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Frequency of Birt-Hogg-Dubé Syndrome in Patients with Renal Tumor Using only Chest Computed Tomography Images

Motoki Sakuraba[1*], Shinichi Kusudo[4], Hiroaki Usubuchi[2], Hiroshi Tanaka[3], Akihiko Tanaka[1]

[1]*Department of General Thoracic Surgery, Sapporo City General Hospital, Japan*

[2]*Department of Radiology, Sapporo City General Hospital, Japan*

[3]*Department of Urology, Sapporo City General Hospital, Japan*

[4]*Department of Respiratory Medicine, Sapporo Central Hospital, Japan*

Corresponding Author: Motoki Sakuraba**, *Department of General Thoracic Surgery, Sapporo City General Hospital, Japan.* ***Email: *m-sakuraba@hotmail.co.jp*

Abstract

Background: *Patients with Birt-Hogg-Dubé syndrome (BHDS) are at high risk of developing renal carcinomas. We determined the frequency of BHDS among patients who underwent surgery for renal tumors using only chest computed tomography (CT) scan.*

Methods: *Between January 2010 and December 2016, a total of 427 Japanese patients were enrolled. One surgeon, 1 physician and 1 radiologist familiar with BHDS each independently reviewed every patient's chest CT scan. Definitive cases of BHDS were those diagnosed by all 3 reviewing physicians.*

Results: *Of 427 patients, BHDS was definitively diagnosed in only 1 case (0.2%). This patient with definitive BHDS had papillary renal cell carcinoma, and genetic analysis provided the BHDS diagnosis. The majority of renal tumors in patients with BHDS are chromophobe renal cell carcinomas.*

Conclusions: *BHDS was definitively diagnosed in only 1 (0.2%) of 427 patients with renal tumors. Physicians should be aware that the presence of pulmonary cyst on the chest CT necessitates asking the patients with renal tumors about family history and history of pneumothorax, and skin lesion. Patients strongly suspected of having BHDS should undergo genetic testing for mutations in the folliculin gene.*

Keywords: *renal tumor, pulmonary cyst, Birt-Hogg-Dubé syndrome, chest CT image*

Abbreviations: *BHDS: Birt-Hogg-Dubé syndrome, CT: computed tomography*

1. Introduction

Birt-Hogg-Dubé syndrome (BHDS) is a hereditary disorder characterized by 3 findings: repeated pneumothoraces associated with pulmonary cysts, skin lesions such as fibrofolliculoma, and kidney tumor. Chest surgeons often treat patients with pneumothorax. In patients with small lung cysts, pneumothorax does not develop, and patients will not show signs of disease, so any findings cannot support a diagnosis of BHDS. The purpose of this study was to determine the frequency of lung cysts characteristic of BHDS on chest computed tomography (CT) images of patients undergoing surgery for renal tumor at the Department of Urology in our hospital.

2. Materials and Methods

Between January 2010 and December 2016, a total of 427 patients who underwent renal tumor surgery at the Department of Urology at Sapporo City General Hospital were enrolled.

One surgeon, 1 physician and 1 radiologist familiar with BHDS independently reviewed each chest CT image. We extracted cases with findings suggesting BHDS, and defined definitive cases as those diagnosed by all 3 reviewing physicians. CT findings characteristics of BHDS consisted of the following: 1) distribution of pulmonary cysts mainly in the lower lung fields and on the pleural surface of the mediastinum and/or diaphragm; 2) multifocal pulmonary cysts with irregular instead of round shapes; and 3) pulmonary cysts abutting or including the proximal portion of lower pulmonary arteries or veins. This retrospective study was approved by the ethics committee of our institution (IRB No. H30-059-537, February 20th, 2019).

