CASE REPORTS

Birt-Hogg-Dubé Syndrome in a Patient With Cutaneous Symptoms and a c.1429 C>T; p.R477X Mutation in Exon 12 of the Folliculin Gene

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Abstract. Birt-Hogg-Dubé syndrome is an autosomal dominant genodermatosis characterized by the presence of fibrofolliculomas, renal cancer, pulmonary cysts, and spontaneous pneumothorax. Recently, the folliculin gene responsible for this process has been identified, located on the short arm of chromosome 17. We present the case of a 49-year-old man with multiple whitish papules on the face, neck, and retroauricular area. Histology was compatible with fibrofolliculoma and genetic study showed a pathogenic mutation of the folliculin gene.

Key words: Birt-Hogg-Dubé syndrome, fibrofolliculoma, folliculin gene.

Introduction

Birt-Hogg-Dubé syndrome is a rare genodermatosis of autosomal dominant transmission caused by a mutation in the folliculin gene. Clinically, the syndrome presents as a triad of skin lesions comprising fibrofolliculomas, trichodiscomas, and acrochordons, and is associated with an increased risk of pulmonary cysts, spontaneous pneumothorax, and renal cell carcinoma. The incidence of this syndrome is unknown but it is probably underdiagnosed given its variable penetrance and consequent range of clinical manifestations.

We present the case of a 49-year-old man who consulted for multiple asymptomatic papules on his face, behind his ears, and on his neck. These were associated with lesions—suggestive of acrochords—that had appeared 10 to 15 years earlier. Histological study of the skin lesions was essential for diagnosis of Birt-Hogg-Dubé syndrome, which was later confirmed by genetic study.

Case Description

The patient was a 49-year-old man whose personal history of note included hyperuricemia under pharmacological treatment and chronic hepatitis C virus (HCV) infection on ultrasound follow-up. He attended our clinic for multiple asymptomatic papules on the face that first appeared 10 to 15 years earlier.

On physical examination, numerous papular skin lesions measuring 1 to 3 mm in diameter of whitish appearance and firm to touch were found on the frontal region,
behind the ears, and on the neck (Figures 1 and 2). In addition, numerous acrochordon-like lesions were present on the neck and upper torso. The patient presented no other cutaneous or mucosal lesions.

With a diagnosis of multiple adnexal tumors in mind, histological study of 1 of the lesions on the frontal area was ordered.

The biopsy revealed clumps of collagen and fibroblasts arranged concentrically around hair follicles, a finding consistent with perifollicular fibroma (Figures 3 and 4).

Given that our patient had multiple perifollicular fibromas on the face, neck, and upper torso, we decided it was necessary to rule out Birt-Hogg-Dubé syndrome, and a genetic study was requested.

The genetic study detected a heterozygotic mutation in exon 12 of the folliculin gene (also known as the BHD gene). This mutation corresponded to a change in nucleotide 1429 and affected codon 477, with a change from arginine to a stop codon. This mutation has been described previously, and we can consider it as responsible for Birt-Hogg-Dubé syndrome in our patient.

**Discussion**

In 1977, the Canadian physicians Birt, Hogg, and Dubé described the presence of small multiple papular skin lesions, which were firm to touch, on the face, scalp, and neck of 15 individuals of 3 successive generations of the same family. The disease was transmitted according to a autosomal dominant pattern. Histological study was able to distinguish 2 types of benign tumors that affected the hair follicles. These were diagnosed as fibrofolliculomas and trichodiscomas. Characteristically, these patients also presented multiple acrochordons. This skin triad was given the name Birt-Hogg-Dubé syndrome.
It is currently accepted that fibrofolliculomas and trichodiscomas are clinically indistinguishable and form part of the same histological spectrum. Likewise, it has been shown that some of the lesions diagnosed clinically as acrochordons present histological features consistent with fibrofolliculomas, and so can be considered a phenotypic variant of those lesions. In our patient, we ordered a histological study of one of the multiple acrochordons on the neck area. The study did not find, however, signs consistent with fibrofolliculoma. Given the benign nature of the lesions, and that we had sufficient information for diagnosis, we decided further biopsies were not necessary.

Today, we know that Birt–Hogg–Dubé syndrome is a rare genodermatosis although the incidence is unknown and penetrance is very variable. Transmission from one generation to the next follows an autosomal dominant pattern.

In 2001, an association was shown between this syndrome and chromosome 17p11.89 and, 1 year later, the folliculin gene was identified at that locus. To date, several mutations have been reported, and most of these deactivate the folliculin gene, thereby also deactivating the folliculin protein that this gene encodes. The exact function of this protein is still unknown, but recent studies have suggested that it might have tumor-suppressor activity.

In addition to skin manifestations, which are not always present, patients with Birt–Hogg–Dubé syndrome are also at greater risk of pulmonary cysts, spontaneous pneumothorax, and renal cell carcinoma.

With regard to pleuropulmonary disease, Zbar et al. found a 32-fold increase in risk (adjusted for age and other factors such as smoking habit) compared to the normal population for spontaneous pneumothorax in patients with Birt–Hogg–Dubé syndrome. It is also characteristic that the pulmonary cysts in these patients affect the lung bases in contrast to other more common processes such as emphysema. These cysts may rupture giving rise to pneumothorax. We should not therefore consider them as spontaneous pneumothoraces as they are caused by the rupture of a pulmonary cyst.

The association with renal cell carcinoma was reported for the first time by Roth et al. in 1993. It seems that renal cell carcinoma in these patients tends to appear at earlier ages and presents more often in both kidneys or as multiple tumors. Several histological subtypes have so far been described. Of the tumors that affect the distal segments of the nephron, the hybrid oncocytic tumors and the chromophobe carcinomas are the most common. However the incidence of clear cell renal carcinoma and papillary carcinoma is relatively low in patients with Birt–Hogg–Dubé syndrome. Pleuropulmonary and renal lesions influence the prognosis in patients with Birt–Hogg–Dubé syndrome and regular monitoring with computed tomography and abdominal ultrasonography are required to ensure early detection. In such cases, patients would be referred to the appropriate specialists.

The treatment of skin manifestations is mainly cosmetic. The few references in the scientific literature support the use of physical measures.

The mutation detected in the genetic study of our patient had been previously reported in one of the families studied by the group led by Dr. Schmidt. That mutation—diagnosed according to clinical features—was described in a patient with skin manifestations and pulmonary disease (spontaneous pneumothorax). In our patient, no other diseases associated with the skin lesions have been detected. Currently, there are no studies that point to a specific correlation between a given mutation and a phenotype of the syndrome. We therefore believe that our patient, like other sufferers of Birt–Hogg–Dubé syndrome, should be carefully monitored to ensure that any of the potentially serious related diseases can be detected early, regardless of the mutation responsible.

**Conflicts of Interest**

The authors declare no conflicts of interest.

**References**