Birt-Hogg-Dubé Syndrome*

Síndrome de Birt-Hogg-Dubé

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Abstract: A 45-year-old woman with a history of renal carcinoma was observed for facial, cervical and truncal flesh-colored papules. Relatives had similar skin findings and a brother had repeated episodes of pneumothorax. The computerized tomography scan revealed multiple cysts on both lungs. A skin biopsy revealed a perifollicular fibroma. The clinical diagnosis of Birt-Hogg-Dubé syndrome (BHDS) was corroborated by identification of a novel frameshift c.573delGAinsT (p.G191fsX31) mutation in heterozygosity on exon 6 of the folliculin gene. The presence of multiple and typical benign hair follicle tumors highlights the role of the dermatologist in the diagnosis of this rare genodermatosis that is associated with an increased risk of renal cell cancer and pulmonary cysts, warranting personal and familial follow-up and counseling.
Keywords: Birt-Hogg-Dube Syndrome; Frameshift mutation; Hair follicle

Resumo: Uma mulher de 45 anos com história de carcinoma renal foi observada por pápulas cor da pele, faciais, cervicais e tronculares. Referia história familiar de achados cutâneos semelhantes e irmão com episódios repetidos de pneumotórax. Identificaram-se múltiplos quistos pulmonares por tomografia computorizada. Uma biópsia cutânea revelou fibroma perifolicular. O diagnóstico clínico de síndrome de Birt-Hogg-Dubé (BHDS) foi contudo corroborado pela identificação de uma nova mutação frameshift c.573delGAinsT (p.G191fsX31) em heterozigotia no exão 6 do gene da foliculina. A presença de múltiplos e típicos tumores benignos do folículo piloso, realça o papel do dermatologista no diagnóstico desta rara genodermatose, que está associada a um risco aumentado de tumores de células renais e cistos pulmonares, exigindo seguimento e aconselhamento pessoal e familiar.
Palavras-chave: Folículo piloso; Mutação da fase de leitura; Síndrome de Birt-Hogg-Dubé

INTRODUCTION

Hornstein-Knickenberg Syndrome or Birt-Hogg-Dubé Syndrome (BHDS), as it came to be more commonly known, is an apparently rare, autosomal dominant genodermatosis caused by mutations of the folliculin codifying gene (*FLCN*) located on the 17p11.2 region.[1,2] The first description of a case of what would later be recognized as BHDS was probably presented by Burnier and Rejsek.[3] BHDS predisposes to: **1)** benign hair follicle hamartomas known as fibrofolliculoma (FF) and trichodiscoma (TD), acrochorda and angiofibroma; **2)** pulmonary lesions (bibasilar cysts and, less frequently, pneumothorax); and **3)** mainly malignant renal tumours (of various histologic types).[2,4]

CASE REPORT

A 45-year-old woman with a prior history of: **1)** total right nephrectomy due to clear cell carcinoma (T1, N0, M0) at 41 years of age; **2)** multinodular goiter; **3)** fibrocystic mammary disease; was referred to our department for evaluation of long-standing multiple facial, cervical and upper thoracic small, flesh-colored papules (Figure 1). Scarce improvement was noted in the past with topical aluminum oxide or alpha-hydroxy-acids treatment.

The patient denied any respiratory signs or symptoms and mentioned a family history of similar dermatological findings (father, brother and paternal aunts). Her father died of colon cancer and her broth-

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er had a history of repeated episodes of spontaneous pneumothoraxes.

Computerized tomography scan (CT-scan) of the chest, abdomen and pelvis revealed multiple small-sized cysts in both lungs. Thyroid ultrasonography and scintigraphy were performed and cytology of otherwise suspicious nodules did not reveal any cancer findings. Colonoscopy was normal.

Skin biopsies of the face, neck and abdomen revealed findings consistent with angiofibroma, cellular fibroma and fibroma (acrochordon). Only one biopsy of a lesion of the face showed a discrete dermal proliferation of basaloid epithelial nests around a normal hair follicle, with surrounding fibrosis, consistent with perifollicular fibroma (Figure 2).