3. Results

There were 288 male and 139 female patients with a mean age of 64.8 years age (range 33 to

95 years). Renal tumor classifications are shown in Table. 1. The majority of patients had clear cell renal carcinoma, and 15 patients had chromophobe renal cell carcinoma. No patients had oncocytoma, and 14 patients had angiomyolipoma. Of 427 patients, BHDS was definitively diagnosed in 1 (0.2%). Table 1 shows the classifications of renal tumor according to the definitive diagnosis of BHDS. The BHDS case was 67-year-old woman who underwent renal resection for papillary renal cell carcinoma. Chest CT findings showed irregularly shaped pulmonary cysts on the interlobar surface of the lungs and pleural surface of the mediastinum and around the hilar vessels (Figures 1,2). However fibrofolliculomas were not found on her face. Genetic analysis showed an insertion in the folliculin gene which confirmed the diagnosis of BHDS.

Table1. *Diagnosis of Birt-Hogg-Dubé Syndrome on chest computed tomography images according to type of renal tumor*

	Total enrolled	Definitive
Clear cell renal carcinoma	339	
Papillary renal cell carcinoma	29	1
Chromohobe renal cell carcinoma	15	
Spindle cell carcinoma	2	
Unclassified renal cell carcinoma	4	
Other	24	
Oncocytoma	0	
Hybride oncocytic/chromophobe renal cell carcinoma	0	
Angiomyolipoma	14	
Total	427	1

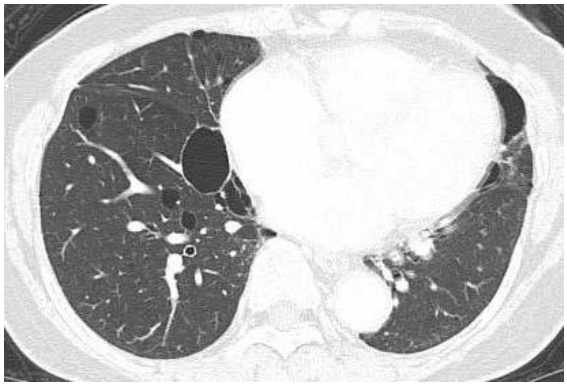

Figure1. *Chest computed tomography findings of a 67-year-old woman. Irregularly shaped pulmonary cysts are seen on the pleural surfaces of the mediastinum and around the hilar vessels*

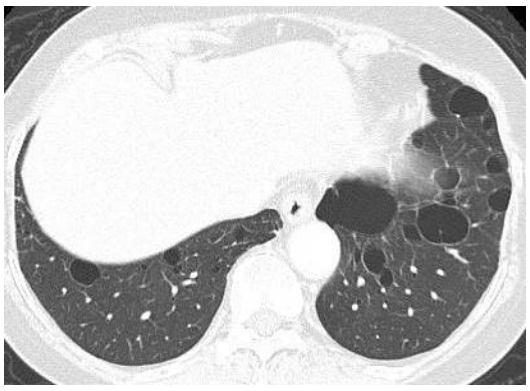

Figure2. *Chest computed tomography findings. Multifocal pulmonary cysts with irregular shapes are seen on the diaphragm.*

The majority of renal tumors in patients with BHDS are chromophobe renal cell carcinomas. In our study, there were 2 patients with chromophobe renal cell carcinomas, and they had pulmonary cysts, but definitive diagnosis of BHDS could not be made because of the small number of cysts. Case 1 was 80-year-old woman who had only two irregularly pulmonary cysts in middle lobe (Figures 3). Case 2 was 89-year-old woman who had four pulmonary cysts. Three

cysts were round-shaped cysts and located upper lobe. Only one irregularly pulmonary cyst including pulmonary vein was located in middle lobe (Figures 4).

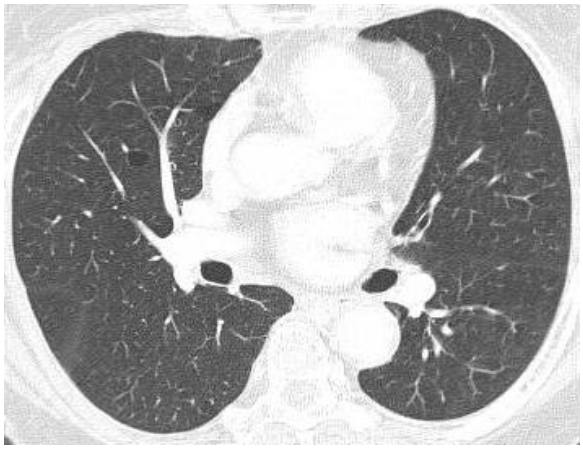

Figure3. *Chest computed tomography findings of patient with chromophobe renal cell carcinoma (Case1). Two pulmonary cysts with irregular shapes are seen only in middle lobe*

