

PARSIMONY OR POOR LUCK: CONCURRENT BIRT-HOGG- DUBÉ SYNDROME AND SARCOIDOSIS

Brooks Kuhn, Priyanka Teckchandani, Richart Harper

Department of Pulmonology and Critical Care, UC Davis Medical Center

ABSTRACT. While sarcoidosis is notorious for myriad manifestations including cystic lung changes, we present a case with both Birt-Hogg-Dubé syndrome (BHD) and pulmonary sarcoidosis. BHD is a rare, autosomal dominant genetic disorder characterized by numerous thin-walled, irregular cysts, but lung function is typically normal otherwise. We present a case with confirmed BHD syndrome and concurrent granulomatous lung disease consistent with sarcoidosis. (*Sarcoidosis Vasc Diffuse Lung Dis* 2017; 34: 194-196)

KEY WORDS: sarcoidosis, Birt-Hogg- Dubé Syndrome, cystic lung disease

CASE STUDY

A Caucasian man in his 50's initially presented with a pneumothorax and multiple cystic lesions on CT chest. He was subsequently diagnosed with cystic sarcoidosis after surgical lung biopsy revealed non-caseating granulomas in the mediastinal lymph nodes and lung parenchyma and he was started on prednisone. He was seen in our clinic several years later due to worsening dyspnea after stopping immunosuppressive therapy. Of note, he had two siblings with cryptogenic cystic lung disease.

Significant physical exam findings included multiple, flesh-colored small nodules covering most of his face and fine rales at the bases of his lungs. Pulmonary function tests demonstrated severe restriction and a severe decrease in diffusion capacity. CT scan of the chest showed thin-walled, irregularly shaped cysts predominantly in the lower lobes, peri-

bronchial thickening, and bulky hilar adenopathy (figure 1). Complicated renal cysts were apparent in the apical pole of the left kidney. Serologic testing revealed an elevated angiotensin converting enzyme of 133 units per liter. Complete blood count, metabolic panel, and renal function were normal. Genetic testing for mutations in the folliculin gene (*FLCN*) was performed and was positive, confirming the diagnosis of Birt-Hogg-Dubé syndrome (BHD).

Given the unlikely possibility that this patient would have two rare diseases, we obtained and re-

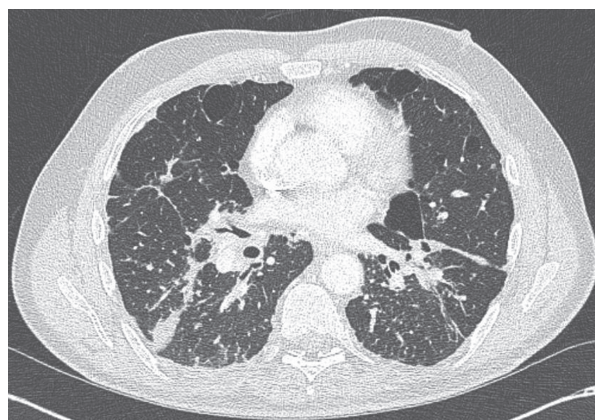


Fig. 1. CT of the chest. Note the dense peribronchiolar consolidations and irregularly shaped, peripheral cysts