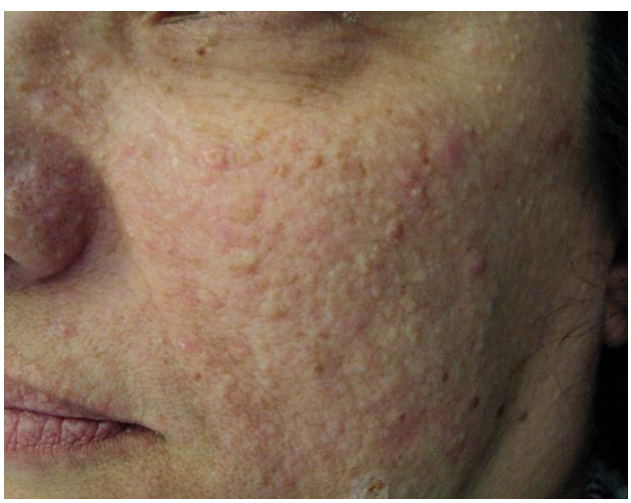

Figure 1: Detail of the left aspect of the face where skin-colored papules are observed in the nasal and malar region

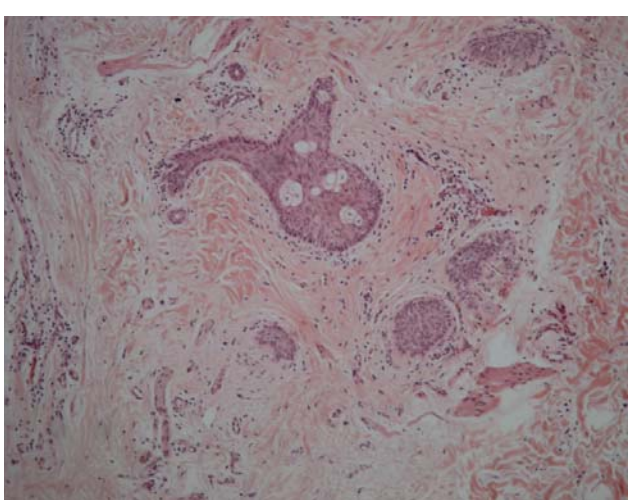

Figure 2: Detail of epithelioid cell nests and perifollicular dermal fibrosis (H&Ex100)

Despite the absence of FF or TD identification, a clinical diagnosis of BHDS was made, corroborated by the identification of a previously undescribed, frameshift c.573delGAinsT (p.G191fsX31) mutation in heterozygosity on exon 6 of the *FLCN* gene (Figure 3).

Carbon-dioxide laser ablation produced unsatisfactory results in the patient's opinion, who declined further treatment. The patient and her immediate family are annually screened for the development of renal neoplasia. The patient's brother refused medical care.

DISCUSSION

The pathogenesis of BHDS remains ill-defined. Several different *FLCN* gene mutations have been reported, with unknown phenotype-altering implications. Folliculin is expressed in most major adult tissues, including skin, lung and kidney. Changes in the activity of this protein, presumably with still unconfirmed tumor suppressor activity (via mTOR signaling), may favor the appearance of several of these skin malformations, lung cysts and renal cancer, denoting the higher severity of this syndrome's prognosis.[2]

FF and TD, the hallmarks of BHDS, present as asymptomatic single or multiple, smooth, skin-colored, dome-shaped papules commonly located on the head, neck, back, and arms. Fibrous papules/Angiofibroma may be similar and are mainly located on the head and upper trunk. Perifollicular fibromas (PFF) favor the head and neck.[5] Clinically these are virtually indistinguishable and further differentials of these similar papules include dermatofibroma, trichilemmoma, neurofibroma and trichoepitheliomas.

