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Birt-Hogg-Dubé Syndrome – report of two cases with two new mutations

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Abstract

Introduction: Birt-Hogg-Dubé syndrome (BHDS) is a rare autosomal dominant genodermatosis characterized by cutaneous fibrofolliculomas and/or trichodiscomas, lung cysts, spontaneous pneumothorax and renal tumors. However, its clinical expression is highly variable. This syndrome is caused by germline mutations in the *folliculin* gene (*FLCN*) on chromosome 17p11.2.

Main observations: Two men, 60 and 39-year-old, presented with a several year history of asymptomatic whitish papules scattered over the face and neck. Skin biopsies revealed fibrofolliculomas. The clinical diagnosis of BHDS was corroborated by identification of new heterozygotic mutations in *FLCN* gene, in exon 6 (C.573_574delinsT) and in exon 9 (c.1015C>T), respectively. Computed tomography scan of the thorax and abdomen showed pulmonary cysts with no suspicious kidneys lesions, and, in the case of the second patient, a mass in left adrenal gland. Laparoscopic left adrenalectomy was performed and histopathological examination was compatible with a malignant perivascular epithelioid cell tumor.

Conclusions: The presence of multiple fibrofolliculomas should raise the suspicion of BHDS. Patients with this syndrome, regardless of the detected mutation, should be carefully monitored to ensure that potentially serious disease-related conditions can be detected early. (*J Dermatol Case Rep*. 2017; 11(1): 12-15)

Introduction

Birt-Hogg-Dubé Syndrome (BHDS) is an apparently rare, autosomal dominant genodermatosis caused by germline mutations in the *folliculin* gene (*FLCN*) located on the 17p11.2 region.[1-8,10-12] BHDS predisposes to benign hair follicle hamartomas known as fibrofolliculomas (FF) and trichodiscomas (TD), acrochorda; lung disease (bibasilar cysts and, less frequently, pneumothorax); and kidney neoplasms with different histologic presentations.[1-8,10-12] The incidence of this syndrome is unknown but it is probably underdiagnosed given its variable penetrance and consequent range of clinical manifestations.[1] We describe two patients with BHDS carrying new *FLCN* mutations, not previously described in literature, and one of them with a type of adrenal gland tumor associated for the first time to this syndrome.

Case reports

Case 1

A 60-year-old caucasian man presented with a several years history of multiple asymptomatic skin lesions of the face, scalp and neck. The patient denied any respiratory signs or symptoms. His medical history was consistent with hypertension, diabetes mellitus, dyslipidemia and benign prostatic hypertrophy. The family history was irrelevant.

The general and systemic examination did not reveal any abnormality. The dermatological examination revealed multiple, dome-shaped, whitish and erythematous papules scattered over the scalp, frontal and malar regions, nasolabial folds and upper neck (Fig. 1) with no other relevant cutaneous lesions. Excisional biopsy of two papules showed, in

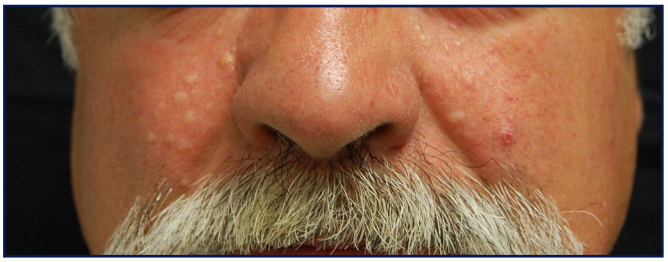

Figure 1
Multiple, dome-shaped, whitish papules on malar regions and nasolabial sulcus.

both, hair follicle with cystic dilation, perifollicular fibrous thickening (particularly peri-infundibulum) where strands of epithelial cells irradiate and partially anastomose (Fig. 2), findings consistent with fibrofolliculoma. The patient was referred to genetic study which revealed a new heterozygotic mutation in exon 6 of the *FLCN* gene (p.Lys192Argfs*31). This mutation has not been reported previously but as it originates a stop codon it can be expected to be pathogenic and therefore confirms the diagnosis of BHDS. Computed tomography (CT) scan of the thorax and abdomen showed numerous bilateral lung cysts without suspicious kidneys lesions. Patient had no history of spontaneous pneumothorax. Pulmonary function tests, including spirometry and diffusing capacity for carbon monoxide were normal. Thyroid ultrasonography and colonoscopy were normal.

