Metastatic Follicular Thyroid Cancer in a Patient with Birt-Hogg-Dubé Syndrome

Elisa K. Bongetti[1], Rajesh Raj[1], Duncan R. Cooke[1], Mathew C. Mathew[1]

1. Launceston General Hospital, Launceston, Tasmania, Australia

Correspondence: Dr. Elisa Bongetti, Launceston General Hospital, Charles Street, Launceston, Tasmania, Australia 7250, elisabongetti@gmail.com +613 6700 6700

No conflicts of interest to declare

Author contributions:

EKB: Oversaw the synthesis of the manuscript and review of relevant literature

RR: significant contribution towards editing of the manuscript

DC: significant contribution towards editing of the manuscript

MM: significant contribution towards editing of the manuscript

Key Words: Neoplastic Syndromes, Hereditary, Birt-Hogg-Dube Syndrome, renal replacement therapy, Thyroid Neoplasms, Kidney Neoplasms

Key Clinical Message

Birt-Hogg-Dubé Syndrome predisposes to renal cell carcinoma but it is unclear whether it is also associated with thyroid cancer. Clear screening guidelines are imperative, particularly given patients' increased requirement for renal transplantation.

Abstract

A patient with Birt-Hogg-Dubé Syndrome (BHDS) developed metastatic follicular thyroid cancer, which until now has never been described in someone with BHDS. Thyroid cancer is not currently recommended for screening with BHDS. This case presents implications for future guidelines and planning for renal transplant in patients with this condition.

Case History

A forty-five-year-old woman was detected to have bilateral renal masses on computed tomography (CT) (2 cm in diameter left and 3.6 cm in diameter right) when being investigated for lower abdominal pain. The patient was previously well, with no significant past medical history and was not taking regular medications. There was no known family history of malignancy or kidney disease. Angiography demonstrated normal renal vasculature but peripheral enhancement of the renal masses. The patient underwent left partial nephrectomy and a biopsy-proven chromophobe renal cell carcinoma was excised. Three months later she had a right partial nephrectomy. Intra-operatively it was discovered there were in fact two different lesions; a benign oncocytic tumour and a second, hybrid oncocytic/chromophobe tumour (95% oncocytic, 5% chromophobe). Following her second partial nephrectomy the patient suffered irretrievable kidney injury and was commenced on long-term intermittent haemodialysis thrice a week.

The following year the patient was referred for genetic counselling to consider whether the occurrence of bilateral renal tumours was secondary to a genetic disorder. During this

consultation, it was noted on examination that she had multiple skin tags on her neck and chest. The patient was tested for the Birt-Hogg-Dube Syndrome (BDHS) with genetic testing for the disease-causing variant in the *folliculin (FLCN)* gene. Results from this testing was unable to confirm a diagnosis of BHDS. Nevertheless, it was recommended her sons receive screening with renal tract ultrasound from age thirty, every five years. The patient remained stable for two years, receiving thrice weekly haemodialysis at a satellite unit.

Investigations

The patient was subsequently considered for renal transplantation. Her case was reviewed by a team of specialist renal transplant physicians and surgeons, and it was recommended she undergo a nephrectomy to remove remaining renal tissue to minimise the risk of future malignancy. The surgery was complicated by splenic capsular tear, left adrenalectomy and partial pancreatectomy. She suffered severe hypovolaemic shock which required resuscitation in the intensive care unit but recovered and was later discharged following a prolonged admission to continue ongoing regular haemodialysis.

Additional investigations were undertaken to assess the patient for renal transplant. CT of the chest demonstrated bilateral pulmonary cysts. These cysts were asymptomatic and associated with normal lung function testing. Specialist respiratory and surgical opinions were sought, and no intervention was advised as the risk for pneumothorax was deemed low. Further genetic testing undertaken using multiplex ligation-dependent probe amplification testing in Germany, which revealed a deletion in major functional parts of *folliculin* gene in exon 14. Based on this information, a formal diagnosis of BHDS was made.

During an outpatient clinic appointment a large left thyroid nodule on examination. Ultrasound-guided fine needle aspiration of the mass demonstrated highly atypical epithelial proliferation, suspicious for thyroid follicular neoplasm. She had a total thyroidectomy and left neck

dissection to remove a 60mm, poorly differentiated follicular thyroid carcinoma. The patient was treated with liothyronine tablets and an I^{123} scan did not demonstrate residual thyroid tissue in the neck.

