OPEN

Development of Bilateral Renal Cell Carcinoma in the Birt-Hogg-Dubé Syndrome Before and After Living-Related Kidney Transplantation

Yuko Miyazaki, MD,[1] Keiji Yoshiya, MD,[1] Gakusen Nishihara, MD,[1] Morishige Takeshita, MD, PhD,[2] and Chikao Yasunaga, MD, PhD[1]

The Birt-Hogg-Dubé (BHD) syndrome is a rare, inherited, autosomal dominant disorder that was first described by Birt et al in 1977.[1,2] It is characterized by cutaneous lesions on the face and neck, multiple pulmonary cysts, and renal cell carcinomas (RCCs).[3,4] Furthermore, renal "oncocytosis" is a specific feature of patients with BHD syndrome; these nodules are presumed to be precursor lesions to malignant tumors.[5] Renal lesions are the major cause of morbidity and mortality in BHD syndrome, and their diagnosis and management are crucial. Herein, we report a case of BHD syndrome with RCC development before and after living-related kidney transplantation. To our knowledge, this is the first report of BHD syndrome in a recipient of kidney transplantation.

CASE DESCRIPTION

A 35-y-old man was referred to our department for preemptive kidney transplantation, with his mother as a potential donor. He had a history of gross hematuria after a fever of 38 °C in his 20s and had developed proteinuria and hypertension in his 30s. He was clinically diagnosed with IgA nephropathy at the age of 33 y and was followed up by a personal nephrologist. His renal function worsened progressively; 10 y later, his creatinine level had reached 4.0 mg/dL before his first visit to our hospital. Whole-body computed tomography (CT) did not reveal any abnormal findings at that time. In April 2016, he was admitted for kidney transplantation because of an increased creatinine level (6.6 mg/dL). Physical examination on admission revealed papular lesions on the face and neck (Figure 1). Preoperative whole-body CT revealed multiple pulmonary cysts (Figure 2) and a 1.7-cm isodense mass bulging from the left kidney. Additional dynamic CT revealed early enhancement of the renal tumor, suggestive of RCC (Figure 3).

Thus, we decided on the following treatment courses. We initiated the patient on hemodialysis and performed left nephrectomy under dialysis treatment.

Histological findings of the tumor in the left kidney revealed hybrid oncocytic/chromophobe tumors (HOCTs; Figure 4A–C) without any vascular invasion or metastases to the adjacent lymph nodes.[3,6] However, multiple small nests of clear epithelial cells were remarkable besides the main tumor.

After considering the histological findings of the tumor, kidney transplantation was scheduled. Three months after nephrectomy, we performed ABO-compatible living-related kidney transplantation, with the patient's mother as the donor. He was discharged from the hospital with a creatine level of 1.5 mg/dL and without any rejection episodes or complications.

Three years later, his father was diagnosed with BHD syndrome; he had divorced his mother a decade ago. Based on the face papulae, multiple pulmonary cysts, and renal HOCTs, the patient was also diagnosed with BHD syndrome.

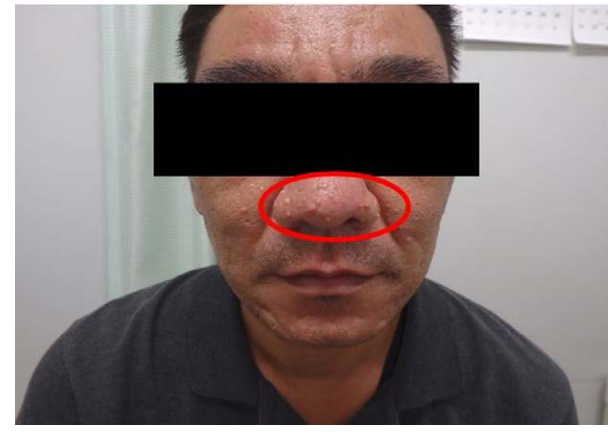

FIGURE 1. Physical findings reveal multiple white dome-shaped papules on the nose and cheek that are compatible with fibrofolliculomas.

Received 9 February 2023. Revision received 28 April 2023.

Accepted 3 May 2023.

