Spontaneous Pneumothorax and Facial Papules: Birt-Hogg-Dubé Syndrome

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Citation

K Herring, S Reed, D O'Hearn, C White, K White, E Simpson. *Spontaneous Pneumothorax and Facial Papules: Birt-Hogg-Dubé Syndrome*. The Internet Journal of Pulmonary Medicine. 2008 Volume 11 Number 1.

Abstract

Spontaneous pneumothorax typically occurs sporadically, however, familial cases occur. We report a case of familial spontaneous pneumothorax secondary to Birt-Hogg-Dubé syndrome (BHDS) diagnosed after the development of characteristic facial papules.BHDS is an autosomal dominant genodermatosis characterized by a triad of spontaneous pneumothorax, facial papules, and renal neoplasms. Clinicians should perform cutaneous exams and ask about a family history of facial papules in patients with familial spontaneous pneumothorax to identify this syndrome and consider screening for underlying renal neoplasms.

INTRODUCTION

Primary spontaneous pneumothorax occurs in the absence of precipitating trauma or underlying lung disease [1]. Although most cases are sporadic, typically occurring in thin young male smokers at rest, familial cases have been reported. We report a case of familial spontaneous pneumothorax secondary to Birt-Hogg-Dubé syndrome (BHDS) diagnosed by cutaneous examination and confirmed by biopsy in a patient with a personal and family history of multiple spontaneous pneumothoraces. We highlight its key diagnostic features and management.

CASE REPORT

A 45-year-old gentleman presented with a five-year history of multiple, small, skin-colored, asymptomatic papules on his face. The papules had increased in number vover time, and he presented to the dermatology service seeking cosmetic improvement.

His medical history was notable for two right-sided spontaneous pneumothoraces at ages 18 and 25 requiring thoracostomy tubes and subsequent pleurodesis. At age 30, he experienced a left-sided spontaneous pneumothorax requiring tube thoracostomy. He had no other past medical history and took no medication. He was a lifelong non-smoker.

His mother had a history of spontaneous pneumothorax, as did five of her seven siblings.

Many of these relatives were also reported to have multiple facial papules. One maternal sibling required bilateral bullectomies before the age of 40.

Physical exam revealed a well-nourished man of appropriate weight, appearing his stated age, with greater than 20 skin-colored, dome-shaped, 2-4

mm papules along his nasolabial folds and nasal alae, with subtle papules on his pinnae (Figs. 1 a and b).

{image:1}

Punch biopsies revealed characteristic features of trichodiscoma including

delicate collagen bundles arranged around vellus hair follicles and sebaceous glands, aswell as stellate fibrocytes and small blood vessels. Renal ultrasonography did not reveal any evidence of a renal mass.

DISCUSSION

We present a patient in whom cutaneous examination and histopathology

confirmed the diagnosis of BHDS in a family with multiple facial papules and recurring pneumothoraces. In 1977, Birt, Hogg, and Dubé described three generations of family members in which 15 of 70 members exhibited multiple small, gray to skin-colored, dome-shaped papules distributed over the face, neck, and upper trunk [2]. The key features of

BHDS are now known to include facial fibrofolliculomas/trichodiscomas, renal neoplasms, and recurring spontaneous pneumothorax, although not all features are always present in the same patient. A variety of disease-causing mutations have been mapped to the BHD gene (FLCN) on chromosome 17p11.2, resulting in early truncation of the BHD tumor suppressor gene product folliculin. FLCN is conserved across species, and expressed in many tissues of the human body including the lung, skin, and

kidney [3]. Recent studies suggest that BHDS may be similar to other inherited hammartoma syndromes in which loss of tumor suppressor gene function leads to dysregulation of proteins important in cell growth [456]. A study by Toro et al. aimed to find genotype-phenotype correlations in 50 BHDS families reported variable phenotypic expression among and within these families. Interestingly, one quarter of the families studied had the classic triad of pulmonary, cutaneous, and renal involvement, one quarter had only cutaneous and pulmonary involvement, and one quarter had only cutaneous involvement [7].