Outcome and follow-up

Six months following her surgery, the patient reported severe back pain. CT showed multiple nodules throughout the lungs and lytic lesions in T8 and T12 vertebra. Magnetic resonance imaging confirmed metastases to T1, T2, T9, L1. Biopsy of a lung lesion confirmed metastatic follicular thyroid carcinoma. The patient received palliative lenvatinib, an oral multiple kinase inhibitor, and continued to live an active life. She survived for 15 months on this therapy whilst still receiving thrice-weekly haemodialysis. She subsequently died from complications of her metastatic disease.

Discussion

BHDS an extremely rare condition caused by a germline mutation in the tumour suppressor *folliculin (FLCN)* gene of which greater than 150 disease-causing variants have been discovered [1]. BHDS predisposes to chromophobe renal cell carcinomas, benign oncocytic renal tumours, hybrid oncocytic renal tumours, pulmonary cysts, spontaneous pneumothorax and cutaneous fibrofolliculomas [2]. Thirty percent of patients with BHDS develop renal cell carcinoma (RCC), however it is unusual for thyroid cancer to occur in association with the syndrome [3]. Current recommendations for routine screening in patients with BHDS do not include thyroid examination or imaging [2]. To our knowledge, a patient with BHDS has never undergone solid organ transplantation. This case highlights potential challenges encountered for patients with hereditary renal cancer syndromes.

RCC is uncommon and usually attributable to sporadic synchronous renal cell carcinoma, as only 2-5% of renal cell carcinomas are believed to be inherited [1]. Up to five percent of patients

with RCC have bilateral disease, and survival is similar to unilateral disease [4]. Differential diagnoses for bilateral RCC include metastatic disease and genetic syndromes [4]. Lymphoma, lung cancer, melanoma have been found to be the three most common primary malignancies that metastasized to kidneys [4]. Renal metastases are invariably associated with advanced malignancy and other sites of metastatic disease. Genetic syndromes include Von-Hippel-Lindau disease, Tuberous Sclerosis, Hereditary papillary RCC and BHDS [5]. These syndromes are rare; fewer than five percent of cases of bilateral RCC is due to hereditary renal cancer syndrome [4].

In the present case, a patient with BHDS developed metastatic follicular thyroid cancer. There are reports of clear cell and papillary thyroid cancers occurring in patients with BHDS [2,6]. To our knowledge, however, this is the first reported case of follicular thyroid cancer with BHDS.

Currently, screening for thyroid cancer in BHDS is not included in recommendations for surveillance [2]. Guidelines suggest abdominal imaging every 36 months for life utilising computerised tomography or magnetic resonance imaging to monitor for renal cancers [2]. Pulmonary assessment prior to any surgeries is also recommended due to risk of pulmonary cysts and spontaneous pneumothorax [2].

Patients with hereditary cancer syndromes who are being considered for solid organ transplantation require extensive screening and surveillance for malignancy to avoid devastating outcomes [3]. In patients with Von-Hippel Lindau syndrome who have undergone renal transplantation following bilateral nephrectomies had similar patient survival to aged-matched transplant recipients without the genetic condition [7]. Solid organ transplantation in patients with hereditary cancer syndromes is therefore feasible, but as this case reinforces, an individualised approach to screening for other cancers is to be considered.

References

1. Haas NB, Nathanson KL. Hereditary kidney cancer syndromes. *Adv Chronic Kidney Dis*. 2014;21(1):81-90.
2. Schmidt LS, Linehan WM. Molecular genetics and clinical features of Birt-Hogg-Dube syndrome. *Nat Rev Urol*. 2015;12(10):558-569.
3. Toro JR, Wei MH, Glenn GM, et al. BHD mutations, clinical and molecular genetic investigations of Birt-Hogg-Dube syndrome: a new series of 50 families and a review of published reports. *J Med Genet*. 2008;45(6):321-331.
4. Patel AR, Lee BH, Campbell SC, Zhou M, Fergany AF. Bilateral synchronous sporadic renal tumors: pathologic concordance and clinical implications. *Urology*. 2011;78(5):1095-1099.
5. Ho TH, Jonasch E. Genetic kidney cancer syndromes. *J Natl Compr Canc Netw*. 2014;12(9):1347-1355.
6. Dong L, Gao M, Hao WJ, et al. Case Report of Birt-Hogg-Dube Syndrome: Germline Mutations of FLCN Detected in Patients With Renal Cancer and Thyroid Cancer. *Medicine (Baltimore)*. 2016;95(22):e3695.
7. Goldfarb DA, Neumann HP, Penn I, Novick AC. Results of renal transplantation in patients with renal cell carcinoma and von Hippel-Lindau disease. *Transplantation*. 1997;64(12):1726-1729.