[1] *The Kidney Center, Saiseikai Yahata Hospital, Kitakyushu, Japan.*

[2] *The Department of Pathology and Laboratory Medicine, Saiseikai Yahata Hospital, Kitakyushu, Japan.*

The authors declare no funding or conflicts of interest.

K.Y. and G.N. participated in the performance of the research. M.T. participated in data analysis. C.Y. participated in the performance of the research and in the writing of the article.

Correspondence: Yuko Miyazaki, MD, The Kidney Center, Saiseikai Yahata Hospital, 5-9-27 Harunomachi, Yahata Higashi-ku, Kitakyushu 805-0050, Japan. (yuko.miyazaki36@gmail.com)

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001502

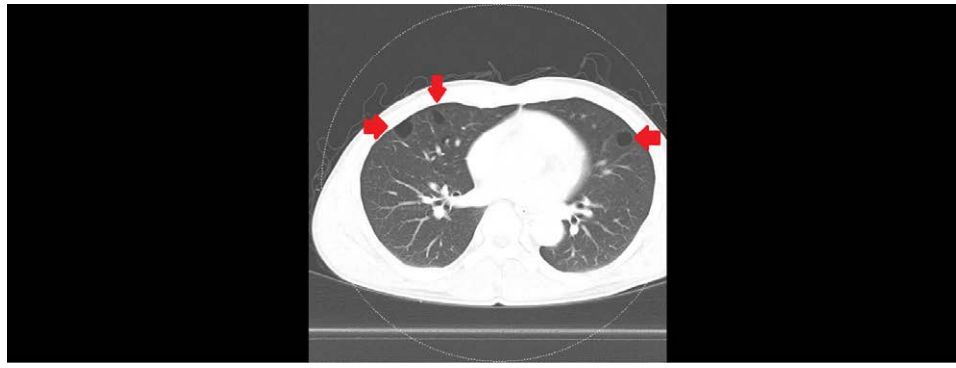

FIGURE 2. Chest computed tomography reveals bilateral cysts in various shapes and sizes, located predominantly within the lower lobes.

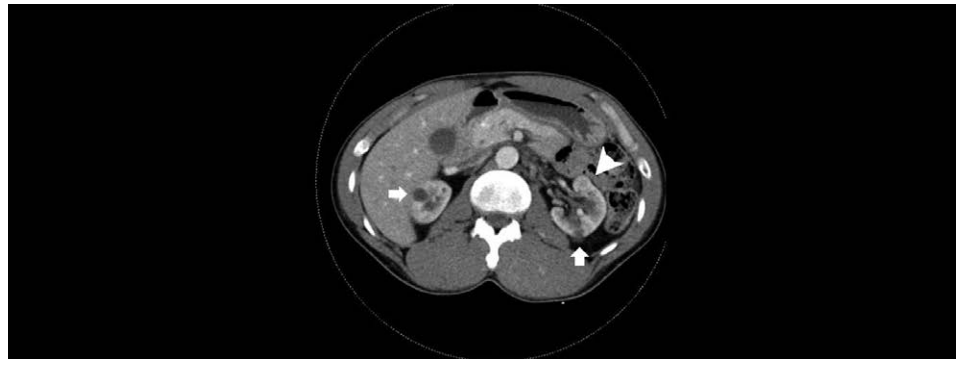

FIGURE 3. At the first admission, enhanced abdominal computed tomography revealed a 1.7-cm solid lesion in the left kidney (arrow head), suggestive of renal cell carcinoma. Multiple cystic lesions are also noted (arrows).