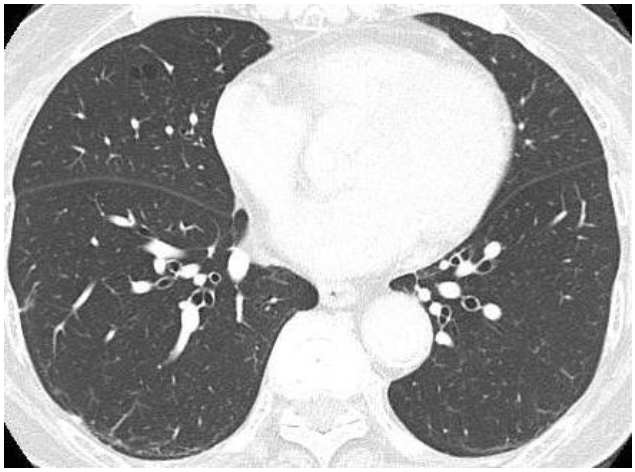

Figure4. *Chest computed tomography findings of other patient with chromophobe renal cell carcinoma (Case2). One irregularly pulmonary cyst including pulmonary vein was located in middle lobe*

4. DISCUSSION

BHDS is a rare autosomal dominant inherited genodermatosis characterized by clinical manifestations that include skin hamartomas (fibrofolliculomas, trichodiscomas, scrochordons), renal tumors (chromophobe renal cell carcinoma, oncocytoma, hybrid oncocytic /chromophobe renal cell carcinoma, papillary renal cell carcinoma), and pulmonary cysts with spontaneous pneumothorax1,2). The folliculine gene (FLCN), a tumor suppressor gene located in chromosome 17p11.2, was recently identified to be defective in patients with BHDS3). Tobino et al reported that the CT findings of patients with BHDS are multiple irregularly shaped cysts of various sizes with predominance in the lower medial lung zones. Cysts abutting or including the proximal portions of lower pulmonary arteries or veins can also be present4). Pulmonary cysts in BHDS patients are differentiated from lymphangioleiomyomatosis by their morphology and distribution5). The 3 diagnosticians independently evaluated the chest CT images of our patients with renal tumors, based on the criteria4, 5).

Pavlovich et al reported a study of 124 patients with BHDS, and found renal tumors of various tissue types in 34 (27%)6). The histopathological diagnoses were as follows: hybrid oncocytic/chromophobe (67%), chromophobe renal cell carcinoma (23%), and clear cell renal carcinoma (7%). A high proportion of patients with renal tumors have clear cell renal carcinoma, whereas chromophobe renal cell carcinomas and oncocytomas occur at low rates. In our study of patients with renal tumors, the diagnosis of BHDS was made for only1 patients (1 of 427 [0.2%]).

Among the histological types of renal tumors

affecting the patients in our study, we could only identify 1 patient with the definitive diagnosis of BHDS in our institution, which performs a large number of renal tumor surgeries on a daily basis. Our patient had papillary renal cell carcinoma and unfortunately, none of the patients with chromophobe renal carcinoma had a diagnosis of BHDS. In our study, 2 cases of chromophobe renal cell carcinoma had pulmonary cysts, but a definitive diagnosis could not be made because of the small number of cysts. Chromophobe renal cell carcinoma and oncocytoma are characteristic tumors of patients with BHDS, and our results were accounted for by the fact that both types of these tumors occur with low frequency, and the frequency of BHDS is low among patients with renal tumors.

