Pulmonary Cysts, Appendiceal Diverticulosis, and Birt-Hogg-Dubé Syndrome, a Genetic Connection?

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Learning objectives

Learn and recognize the clinical and radiological presentations of Birt-Hogg-Dube syndrome.

Discuss genetic links between thoracic and abdominal findings.
Background

Birt-Hogg-Dubé syndrome (BHD) is a rare autosomal dominant disorder that predisposes patients to cutaneous tumors, pulmonary cysts with recurrent spontaneous pneumothoraces due to cyst rupture, and a variety of renal neoplasms including hybrid oncocyic and chromophobe renal cell carcinomas. There has been much debate with regard to the relationship between the germline mutation found in BHD, which is thought to result in down-regulation of the \textit{FLCN} tumor suppressor gene in renal tissue, and the occurrence of colorectal cancer and other colonic anomalies.

Cutaneous Manifestations

First defined as an inherited dermatologic disorder in 1977, Birt-Hogg-Dubé syndrome (BHD) is a rare dominantly inherited autosomal disease reported in more than 100 families worldwide that is characterized by a triad of cutaneous manifestations including fibrofolliculomas, trichodiscomas, and acrochordons in 75% of cases.\textsuperscript{1,2,3} Fibrofolliculomas arise as dome-shaped papules often found on the face. They represent proliferation of the perifollicular connective tissue. Trichodiscomas also form as papules, and they arise as parafollicular mesenchymal hamartomas from the hair disc. Acrochordons present as pedunculated, fleshy outgrowths of epidermal and dermal tissue, which occur predominantly on the neck, eyelids, upper chest, and axillae.\textsuperscript{4} These phenotypic hallmarks of BHD are usually benign and asymptomatic, typically manifesting after 20 years of age.\textsuperscript{1,5}

Extracutaneous Manifestations and Screening

Patients with BHD may exhibit extracutaneous clinical manifestations that may either precede or follow integumentary abnormalities.\textsuperscript{1} In a 2013 study of 36 patients conducted by Kunogi et al, pneumothorax and/or multiple lung cysts, rather than the typical cutaneous triad, were the presenting features of BHD, confirmed with genetic analysis via quantitative polymerase chain reaction.\textsuperscript{6} Birt-Hogg-Dubé syndrome predisposes afflicted patients to a 32-fold to 50-fold increased risk for spontaneous pneumothoraces, which are typically secondary to basilar and peripheral bullous changes and rupture of lentiform parenchymal cysts.\textsuperscript{2,7,8} It has been noted that up to 35% of BHD patients will have a family history of pneumothorax. Pulmonary involvement in BHD has been reported to show 80-100% penetrance. In a cohort of 198 patients with BHD studied by Toro et al, 89% of patients had characteristic cystic changes within the lungs found on chest CT.\textsuperscript{9} Cystic changes seen in BHD are often confused with bullae or blebs. However, they are typically
found in basilar regions, rather than the apices as seen in spontaneous pneumothorax or emphysema. According to Tobino et al, the majority of BHD pulmonary cysts are located in medial basilar regions (58%) followed by lateral basilar regions (27%). Numbers of cysts and sizes vary, but most are <1 cm in diameter (75.6%). High resolution computed tomography is the modality of choice for diagnosis of pulmonary involvement in BHD. Multiple, small and lenticular, thin-walled cysts predominantly distributed in the lower medial subpleural regions suggest the diagnosis.

Patients with BHD carry a nine times greater risk than the general population to develop multiple, bilateral renal cysts and neoplasms of varying histological features. Mixed chromophobe oncocytoma (50%) and chromophobe renal cell carcinoma (34%), which are thought to originate from intercalated cells of the renal collecting tubules, comprise the majority of renal neoplasms found in patients with BHD. The earliest reported case of renal cancer in a patient with BHD occurred at 20 years of age, and approximately 15% of those with BHD will develop renal cancer by age 70. Hence, periodic surveillance for renal neoplasia and pulmonary cysts after age 20 is recommended, although no steadfast screening imaging protocol has been adopted.

A number of studies report propensity toward the development of a wide spectrum of other neoplastic diseases in patients with BHD. Described in the original series by Birt, Hogg, and Dubé, the original kindred had hereditary medullary carcinoma of the thyroid. Occurrence of multiple lipomas, melanoma, parathyroid adenomas, ovarian cysts, angiolipoma, and breast cancer have been described in association with BHD.

Molecular Genetics of BHD and the Controversy of Colonic Involvement

The gene responsible for Birt-Hogg-Dubé syndrome, folliculin or FLCN, was originally identified in 2001. A mutated copy of the gene is typically inherited in an autosomal dominant fashion, however sporadic mutations in individuals with no family history of BHD have also been described. Functions of this gene are not fully understood, but it encodes for the folliculin protein, which has been found to have normal predominance of mRNA expression in tissues of the skin, distal nephrons of the kidney, stromal cells and Type I pneumocytes, epithelial ducts of the breast, pancreatic acinar cells, and serous glands of the parotids and ovaries. With regard to BHD tumoral tissues, FLCN is overexpressed in proliferating fibrofolliculomas, and underexpressed in renal neoplasms from patients with BHD. This supports the role of FLCN as a tumor suppressor in renal cancers. To date, no expression of FLCN mRNA has been noted in colonic mucinous glands, epithelium, or samples of colorectal tumors. Data from 2003 suggests that FLCN does not act as a tumor suppressor in colorectal cancer as it has been observed in renal neoplastic disease.
Rather, FLCN has been implicated as a target gene in the development of colorectal carcinomas with microsatellite instability among patients with BHD.\textsuperscript{15}