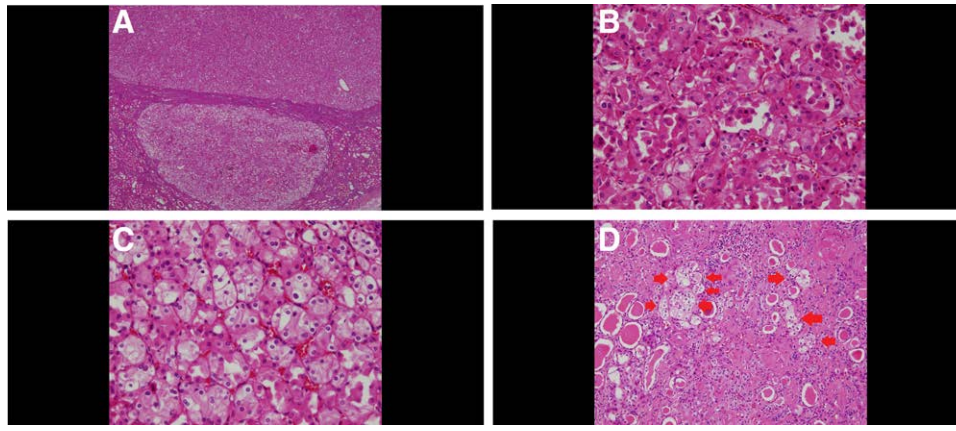

FIGURE 4. Pathological findings of the renal tumor. The tumor was considered an oncocytic hybrid tumor, composed of both chromophobe renal cell carcinoma and renal oncocytoma. A, Left nephrectomy before kidney transplantation (low-power view; hematoxylin and eosin staining). The lesion had well-defined boundaries and was composed of an eosinophilic nodule (upper panel) and an adjacent peripherally clear nodule (lower panel). B, Upper nodule in (A) (high-power view; hematoxylin and eosin staining). The nodule shows solid-tubular growth of tumor cells with eosinophilic and granular cytoplasm. C, Lower nodule in (A) (high-power view; hematoxylin and eosin staining). The nodule shows a cord-like growth of tumor cells with clear cytoplasm, round nuclei, and perinuclear halo. D, Right nephrectomy after kidney transplantation (low-power view; hematoxylin and eosin staining). Multiple clear cell foci are observed in the renal parenchyma (arrows); these are considered precursor lesions of renal cell carcinomas. The surrounding renal tissue has a thyroid-like appearance.

Ultrasonography revealed a 1.2-cm mass lesion in the right kidney; followed up by annual ultrasound or CT imaging.

Five years after transplantation, follow-up CT revealed that the mass had grown to 1.6 cm; it was strongly suspected to be RCC. Right nephrectomy was performed, and histological examination revealed HOCTs and multiple clear cell foci, similar to those in the left kidney that had been removed previously (Figure 4D). The postoperative course has been excellent without recurrence for 1 y to date.

DISCUSSION

The exact prevalence of BHD syndrome in Japan is unknown. It is characterized by cutaneous lesions, pulmonary cysts with or without spontaneous pneumothorax, and RCC

of diverse morphological types.[7] In 2002, it was reported that the syndrome is caused by a mutation in the *FLCN* gene (a tumor suppressor gene located on the short arm of chromosome 17).[8]

The clinical picture of BHD syndrome is variable, with cutaneous lesions, pulmonary cysts, and pneumothorax observed in up to 90%–92%, 90%, and 24%–38% of the cases, respectively.[8]

Approximately 30% of the patients with BHD syndrome develop renal tumors, which are typically bilateral and multifocal and appear simultaneously or metachronously. The median age at tumor diagnosis is 46 to 50 y. The most common tumors are hybrid oncocytic tumors (with features of oncocytomas and chromophobe histological cell types [50%]), chromophobe RCC (34%), and oncocytomas (9%). Clear cell and papillary tumors have been described; however, they make up for <10% of BHD renal tumors.[4,8,9]

The odds ratios for renal tumors in BHD syndrome–affected family members were reported to be 6.9 (95% confidence interval, 1.5-31.6) after adjusting for age and approximately 9.0 after considering other risk factors (sex, smoking status, hypertension, and body mass index).[10]

Once the diagnosis of the BHD syndrome is established, serial baseline chest and abdominal imaging should be performed. Chest CT identifies cysts within the lung or occult pneumothorax. Abdominal CT and MRI with intravenous contrast enable the best visualization of the anatomic details of the kidneys as well as the characterization of cystic or solid renal lesions.

The approach for managing renal lesions depends on size, location, and growth rate of lesions; number of tumors; and the patient's general condition. Surgical resection is generally recommended once a solid lesion (or a solid portion in a mixed lesion) exceeds the 3-cm diameter threshold. Each kidney is considered individually; surgical management is recommended only for kidneys with a dominant tumor exceeding the 3-cm threshold.

