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【 CASE REPORT 】

Birt-Hogg-Dubé Syndrome with Renal Cancer Treated as Multiple Metastases of Cancer of Unknown Primary

Natsuko Atsukawa[1,2], Toshinari Yagi[3], Chiaki Kubo[4], Katsuyuki Nakanishi[1] and Keigo Osuga[2]

Abstract:

A 60-year-old woman presented with multiple lung and bone metastases with unknown primary cancer. Chest CT images showed multiple pulmonary cysts, predominantly of the middle and lower lobes. She also had a history of pneumothorax. Four years after chemotherapy and radiation therapy, multiple hypervascular tumors eventually developed in the bilateral kidneys, suggesting the possibility of Birt-Hogg-Dubé (BHD) syndrome. Genetic testing revealed a *folliculin* mutation, which confirmed the diagnosis of BHD syndrome. When we encounter cancer of unknown primary with multiple pulmonary cysts in a patient with a history of pneumothorax, thorough imaging of the kidneys and genetic testing for BHD syndrome is necessary.

Key words: Birt-Hogg-Dubé syndrome, cancer of unknown primary, renal cancer, multiple lung cysts

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Introduction

Birt-Hogg-Dubé syndrome (BHD) is a rare autosomal dominant disease (1). It is caused by constitutional mutations in the *folliculin* (*FLCN*) gene. The disease is characterized by fibrofolliculoma, which frequently occurs on the trunk and face, multiple pulmonary cysts, pneumothorax (due to rupture of the cysts), and renal tumors (2). In nature, the renal tumors associated with BHD syndrome are multifocal, bilateral, and low-grade (3).

We herein report a case of renal carcinoma in BHD syndrome, wherein the carcinoma was treated as a cancer of unknown primary (CUP) due to the delayed appearance of renal tumors in comparison to lung and bone metastases.

Our search of the relevant literature revealed no cases of BHD syndrome treated as CUP. We therefore want to report the course of the present case with some discussion and draw the attention of treating physicians.

Case Report

A 60-year-old woman presented with a chief complaint of back pain. She had a past history of pneumothorax at around 30 years of age. She did not have a family history of pneumothorax or cancer. She was a never smoker. Her current medical history included back pain, which had persisted for one year. At another hospital, where the patient presented with back pain, a computed tomography (CT) scan revealed multiple pulmonary nodules and osteolytic lesions in the sacrum. This patient was therefore referred to the oncology department of our hospital due to CUP.

A physical examination revealed clear respiratory sounds, no obvious skin lesions, and no other notable findings. Blood biochemistry revealed no obvious abnormalities. CT revealed multiple lung nodules with suspected metastasis in both lungs and irregular multiple cysts that were predominantly located in the lower lung field (Fig. 1), and osteolytic changes indicative of metastasis to the 3rd lumbar vertebrae and the sacral vertebra (Fig. 2). The primary organ could not be identified.

Biopsy of the lung tumors was not performed due to the high risk of pneumothorax. Biopsy of the sacral osteolytic lesions was performed to identify the primary lesion. Histopathology showed relatively uniform small round cells proliferating like follicle nests or fences, indicating tissue archi-

[1]Department of Diagnostic and Interventional Radiology, Osaka International Cancer Institute, Japan, [2]Department of Diagnostic Radiology, Osaka Medical College, Japan, [3]Department of Outpatient Chemotherapy, Osaka International Cancer Institute, Japan and [4]Department of Pathology and Cytology, Osaka International Cancer Institute, Japan
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Correspondence to Dr. Natsuko Atsukawa, rad122@osaka_med.ac.jp