Several authors point out that FF and TD (and even acrochorda) may actually represent different stages of evolution within one same lesion. They are immunophenotypically similar and thus derived from the same histiogenic precursor. Differences in histology might also be related to differences in planes of section.[5] Some have also pointed out the possibility that PFFs may actually represent FF in the setting of BHDS, an event that may be related to sectioning as well.[6-8] In fact, the first cases ever described to be compatible with BHDS were characterized by numerous PFF.[3] Again, the association of PFF with BHD has been recently reviewed in a recent series of four cases.[9]

We believe that FF, TD and PFF are hamartomatous hair-follicle tumours, and should be considered as a part of BHDS in the appropriate clinical setting, along with achrocordon and angiofibroma.

According to the diagnostic criteria proposed by Menko *et al*., our patient met 1 major and 2 minor criteria.[10] Despite the fact that BHDS is characteristically associated with FF and/or TD, surgical pursuit of diagnostic histological findings is not always rewarding. Selection of appropriate lesions for biopsy

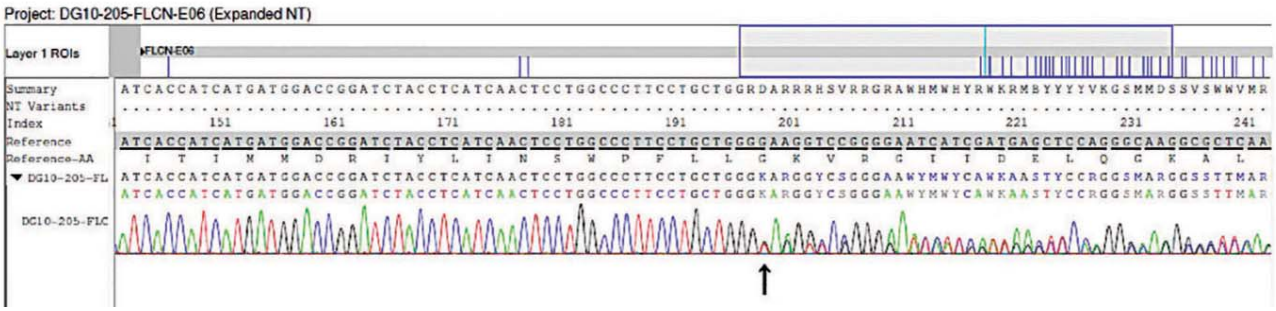

Figure 3: Automatic sequencing of exon 6 of the FLCN gene (the arrow shows the point where the frameshift mutation started)

is troublesome, due to the relatively dubious differential diagnosis with other similar-looking lesions that may be associated with the disease as well (e.g. acrochorda). On the other hand, multiple excision may perhaps be unreasonable. These assumptions applied to this case. Furthermore, others have highlighted the existence of BHDS in the absence of FF/TD.[4]

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. When we first observed our patient, she had already undergone treatment for a renal tumor that had been an incidental finding, 4 years before.

Other well-recognized components of BHD syndrome are pulmonary cysts, detectable by CT-scan in about 90% of BHDS patients. Pneumothorax occurs in 25% of BHDS patients and is not spontaneous, but rather secondary to rupture of pulmonary cysts under pressure of inhalation.[2]

Currently there are no published guidelines for screening renal cancer or pulmonary cysts in asymptomatic BHDS patients or their relatives. Provisional recommendations include surveillance of: **1)** renal cancer, starting at age 20 (through magnetic resonance imaging or ultrasound, to avoid long time exposure to CT-scan radiation), with individualized intervals; **2)** pulmonary cysts, with an initial baseline high resolution CT-scan and follow-up every 3-5 years. Symptomatic patients with lung lesions should have individualized follow-up and all should be reminded of the higher risk of pneumothorax with general anesthesia or traveling to high altitudes (including air travel).

When examining patients with multiple facial papules and a personal and/or family history of renal cancer, the dermatologist should consider BHDS. Maintaining a low threshold for clinical suspicion is perhaps advisable, as the diagnosis may imply an early detection of cancer in affected patients and their families. ❑

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