Received: 3 May 2016

Accepted after revision: 6 September 2016

Correspondence: Brooks Kuhn, MD

4150 V Street, Suite 3400

Sacramento, CA 95818

United States of America

01 415-847-2172

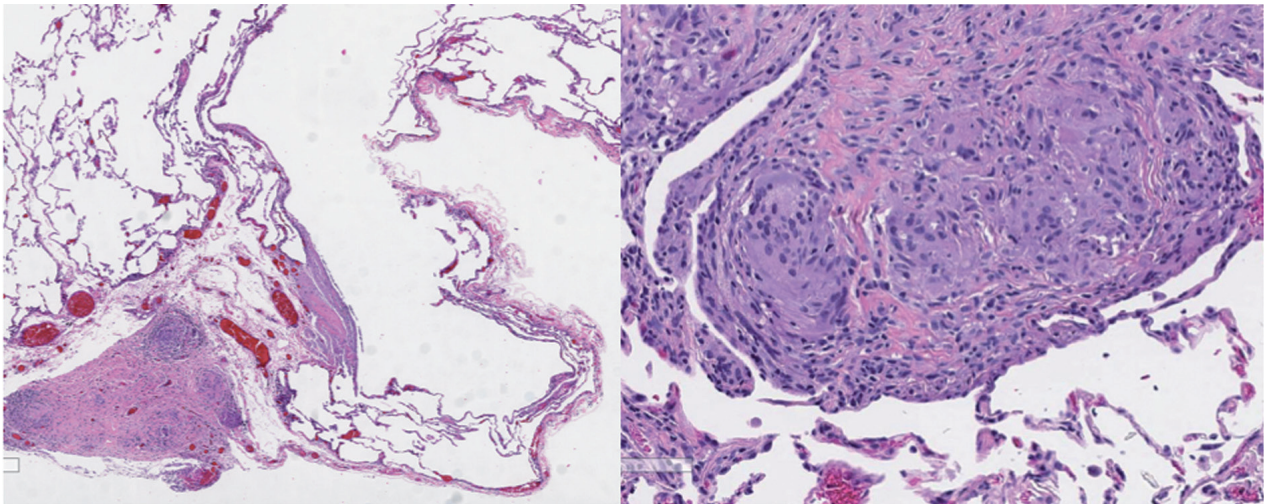


Fig. 2. Surgical biopsy of the left lower lobe. Numerous thin-walled cysts are seen adjacent to areas of consolidated, non-caseating granulomas. The image on the right exemplifies the numerous granulomas

viewed the pathology slides from his previous surgical biopsy (figure 2), which confirmed the presence of sarcoid-like granulomas. Mycobacterial, fungal, and bacterial cultures from the biopsy specimens were negative.

The patient was given both the diagnosis of Birt-Hogg-Dubé syndrome and sarcoidosis.

DISCUSSION

Birt-Hogg-Dubé syndrome (BHD) was first described in 1977 as a series of related patients with cutaneous fibrofolliculomas (1). Further characterization of these families revealed a clinical triad of fibrofolliculomas, premature renal cell carcinoma, and lung cysts. In the lung, BHD manifests with multiple, predominantly lower lobe, irregularly shaped, thin-walled cysts which frequently lead to pneumothorax in over 90% of cases (2-4). Uniquely, the cysts frequently abut pulmonary vessels and the pleura, and are additionally characterized by the lack of inflammation (2,5). Kumasaka et al. analyzed pathology of 229 BHD cysts from 50 unique individuals, finding a paucity of inflammation: 77.9% of intrapulmonary BHD cysts and 31.9% of subpleural cysts showing no inflammation (5). The majority of the inflammation seen was peripheral, and they concluded that this was likely secondary to pneumothoraces. Two individuals

were noted to have granulomas, but without description of the location or burden of disease.

The incidence of sarcoidosis in white men in the US is 10.9 per 100,000. BHD is a very rare disease with approximately 100 families identified, therefore prevalence is difficult to assess, but has been estimated at 1 per 200,000 (6). Reasonably assuming there is no genetic linkage or shared pathophysiology, the probability of concurrently having BHD and sarcoidosis would be 1 in 9.5 billion.

The mechanism that leads to pulmonary cysts in BHD remains unclear and is debated (5, 7, 8). A genetic cause was long hypothesized to drive this syndrome due to the autosomal dominant inheritance, but it was not until 2002 when the gene *FLCN* on chromosome 17p11.2, which encodes the protein folliculin, was identified as the cause (9). Folliculin is a tumor suppressor protein that is expressed in type I pneumocytes, skin, and kidney (5, 7, 8). Dysregulation of the mammalian target of rapamycin (mTOR) has been implicated in development of non-neoplastic pneumocyte proliferation contributing to cyst formation. mTOR complex 1 (mTORC1) has been found in increased concentration in BHD cysts (10). Folliculin is known to complex with folliculin-interacting proteins 1 and 2 (FNIP1/2), subsequently regulating mTOR. Lack of folliculin in BHD leads to dysregulated AMP kinase, mTORC1, hypoxia inducible factor, and transforming growth factor- β

(TGF- β), which can lead to cell proliferation and angiogenesis (8, 10, 11).

Alternatively, dysfunctional cell-cell adhesion has been implicated through e-cadherin and adherin junction protein p0071, leading to increased susceptibility to the shear stress of normal ventilation, explaining the progressive enlarging and coalescence of cysts, lower lobe predilection, and lack of inflammation (5, 11, 12).

The likelihood of having both sarcoidosis and BHD is exceptionally unlikely, so the observation that at least three individuals have BHD and granulomatous inflammation, suggests a shared pathophysiology. However, our current understanding of the pathophysiology of BHD does not immediately suggest clear overlap with sarcoidosis. Abnormal cell-cell adhesions are unlikely to lead to sarcoidosis. In fact, intact e-cadherin is key in the formation of multinucleated giant cells (13). Folliculin-FNIP1/2 complex-mediated mTORC1 pneumocyte type II proliferation is unlikely, as this would likely lead to proteolysis as in other diseases with this pathology (e.g. lymphangiomyomatosis) (5).