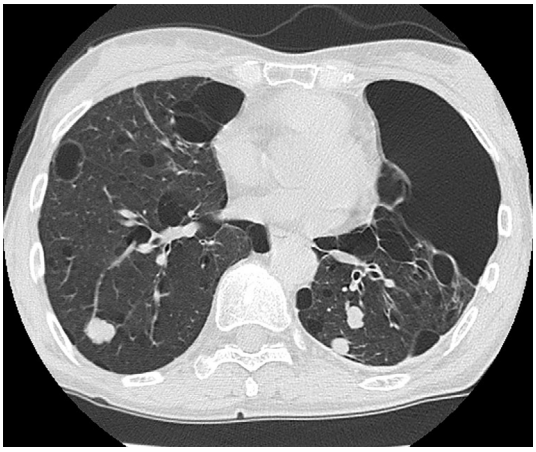

Figure 1. **Chest computed tomography. Multiple lung nodules with suspected metastasis in both lungs and irregular multiple cysts in both lungs, predominantly in the lower lung field.**

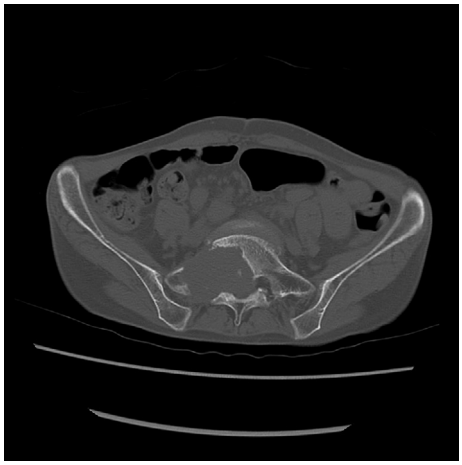

Figure 2. **Pelvic computed tomography. Osteolytic changes indicative of metastasis to the sacral vertebra.**

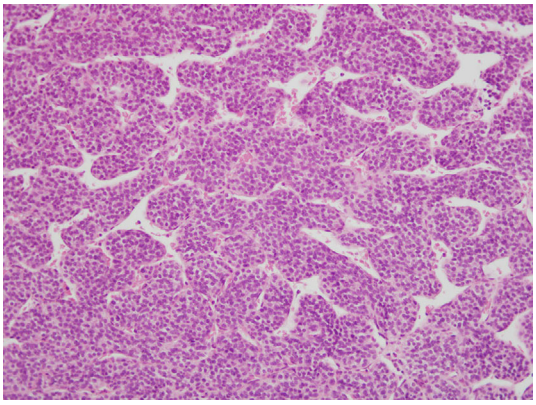

Figure 3. **Pathological findings of bone metastasis. Relatively uniform small round cells proliferate like follicle nests or fences, indicating tissue architecture mediated by sinusoidal vascular networks (Hematoxylin and Eosin staining, ×200)**

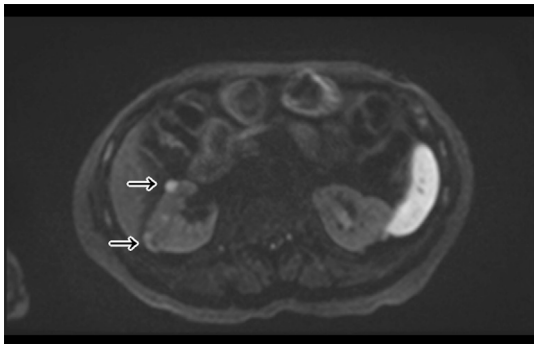

Figure 4. **Abdominal magnetic resonance imaging. Multiple renal nodules with high signal on diffusion-weighted imaging (arrows).**

tecture mediated by sinusoidal vascular networks (Fig. 3). So-called small round cell tumors, with diffuse strong positivity for cytokeratin AE1/AE3 on immunohistochemistry were observed. Based on these findings, carcinoma was considered the most likely candidate. The cell morphology was reminiscent of the mammary duct and urinary tract epithelium. However, the primary organ could not be identified.

Six courses of chemotherapy (carboplatin+nab-paclitaxel) were administered for CUP. Radiation therapy was performed to treat bone metastases located at the 3rd lumbar vertebrae and sacral vertebra. The pulmonary nodules did not change significantly from the first consultation, and the final effect was stable disease. Bone metastases did not increase after radiotherapy. Three years later, radiation therapy was performed for new bone metastasis at the 5th thoracic vertebrae.