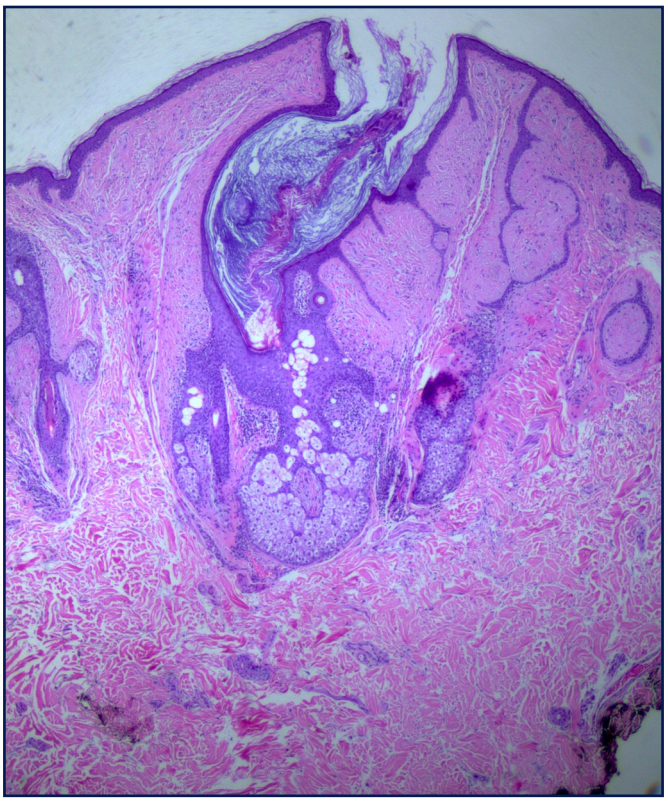

Figure 2
Fibrofolliculoma. *Cystic dilatation of the centrally located infundibulum from which anastomosing thin cellular cords irradiate into the surrounding stroma (hematoxylin-eosin stain, original magnification 20x).*

Case 2

A 39-year-old caucasian man with a prior history of epilepsy and asthma since early childhood was referred to our department for evaluation of multiple asymptomatic skin lesions located on the face, retroauricular region and neck, that started to appear in the third decade of life. The patient mentioned a family history of similar dermatological findings (sister, two paternal uncles and nephew).

On physical examination numerous whitish papules, firm to touch and measuring 1 to 3 mm in diameter, were found on the frontal, malar and retroauricular regions and upper neck (Fig. 3). In addition, numerous acrochordon-like lesions were present on the neck. General examination was normal. Excisional biopsy of two papules was performed and histopathological analysis was compatible with fibrofolliculoma.

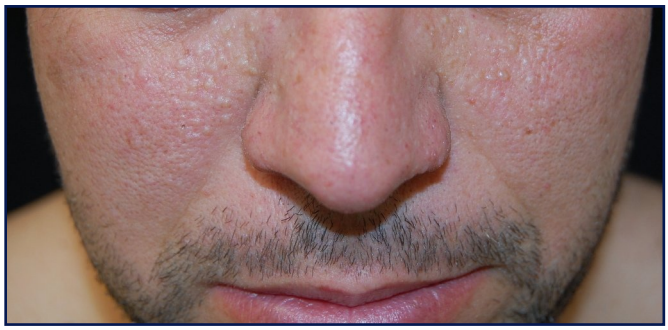

Figure 3
Whitish papules are observed in malar regions.