In patients presenting with familial spontaneous pneumothorax, obtaining a thorough family history of facial lesions, with examination of potentially affected family members, becomes paramount. The presence of multiple fibrofolliculomas should prompt further evaluation for BHDS. Toro et al. reported 90% of BHDS families had characteristic facial papules [7]. These facial lesions present as multiple skin-colored papules on the nasolabial folds, perinasal area, neck, and ears. Characteristic papules typically appear in patients with BHDS by age 40, usually after a pneumothorax has developed, but prior to the development of renal tumors. Exceptions exist as Welsch et al. reported a patient who suffered from bullous lung disease and recurrent spontaneous pneumothoraces years after the development of facial papules [8]. Skin biopsy of characteristic facial papules reveals fibrofolliculomas, trichodiscomas, or perifollicular fibromas. Studies suggest these benign follicular neoplasms represent different stages of development along a single pathologic process [9]. The precise number of lesions required to make the diagnosis remains uncertain; however the presence of facial fibrofolliculomas/trichodiscomas should suggest a diagnosis of BHDS. Genetic testing of blood, buccal mucosa, or amniotic fluid for mutations in the BHD gene is commercially available, if needed [10].

Familial spontaneous pneumothorax is an important feature of BHDS, but large cohort studies of BHDS families by Zbar et al. and Toro el al. reveal a family history of spontaneous pneumothorax in only 23 and 38% of affected members, respectively [711].

There is no known predilection for a right or left sided pneumothorax. While recurrence of spontaneous pneumothorax similar to our case is often described in BHDS, the rate of recurrence is unknown. Toro et al. described a statistically significant trend in BHDS patients toward having a greater number of pneumothoraces if the patient had a family history of pneumothoraces [7]. It is unclear whether there are radiologic precursor findings specific to BHDS which differ from those seen in spontaneous pneumothorax not related to the syndrome. Zbar et al. examined the lungs of BHDS families with computed tomography (CT), and found pulmonary cysts in 83% of affected family members, compared to 10% in unaffected members [11]. The former rate is similar to that reported for the presence of blebs and bullae on CT in spontaneous pneumothorax not related to BHDS [12]. However, the pulmonary cysts reported by Zbar et al. were usually well-circumscribed, basilar, and subpleural, thus differing from the apical and upper lung predominance of bullae thought to be more typical in non-BHDS primary spontaneous pneumothorax [1314]. Until recently, it was controversial whether these blebs, bullae, or cysts were the actual cause of spontaneous pneumothorax [12]. However, Toro et al. found that the presence of lung cysts, and every parameter they measured related to the number of lung cysts, was statistically associated with a history of pneumothorax, while the other categorical parameters including sex, smoking, and severity of fibrofolliculomas were not [15].

Identification of patients with BHDS is important as it allows for proper screening and treatment of the estimated 27% of BHDS patients that will develop underlying renal neoplasms [16]. These patients are predisposed to the development of bilateral and multifocal renal neoplasms, with a range of histological subtypes particularly chromophobe and hybrid oncocytic renal carcinomas, and have a mean age of diagnosis at 50 years [17]. Diagnosing a renal neoplasm resulting from an inherited disease is of critical importance in the management of these patients because they are predisposed to developing multiple renal neoplasms, thus making nephron-sparing approaches the treatment of choice in an effort to reduce morbidity after treatment [714]. In the absence of strictly defined guidelines,

Kim et al. recommends BHDS patients begin routine screening with abdominal CT and/or ultrasound at initial diagnosis, followed by interval screening every 3 to 5 years [18].

CONCLUSION

In conclusion, BHDS is a rare genodermatosis characterized by skin-colored facial papules, and an increased risk for developing spontaneous pneumothoraces and renal neoplasms. When evaluating patients with a spontaneous pneumothorax, especially those with a family history of spontaneous pneumothoraces, cutaneous exam should look for the characteristic facial papules suggestive of Birt-Hogg-Dubé syndrome, and the family history should iclude the presence or absence of facial papules and renal tumors.

Punch biopsies of affected family members may then be performed to identify fibrofolliculomas or trichodiscomas. Screening for underlying renal carcinoma should be strongly considered upon diagnosis of BHDS, however determining proper screening guidelines is an area where further research is needed.

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