Four years later, a nodule that gradually increased in size was detected in the spleen, and a renal tumor was pointed out on a magnetic resonance imaging (MRI) scan performed to evaluate suspected spleen metastasis. MRI revealed multiple renal nodules with high signal on diffusion-weighted imaging (Fig. 4). Considering the possibility that the primary lesion had become apparent, we performed renal dynamic CT. The CT scan revealed multiple masses with early stain-washout in the bilateral kidneys (Fig. 5). The pulmonary nodules showed a similar early stain-washout pattern (Fig. 6). We suspected multiple lung metastasis, bone metastasis, and spleen metastasis of renal cell carcinoma.

The patient was a non-smoker and had a history of pneumothorax, with multiple renal carcinoma, and multiple pulmonary cysts that were predominantly located in the middle and lower lung fields. These findings suggested BHD syndrome. To confirm BHD syndrome, an *FLCN* germ cell gene analysis was performed. A mutation in Co1533-1536 del *GATG* led to a definitive diagnosis of BHD syndrome. No renal biopsy was performed. We recommended immunotherapy with nivolumab and ipilimumab. However, the patient refused, and only follow-up was performed. The renal tumor and other metastatic tumors are slowly increasing in size.

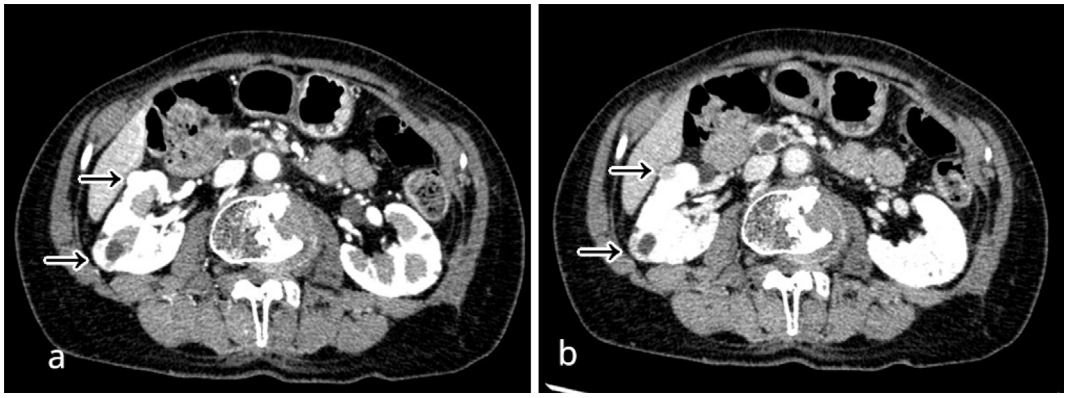

Figure 5. **Abdominal computed tomography. (a) Arterial phase. (b) Renal parenchyma phase. Multiple masses showing early stain washout in the bilateral kidneys are noted, and renal cancer is suspected (arrows).**

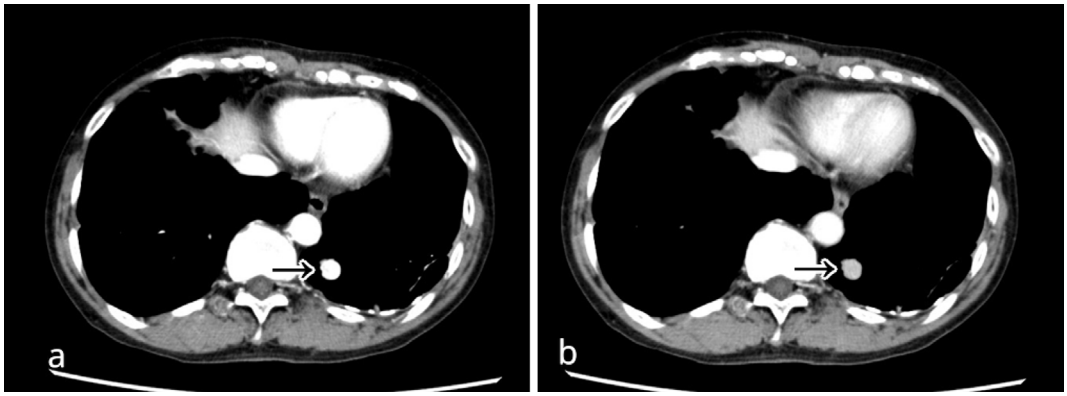

Figure 6. **Chest computed tomography. (a) Arterial phase. (b) Renal parenchyma phase. Pulmonary nodules also show a similar early stain-washout pattern (arrows).**