In the presence of multiple facial papules with histological features of fibrofolliculomas, acrochordon-like lesions and also a family history of similar lesions the diagnosis of BHDS was considered. The patient was assessed for *FLCN* gene mutations in peripheral blood sample. A new heterozygotic mutation was detected in exon 9 of the *FLCN* gene (c.1015C>T), responsible for the introduction of a premature stop codon at position 339 amino acid (p.Gln339*). This mutation has not been described previously but it can be considered pathogenic and so responsible for BHDS in our patient. CT scan of the thorax and abdomen showed a lung cyst in the right middle lobe and a nodular formation in continuity with the external limb of left adrenal gland measuring 56 x 55 mm, suspect of neoformative process. Endocrine evaluation excluded hypercortisolism, pheochromocytoma, hyperaldosteronism and sexual hormones anomalies. Laparoscopic left adrenalectomy was performed and histopathological examination revealed a malignant perivascular epithelioid cell tumor (malignant PEComa).

Pulmonary function tests and thyroid ultrasonography were also normal.

Given the benign nature of skin lesions both patients refused any treatment. Patients and families were referred to the genetic department. Patients are screened for the development of renal neoplasia by contrast-enhanced abdominopelvic CT scan each two years and were advised to not smoke. Symptoms of spontaneous pneumothorax were also taught.

Discussion

The pathogenesis of BHDS remains ill-defined. Several different *FCLN* gene mutations have been reported, with unknown phenotype-altering implications.[2] The product of this gene — folliculin — is expressed in many normal tissues, including skin, lung and kidney.[2-4] Changes in the activity of this protein, presumably with still unconfirmed tumor suppressor activity (via mTOR signaling), may favour the appearance of several of these skin malformations, lungs cysts and renal cancer. [2-5]

Fibrofolliculoma and TD, the hallmarks of BHDS, are clinically indistinguishable and usually appear in individuals in their 20s or 30s and present as asymptomatic multiple, smooth, skin-colored or whitish, dome-shaped papules commonly located on the face (mainly on the nose, forehead and cheeks) although they can also appear on the neck and trunk.[1-3,5] Several authors point out that FF and TD (and even acrochorda) may actually represent different stages of evolution within one same lesion.[1-3] In addition to these lesions, the presence of facial angiofibromas has occasionally been reported, as the involvement of oral mucosa in the form of multiple papules involving the lips, buccal mucosa and gingiva.[1,3] Although skin lesions are a warming sign for dermatologists, they are not present in all patients with BHDS.[3]

The most threatening complication of BHDS is renal cell cancer, which develops in approximately 15% of patients by age 70.[6] It was reported that patients with BHDS had a sevenfold higher risk of renal cancer, with a predilection for men and an age of onset between 20 and 55 years.[1,3,5] The presentation of renal lesions can be bilateral and multifocal, with diverse histologies that include oncocytic-chromophobe hybrid carcinoma (50%), chromophobe carcinoma (34%), clear cell carcinoma (9%), oncocytoma (5%) and papillary carcinoma (2%).[5,7] There is no consensus regarding an optimal screening program, but periodic imaging every 12-36 month starting at age 20 has been suggested.[2,3,6] The optimal method for surveillance is magnetic resonance imaging, because of the high degree of resolution and absence of radiation.[1,2,6]

Other well-recognized components of BHDS are pulmonary cysts, detectable by CT-scan in about 90% of patients and located mainly in the lung bases (in contrast to emphysema) and at the subpleural level.[2,3,7] These cysts may rupture giving rise to pneumothorax (which occurs in about 25% of BHDS patients).[2,7] We should not therefore considerer them as spontaneous pneumothoraces as they are caused by rupture of a pulmonary cyst. A relationship between size and volume of the cysts and the risk of pneumothorax has been reported — the larger the volume the greater the risk.[3,5] The mean age of pneumothorax presentation is 38 years, with no clear predilection for either sex.[3] While the age-adjusted risk of pneumothorax is 50 times higher in patients with BHDS than in the general population, lung function is usually normal.[1,3-6] Although there is no clear indication for routine CT scanning of the lungs in patients with BHDS, the demonstration of multiple lung cysts strengthens the diagnosis when it is in doubt. Symptomatic patients with lung lesions should have individualized follow-up and all should be reminded of the higher risk of pneumothorax with general anesthesia, during journeys in airplanes or aquatic activities such as diving.[2,3,5] Smoking is an important risk factor for both spontaneous pneumothorax and renal cancer.[1] Though there are limited data on smoking and the risk of pneumothorax and renal cancer in BHDS, smoking might increase the risk of these disease manifestations and should be strongly discouraged in these patients.[1,3]

