Birt-Hogg-Dube syndrome presenting as multiple oncocytic parotid tumors

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Abstract

Mutations in FLCN cause Birt-Hogg-Dubé syndrome, an autosomal dominant disorder notable for development of cutaneous fibrofolliculomas or trichodiscomas, a variety of renal tumors, and spontaneous pneumothorax due to cystic lung changes. We present a woman referred for genetic evaluation due to bilateral parotid gland tumors, who was subsequently diagnosed with Birt-Hogg-Dubé syndrome.

Keywords: Salivary gland, Oncocytic, Warthin tumor, Oncocytosis

Introduction

BHD syndrome is an uncommon genodermatosis characterized by the presence of multiple fibrofolliculomas, trichodiscomas, and acrochordons of the skin. There is significantly increased susceptibility to renal tumors, of which about half are hybrid chromophobe/oncocytic renal cancers; about 5% are oncocytomas. Pulmonary cysts occur in the majority of adults with BHD syndrome, leading to spontaneous pneumothorax in at least a quarter of affected individuals. A longer list of tumors have been reported rarely in BHD [1]; parotid tumors have been reported several times but have not served as the sentinel lesion bringing a patient to diagnosis.

Case report

A previously healthy 45 year old Caucasian woman had a magnetic resonance scan for persistent mild hearing loss in her right ear. The cause for the hearing loss was not identified but the magnetic resonance imaging demonstrated multiple small parotid masses: a 9 mm diameter peripherally enhancing/T2 hyperintense lesion in anterolateral aspect of right parotid gland, a few additional smaller T1 hypointense nonenhancing lesions in right parotid gland and additional lesions in the superficial and deep lobes of the left parotid gland (Figure 1). Fine needle aspiration biopsies revealed a mildly hypercellular collection of epithelial cells with oncocytic differentiation and associated lymphoid aggregates; the interpretation was: suspicious for oncocytic neoplasm, favor Warthin tumor. The differential diagnosis included the spectrum of oncocytic proliferations which includes Warthin tumors, nodular oncocytic hyperplasia (nodular oncycytosis), and multiple oncocytomas of the parotid glands. The presence of lymphoid aggregates favors the diagnosis of Warthin tumors. The histologic diagnosis could not be further refined based upon the tissues obtained. Given the FNA findings and the distribution of the lesions, the plan is for observation of the parotid nodules until bothersome (size, cosmesis) and the treatment will require surgery addressing both the superficial and deep lobes of the parotid gland given the diffuse distribution of the nodules. She reported no prior history of tumors but had had several “moles” removed from her face for cosmetic reasons which were labeled only as “benign”. There was no history of spontaneous pneumothorax.

The family history was notable for maternal grandfather with prostate cancer, maternal grandmother with a bladder cancer diagnosed in her 40s and a lung cancer diagnosed in her 50s (she had smoked). A maternal uncle had a throat cancer and died at 58. The paternal family history was negative for neoplasms. Her three siblings and two children were apparently healthy.

Her physical examination was normal except for a striking number of raised, smooth, flesh-colored cutaneous papules most notable around the scalp (Figure 2) and face in a generalized distribution and around the neck accompanied by numerous acrochordons. No intraoral lesions were noted. Skin biopsies showed...
findings of fibrofolliculomas in the scalp lesions and acrochordons on the neck. Imaging of the kidneys by computerized tomography showed only a single small cyst, but the bases of the lungs showed extensive cystic changes. Mutation analysis of \( \text{FLCN} \) revealed a c.779 + 1 G > T mutation which has been reported previously in BHD syndrome. Tissue from the biopsy was not available for further studies such as loss of heterozygosity of \( \text{FLCN} \).
nutrient/energy-sensing pathways involving AMPK and mTOR and may provide a molecular mechanism for the BHD phenotype. No direct link to mitochondrial dysfunction has been proposed yet for this tumor suppressor gene but the oncocytic nature of the tumors in both kidney and now parotid gland raise this as a possibility.

Around half of BHD families recognized to date have a mutation in hot spot involving deletion (c.1285delC) or duplication (c.1285dupC) of a C nucleotide in the polycytosine tract in exon 11 of FLCN [5]. The mutation found in this patient is not in this area but has been reported previously in six individuals from two families [as IVS7 + 1] [7] and has not been reported since, per the Leiden Open Variome Database update of 2011 [https://grenada.lumc.nl/LOVD2/shared1/variants. php?select_db=FLCN&action=view_unique]. The major manifestation in these families generally appeared typical of BHD syndrome with renal tumors in five, lung cysts in six, documented fibrofolliculomas in five. Also reported was an angiofibroma, dermatofibrosarcoma protuberans, cutaneous leiomyosarcoma, and trichodiscoma. No parotid tumors were reported. Combined with the current case report, these families might be perceived as having more diverse dermatological findings than other BHD families, raising the possibility of some genotype-phenotype interaction.

Based upon the DNA diagnosis, the patient was counseled regarding autosomal dominant inheritance of this syndrome and the implications for multiple relatives, and was provided screening recommendations for typical BHD syndrome with regard to renal and pulmonary complications, and she will remain under closer surveillance for changes in the parotid tumors and for additional dermatologic findings [13].

**Consent**
Written consent for use of patient photographs were obtained.

**Competing interests**
All authors have declared that they have no competing interest.

**Author contributions**
All authors contributed to clinical diagnosis and review of the manuscript. All authors read and approved the final manuscript.

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