BHD-associated tumors are most often amenable to nephron-sparing surgery, which can help prevent chronic renal insufficiency in affected individuals. Radical nephrectomy should be reserved only for cases in which partial nephrectomy results in an inferior oncological outcome or a nonfunctioning kidney remnant.[11,12]

However, we performed a radical nephrectomy in the present case because our patient (diagnosed with BHD syndrome) was a transplant recipient; these patients are generally at an increased risk of developing malignancies following immunosuppressive therapy.[13,14]

Our patient developed left and right renal cancer before and after kidney transplantation, respectively. Pathological findings revealed that both the left and right RCCs were HOCTs.

Before kidney transplantation, we assumed that the development of the left RCC was based on acquired cystic kidney disease; however, we should have suspected BHD syndrome based on the histological findings. Furthermore, because BHD syndrome is a genetic disease, the use of immunosuppressants may have been unrelated to the progression of the second tumor. Thus, we reasonably conclude that bilateral native nephrectomy should be performed at the time of diagnosis of BHD syndrome in the context of ESKD/hemodialysis.

In summary, we report a unique case of BHD syndrome with RCC development, both before and after living-kidney transplantation. To our knowledge, this is the first report on a patient with BHD syndrome who underwent living-related kidney transplantation.[15] Because the use of immunosuppressants after transplantation may impact cancer progression, it is necessary to check the patient's family history before transplantation and consider a diagnosis of BHD syndrome if the patient presents with cutaneous lesions and pulmonary cysts.

ACKNOWLEDGMENTS

The authors would like to thank Editage (www.editage.com) for English language editing.

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review upon request.

REFERENCES

1. Birt AR, Hogg GR, Dube WJ. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. *Arch Dermatol*. 1977;113:1674–1677.
2. Daccord C, Good JM, Morren MA, et al. Birt-Hogg-Dube syndrome. *Eur Respir Rev*. 2020;29:200042.
3. Adley BP, Smith ND, Nayar R, et al. Birt-Hogg-Dube syndrome: clinicopathologic findings and genetic alterations. *Arch Pathol Lab Med*. 2006;130:1865–1870.
4. PDQ Cancer Genetics Editorial Board. Birt-Hogg-Dube syndrome (PDQ®): Health Professional Version. In: *PDQ Cancer Information Summaries*. Bethesda, MD: National Cancer Institute; 2002.
5. Schmidt LS, Linehan WM. Molecular genetics and clinical features of Birt-Hogg-Dube syndrome. *Nat Rev Urol*. 2015;12:558–569.
6. Furuya M, Hasumi H, Yao M, et al. Birt-Hogg-Dube syndrome-associated renal cell carcinoma: histopathological features and diagnostic conundrum. *Cancer Sci*. 2020;111:15–22.
7. Furuya M, Nakatani Y. Pathology of Birt-Hogg-Dube syndrome: a special reference of pulmonary manifestations in a Japanese population with a comprehensive analysis and review. *Pathol Int*. 2019;69:1–12.
8. Oliveira RC, Tavares E, Sousa V, et al. Birt-Hogg-Dube syndrome: awareness is important!. *BMJ Case Rep*. 2017;2017:bcr2017221022.
9. Ather H, Zahid N. Recurrent renal cancer in Birt-Hogg-Dube syndrome: a case report. *Int J Surg Case Rep*. 2018;42:75–78.
10. Zbar B, Alvord WG, Glenn G, et al. Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dube syndrome. *Cancer Epidemiol Biomarkers Prev*. 2002;11:393–400.
11. Stamatakis L, Metwalli AR, Middelton LA, et al. Diagnosis and management of BHD-associated kidney cancer. *Fam Cancer*. 2013;12:397–402.
12. Pavlovich CP, Grubb RL 3rd, Hurley K, et al. Evaluation and management of renal tumors in the Birt-Hogg-Dube syndrome. *J Urol*. 2005;173:1482–1486.
13. Frasca GM, Sandrini S, Cosmai L, et al. Renal cancer in kidney transplanted patients. *J Nephrol*. 2015;28:659–668.
14. Kleine-Dopke D, Oelke M, Schwarz A, et al. Renal cell cancer after kidney transplantation. *Langenbecks Arch Surg*. 2018;403:631–641.
15. Coutinho J, de Sa J, Teixeira FC, et al. Renal transplantation in Birt-Hogg-Dube syndrome: should we? *BMC Nephrol*. 2018;19:267.