Less often, BHDS patients may present multiple lipomas and angiolipomas, as well as neural tumours (neurothekeoma, meningeoma), connective tissue nevi and parathyroid adenoma.[1,3,5,7,8] The relationship with colorectal cancer is controversial and no specific indication has been reported for colonoscopy in these patients and so the recommended management is the same as in general population.[3,8] The initially reported association with medullary cancer of thyroid has not been confirmed and was instead associated with the presence of coexistent dominant hereditary multiple endocrine neoplasia type 2.[8]

This case represents, to the best of our knowledge, the first malignant PEComa diagnosed in a patient with BHDS. Perivascular epithelioid cell tumors are unique mesenchymal tumors exhibiting perivascular epithelioid cell differentiation, characterized by a mixed myogenic and melanocytic phenotype. Some types of PEComa are seen at high frequency in tuberous sclerosis complex (TSC), like renal angiomyolipoma, as well as pulmonary lymphangioleiomyomatosis.[9] However, the spectrum of PEComas also includes rarer tumors of variable malignant potential that typically involve the lung, as well as the gynecologic and gastrointestinal systems. This latter subset of PEComa is not particularly common in TSC.[9] The *TSC1* and *TSC2* genes are commonly mutated in both TSC-associated and sporadic PEComas, and mTOR signaling pathway activation is also common in these tumors.[9] As described by some authors

Table 1. Criteria proposed by the European Birt-Hogg-Dubé Consortium for the diagnosis of BHDS.[1]

Major Criteria
At least 5 fibrofolliculomas or trichodiscomas, at least 1 confirmed histologically, of adult onset
Pathogenic *FLCN* germline mutation
Minor Criteria
Multiple lung cysts: bilateral basally located with no other apparent cause, with or without spontaneous pneumothorax
Renal cancer: early onset (<50 years) or multifocal or bilateral cancer, or renal cancer of mixed chromophobe and oncocytic histology
First-degree relative with BHDS
Patients should fulfill 1 major or 2 minor criteria for diagnosis of BHDS

FLCN protein, mutated in BHDS, also lead to activation of mammalian target of rapamycin complex 1 (mTORC1) of the mTOR pathway.[10] At this point, a possible association between BHDS and the occurrence of malignant PEComa in this patient is interesting, but purely speculative.

The current diagnostic criteria proposed by the European Birt-Hogg-Dubé Consortium are shown in Table 1.[1] Differential diagnosis in a patient with multiple facial papular lesions should include Brooke-Spiegler syndrome, Cowden syndrome, Rombo syndrome, tuberous sclerosis and basaloid follicular hamartoma syndrome.[1,3,5]

The management of Birt-Hogg-Dubé patients should be multidisciplinary. Treatment of skin lesions is mainly cosmetic. Some therapeutic options are curettage/shave plus cautery, oral isotretinoin, carbon dioxide and erbium:YAG LASER and topical rapamycin.[1,3,11,12]

Conclusions

Birt-Hogg-Dubé syndrome is probably under-diagnosed because of the wide variability in its clinical expression. When examining patients with multiple facial papules the dermatologist should consider BHDS. Since renal cell carcinomas are reputably clinically silent and late detection associated with worse prognosis, they must be specifically addressed in BHDS patients and their families. A better knowledge of this rare disease and its possible associations is needed and it will likely occur as further understanding of the mTOR pathway is uncovered.

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