table 1: Clinicopathological features of 7 clear cell renal carcinomas with sarcomatoid component.

Legends: F-Female; M-Male; NA-Not Available; CHT-Chemotherapy; ANED-Alive with No Evidence of Disease; MTX-Metastasis.

Ethics approval and consent to participate

Every author has stated that they have no competing interests. Protocols used in any study involving human subjects adhered to the 1964 Helsinki Declaration and its subsequent amendments, as well as similar ethical standards, and were approved by the institutional research committee (IRB approval number 93/2012/U/Oss).

Consent for publication

The patient gave written informed consent for the publication of this case study and the relevant photos.

Authors' contribution

Louise Callens, Louise Wittouck, Kobe Van Hove and Tom Vandaele contributed equally to this article.

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