Now two kinds of diagnosis criteria about BHDS are proposed. European BHD Consortium focuses on the disease specificity of the skin lesion. The definitive diagnosis is possible in either in following two. 1) Exanthem of the adult onset which diagnosed fibro folliculomas or trichodiscomas histo pathologically. 2) Morbid gene variation of the FLCN gene7). On the other hand, in American National Cancer Institute (NCI) group, 2) is required for the definitive diagnosis8). A genetic test is not medical service under health insurance adaptation and is carried out only in a limited research facility. The exanthema of the adult onset tends little in Japan. In addition skin disorders were not reported in the medical records. Therefore it may be limited at an opportunity to discover BHDS having high risk of kidney cancer. However, we searched a pulmonary cyst and worked for discovering BHDS from a kidney cancer operation patient this time.

This study has limitations. First, genetic testing for BHDS was not performed for every study patient, and the diagnosis of BHDS was based on the experience of 3 clinicians who were familiar with the disease. Second, a past history of pneumothorax and family history of pneumothorax were not reported in the medical records. Third, skin disorders were not reported in the medical records. Therefore, whether or not the 2 patients with chromophobe renal cell carcinoma and pulmonary cyst had BHDS remains unclear. We think that in the future, for any similar patient seen at our institution, it might be advisable to find out if the patient has a past history and positive family history of pneumothorax and skin lesions.

5. Conclusion

A total of 1 (0.2%) of 427 patients with renal tumors had definitively diagnosed BHDS. Physicians should be aware that the presence of pulmonary cyst on chest CT necessitates asking the patient about family history and a history of pneumothorax and skin disorder.

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References

[1] Birt AR, Hogg GR, and Dubé W., Hereditary multiple fibrofoliculomas with trichodiscomas and acrochordons, Arch Dermatol. 113 (12), 1674 (1977)

[2] Schmidt LS, Nickerson ML, Warren MB, Glenn GM, Toro JR, Merino MJ, Turner ML, Choyke PL, Sharma N Peterson L, Morison P, Maher ER, Walther MM, Zbar B, and Linehan WM., Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dubé syndrome. Am J Hum Genet 76 (6), 1023 (2005)

[3] Nickerson ML, Warren MB, Toro JR, Matrosova V, Glenn G, Turner ML, Duray P, Mrino M, Choyke P, Pavlovich CP, Sharma N, Walther M, Munroe D, Hill R, Maher E, Greenberg C, Lerman M, Linehan WM, Zbar B, and Schmidt LS., Mutations is a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the Birt-Hogg-Dubé syndrome. Cancer Cell 2 (2), 157 (2002)

[4] Tobino K, Gunji Y, Kurihara M, Kunogi M, Koike K, Tomiyama N, Johkoh T, Kodama Y, Iwakami S, Kikkawa M, Takahashi K, and Seyama K., Characteristics of pulmonary cysts in Birt-Hogg-Dubé syndrome: Thin-section CT findings of the chest in 12 patients. Euro J Radiol 77 (3), 403 (2011)

[5] Tobino K, Hirai T, Johkoh T, Kurihara M, Fujimoto K, Tomiyama N, Mishima M, Takahashi K, and Seyama K., Differentiation between Birt-Hogg-Dubé syndrome and lymphangioleiomyomatosis: Quantitative analysis of pulmonary cysts on computer tomography of the chest in 66 females. Euro J

Radiol 81 (6), 1340 (2012)

[6] Pavlovich CP, Grubb RL 3rd, Hurley K, Glenn GM, Toro J, Schmidt LS, Torres-Cabala C, Merino MJ, Zbar B. Choyke P, Walther MM, and Linehan WM., Evaluation and management of renal tumors in the Birt-Hogg-Dubé syndrome. J Urol 173 (5), 1482 (2005)

[7] Menko FH, van Steensel MA, Giraud S, Friis-Hansen L, Richard S, Ungari S, Norenskjold M, Hansen TV, Solly J, Maher ER; European BHD Consortium., Birt-Hogg-Dubé syndrome: diagnosis and management. Lancet Oncol 10(12), 1199(2009)

[8] Schmidt LS, Linehan WM., Molecular genetics and clinical features of Birt-Hogg-Dubé syndrome. Nat Rev Urol 12(10), 558 (2015)

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