Discussion

BHD syndrome is a neoplastic disorder with an autosomal dominant pattern of inheritance that was first reported by Birt, Hogg, and Dubé in 1977 (1). The *FLCN* gene, which is the causative gene, is a tumor suppressor gene. It is reported that abnormalities in the folliculin protein activate mammalian target of rapamycin (mTOR), resulting in neoplastic changes (2). The disease is characterized by fibrofolliculoma, which frequently occurs on the trunk and face, multiple pulmonary cysts, pneumothorax (due to rupture of the cysts), and renal tumors. However, it is rare for Asian BHD syndrome patients to show all three symptoms of BHD syndrome. Among the 45 cases of BHD syndrome in Asians, fibrofolliculoma was reported in 29% of cases, pulmonary cysts were reported in 89% of cases, and renal tumors were reported 20% of cases (4). Pneumothorax due to BHD syndrome is most commonly observed in patients in their 20s to 40s, while renal tumors are observed in those in their 40s to 50s (5). Pulmonary cysts in BHD syndrome are characterized by the presence of multiple cysts of various sizes in contact with pulmonary arteries and veins in the predominant mediastinal portion of the bilateral lower middle lobe, as observed on chest CT, along with the presence of pulmonary vessels within the cysts (6).

In this case, no fibrofolliculoma was observed. The patient had a history of pneumothorax at around 30 years of age, significant bilateral lower lobe pulmonary cysts were also found, which led to a suspected diagnosis of BHD syndrome. In this case, intracystic pulmonary vascular invasion was also detected in some cysts, and the size of the pulmonary cysts ranged from large to small.

Renal tumors are often bilateral and multiple in BHD syndrome. The most frequent tumors are hybrids of oncocytoma and chromophobe tumor (HOCT) (67%), followed by chromophobe renal cell carcinoma (23%) and renal oncocytoma (3%) (7). In addition, clear cell renal carcinoma and papillary renal carcinoma have also been reported. In nature, the renal tumors associated with BHD syndrome are multifocal, bilateral, and low-grade; thus, it is recommended that renal tumors be followed up until they reach 3.0 cm in size (3).

This case was treated as CUP because of the delayed appearance of renal tumors in comparison to lung and bone metastases. Since the patient was diagnosed with BHD syn-

drome and the lung and renal nodules showed an early dense staining pattern on CT, we suspected that the metastatic lesions of the lung and bone were from renal cancer. However, there is a limitation in our diagnosis. BHD syndrome has also been reported to cause colorectal, thyroid, and salivary carcinoma, and considering the atypical initial pathology of this case and the fact that the renal tumor developed quite late, we cannot exclude the possible hidden existence of a primary tumor at a location other than the kidney. In addition, biopsies of the renal and lung tumors were not performed, thus the concordance of the tissue findings could not be confirmed.

Our search of the relevant literature revealed no cases of BHD syndrome of CUP. Our case suggests that a family history study, thorough imaging of the kidneys, and genetic testing for BHD syndrome are necessary when we encounter CUP with multiple pulmonary cysts that are predominantly located in the middle and lower lung fields or in a patient with a history of pneumothorax.

Conclusion

We report a case of renal cancer in BHD syndrome that was treated as CUP because of the late appearance of renal tumors four years after lung and bone metastases.

A family history study, thorough imaging of the kidneys, and genetic testing with BHD syndrome are necessary when we encounter CUP with multiple pulmonary cysts with predominantly middle and lower lung fields or a history of pneumothorax.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

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