LETTER

Birt-Hogg-Dubé Syndrome and coexistence with adrenocortical carcinoma

Dear Editor,

Birt-Hogg-Dubé syndrome (BHDS), also known as Hornstein-Krickenberg syndrome, constitutes an autosomal dominant disorder caused by mutations in the tumor suppressor gene FLCN, codifying the folliculin protein[1]. Patients manifest benign hamartomas of the hair follicle, pulmonary cysts, recurrent pneumothoraces, and are predisposed to renal cell carcinoma[2].

Cutaneous manifestations are fibrofolliculomas, trichodiscomas, and acrochordons, usually located on the face, neck, and upper trunk[2]. Lung involvement rates 90 % of patients with BHDS and includes multiple pulmonary cysts of various sizes and usually located in the mediastinum. Lung predominance is generally low, nonetheless, recurrent pneumothoraces occur. Compared to the background population, BHDS patients have a 50 times higher risk of spontaneous pneumothorax, usually resulting from pulmonary cysts rupture. Regarding BHDS-associated renal tumors, histology discloses most commonly chromophobe renal cell carcinomas and hybrid oncocytic/chromophobe tumors, both of which show a low malignant potential.

A 30-year-old female patient was examined for multiple white dome-shaped papules on her face and neck. Similar skin lesions were referred in her family history (father, brother, and paternal uncle) along with a personal and familial history of recurrent pneumothoraces.

Histology of the skin lesions showed proliferation of follicular epithelial cells encircled by fibrosis. These findings were consistent with fibrofolliculomas. Suspecting a BHDS, computerized tomography was ordered, where multiple bilateral lung cysts with central and subpleural distribution were observed. To exclude a renal malignancy, the patient underwent a Magnetic Resonance Imaging (MRI) of the abdomen, where a heterogeneous right adrenal mass of a maximum diameter of 4 cm with central necrosis was revealed. Ectopic renal cancer was suspected; therefore, successful right adrenalectomy undertaken. Hematoxylin and Eosin stained sections concluded to a tumor comprised of malignant cells folliae with central necrosis. The immunohistochemical staining showed diffuse synaptophysin expression. The findings were consistent with adrenocortical carcinoma.

Genetic screening of the patient in the Institut of Human Genetics in Munich revealed a heterozygous 2-base-pair deletion in exon 9 (c.941_942del;p.P314fs) of folliculin gene (*FLCN*), confirming the diagnosis of BHDS. No recurrence is observed three years after resection of the adrenocortical tumor, while the patient and her next of kin are screened for renal carcinoma with an annual abdominal MRI.

So far, only five published reports of adrenal tumors in BHDS patients exist. Three concerned oncocytic adrenal tumors, one non-functioning adrenocortical tumor with nonmalignant features, and one ectopic renal tumor in the adrenal gland. Furthermore, the presented case supports that adrenal tumors might be a part of the BHDS tumor spectrum.

To the best of our knowledge, many tumors, including parathyroid adenoma, breast cancer, colorectal carcinoma, and melanoma, have been reported to appear occasionally in BHDS patients. Since *FLCN* has tumor suppressor activity, we believe that a predisposition to tumors exists, and we advocate that tumor surveillance should be considered in all BHDS patients, depending on relevant symptoms.

Concluding, dermatologist involvement corroborates the diagnosis of BHDS, especially when diffuse facial papules and recurrent pneumothoraces are documented. Current detection is important for both the patients and their families who require genetic counseling.

Keywords: Birt-Hogg-Dubé syndrome, folliculin gene, *FLCN*, adrenocortical carcinoma

Conflict of interest
None declared.

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