While the high incidence of recurrent pneumothorax and renal tumors in BHD is extensively documented, colonic anomalies arising in patients with BHD has been disputed. Prior to the complete clinical characterization of Birt-Hogg-Dubé syndrome, reports suggested a predisposition for the development of intestinal adenomatous polyposis and colorectal carcinoma, and further research led to the hypothesis that colon cancer is an associated phenotype of BHD.\textsuperscript{1} This hypothesis has been debated in recent years, especially after a 2002 epidemiological study showed no statistically significant correlation between BHD and colorectal cancer or colonic polyps.\textsuperscript{16} Still, data from a 2003 study on sporadic colorectal carcinomas and colorectal carcinoma cell lines with microsatellite instability in patients with BHD show evidence of a close link between colon cancer and FLCN gene mutations.\textsuperscript{1} In further support of this correlation, a 2010 case series of ten French families with BHD showed 50\% incidence of colorectal polyps in the studied population.\textsuperscript{17}

Colonic abnormalities other than polyps and colorectal carcinoma among BHD carriers have also been described infrequently. According to a study conducted by Khoo et al, three different frameshift mutations of exon 11 on chromosome 17p11.2 were associated with clinical manifestations of BHD. The c.1733delC and c.1733insC germline mutations were detected among 75\% of familial cases and 50\% of sporadic cases of BHD. Twelve kindred over three generations of one family studied had the c.1733delC mutation and varying phenotypic degrees of BHD. Among these, patients displayed cutaneous manifestations ranging from none to greater than 100 lesions. Varying degrees of pulmonary and renal involvement, incidence of tubular and villous colorectal polyps, gastrointestinal cancers, and tonsillar squamous cell cancer were also noted. Sigmoid diverticulosis was reported in only one patient with the c.1733delC mutation. This patient also had a single tubular polyp, fewer than ten cutaneous lesions, and had not developed characteristic pulmonary or renal manifestations at the time of the study.\textsuperscript{18} Colonic abnormalities other than polyposis or colorectal carcinomas are infrequently described in association with Birt-Hogg-Dubé syndrome. However, given this particular patient's known history of BHD, colonic abnormalities such as diverticulosis may be on the phenotypic spectrum of BHD.

Appendiceal Diverticulosis

Diverticulosis of the vermiform appendix was first described by Kelynack in 1893.\textsuperscript{19} Both congenital and acquired appendiceal diverticula are rare with reported incidence rates of 0.014\%-1.7\%.\textsuperscript{20,21} Most acquired appendiceal diverticula form as pseudodiverticulae
with herniation of the mucosa through the muscularis propria, and these are usually found along the mesenteric border of the distal appendix. In contrast, congenital appendiceal diverticula are found along the antimesenteric border. Acquired diverticulosis of the appendix is usually asymptomatic, affects adults greater than 30 years of age, more common in males.\textsuperscript{19} Additionally, primary appendiceal or colonic neoplasms such as adenomas and mucinous tumors may be implicated in 30-48% of acquired cases.\textsuperscript{20} Upon evaluation with CT, appendiceal diverticulosis appears as round outpouchings beyond the appendiceal margin that may contain air, fluid, or enhancing soft-tissue.\textsuperscript{5,22}
A 40-year-old Caucasian woman with a past medical history significant for Crohn's disease and dyspnea and a family medical history of Birt-Hogg-Dubé syndrome presented to our facility in October 2013 for pulmonary and renal surveillance.

Upon computed tomography of the chest, she was found to have small subpleural blebs at the medial left lung base and in the right posterolateral lung base, without pneumothorax (Figure 1). No pleural effusion and no interstitial or infiltrative processes were identified, and there were no pulmonary masses, nodules, or atelectasis.

CT of the abdomen and pelvis revealed a vermiform appendix measuring up to 1.3 cm in diameter with small, fluid-filled diverticula, along the mesenteric and antimesenteric borders, and an overall thickened appearance, which was consistent with appendiceal diverticulosis (Figure 2). There was no adjacent fat infiltration or free fluid to suggest diverticulitis, and there were no appreciable obstructing masses. The small and large intestines were normal in course and caliber. The bilateral kidneys were free of cysts and normal in morphology without evidence of hydronephrosis. Remaining viscera were unremarkable.
Fig. 1: Figure 1a

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Fig. 2: Figure 1b

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Fig. 3: Figure 2a

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**Fig. 4:** Figure 2b

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Conclusion

Although there are no steadfast screening protocols, the need for pulmonary and renal surveillance among those diagnosed with Birt-Hogg-Dubé syndrome and their family members is widely accepted, because of the morbidity associated with this genetic condition. The incidence of cutaneous, pulmonary, and renal manifestations is widely reported, and sigmoid diverticulosis has been described in one patient with a family history of BHD. Our patient is the first known reported case of appendiceal diverticulosis among patients with a personal or family history of BHD. Interestingly, our patient's appendiceal diverticula were unique, presenting on both the mesenteric and anti-mesenteric borders, suggesting both a genetic and acquired entity. Although still debated, susceptibility to colonic anomalies secondary to microsatellite instability seems to be connected to the mutation in the *FLCN* gene seen in Birt-Hogg-Dubé syndrome. Future retrospective studies of those with personal or known family history of BHD may reveal similar anomalies if greater focus is placed on the vermiform appendix and colon. Furthermore, as pulmonary and renal screening studies are performed routinely in those with Birt-Hogg-Dubé syndrome, we recommend that additional focus be given to the gastrointestinal tract (including the appendix) at the time of computed tomography assessment.
References


Personal Information

A. Alexander and K. Hunter contributed equally to this work.