Interestingly, mTOR also interacts with folliculin-independent pathways to form mTOR complex 2 (mTORC2), a less-well defined complex in the mTOR pathway. Delgoffe *et al.* has implicated mTORC2, in the formation of regulatory T cells (14). The differential signaling from the two mTOR complexes appears to regulate the decision between naïve T cells developing into effector cells or regulatory cells. As dysfunctional regulatory T cells have been implicated in sarcoidosis, there is potential overlap via this pathway (15).

In conclusion, this is a unique case of BHD syndrome and sarcoidosis. While conclusions cannot be drawn from a single case report, the extreme rarity of concurrence of granulomas and BHD and previous mention in other case series suggests a potential common pathway in disease. Further understanding of how mTORC2 is regulated, the biologic processes that it controls, and how the two mTORC1 and mTORC2 pathways communicate with each other potentially will reveal important biological processes that are highlighted by this case.

REFERENCES

1. Birt AR, Hogg GR, Dubé WJ. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. *Arch Dermatol* 1977; 113(12): 1674-7.
2. Tobino K, Gunji Y, Kurihara M, et al. Characteristics of pulmonary cysts in Birt-Hogg-Dubé syndrome: Thin-section CT findings of the chest in 12 patients. *European Journal of Radiology* 2011; 77(3): 403-409. doi:10.1016/j.ejrad.2009.09.004.
3. Menko FH, van Steensel MA, Giraud S, et al. Birt-Hogg-Dubé syndrome: diagnosis and management. *Lancet Oncology* 2009; 10(12): 1199-206. doi:10.1016/S1470-2045(09)70188-3.
4. Hasumi H, Baba M, Hasumi Y, Furuya M, Yao M. Birt-Hogg-Dubé syndrome: Clinical and molecular aspects of recently identified kidney cancer syndrome. *Int J Urol* November 2015: n/a-n/a. doi:10.1111/iju.13015.
5. Kumasaka T, Hayashi T, Mitani K, et al. Characterization of pulmonary cysts in Birt-Hogg-Dubé syndrome: histopathological and morphometric analysis of 229 pulmonary cysts from 50 unrelated patients. *Histopathology* 2014; 65(1): 100-10. doi:10.1111/his.12368.
6. Lertsburapant and Yang (2008, November) OrphanNet: Birt-Hogg-Dubé Syndrome. http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=122.
7. Ferreira Francisco FA, Soares Souza A, Zanetti G, Marchiori E. Multiple cystic lung disease. *Eur Respir Rev* 2015; 24(138): 552-64. doi:10.1183/16000617.0046-2015.
8. Furuya M, Nakatani Y. Birt-Hogg-Dubé syndrome: clinicopathological features of the lung. *J Clin Pathol* 2013; 66(3): 178-86. doi:10.1136/jclinpath-2012-201200.
9. Nickerson ML, Warren MB, Toro JR, et al. Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the Birt-Hogg-Dubé syndrome. *Cancer Cell* 2002; 2(2): 157-64.
10. Nishii T, Tanabe M, Tanaka R, et al. Unique mutation, accelerated mTOR signaling and angiogenesis in the pulmonary cysts of Birt-Hogg-Dubé syndrome. *Pathology International* 2013; 63(1): 45-55. doi:10.1111/pin.12028.
11. Medvetz DA, Khabibullin D, Hariharan V, et al. Folliculin, the product of the Birt-Hogg-Dubé tumor suppressor gene, interacts with the adherens junction protein p0071 to regulate cell-cell adhesion. *Nam S-C, ed. PLoS ONE* 2012; 7(11): e47842. doi:10.1371/journal.pone.0047842.
12. Goncharova EA, Goncharov DA, James ML, et al. Folliculin Controls Lung Alveolar Enlargement and Epithelial Cell Survival through E-Cadherin, LKB1, and AMPK. *Cell Reports* 2014; 7(2): 412-423. doi:10.1016/j.celrep.2014.03.025.
13. Wanat KA, Rosenbach M, Zoiber AF, Zhang PJ, Schaffer A. E-Cadherin Is Expressed by Mono- and Multinucleated Histiocytes in Cutaneous Sarcoid and Foreign Body Granulomas. *The American Journal of Dermatopathology* 2014; 36(8): 651-654. doi:10.1097/DAD.0b013e31828de7e0.
14. Delgoffe GM, Kole TP, Zheng Y, et al. The mTOR Kinase Differentially Regulates Effector and Regulatory T Cell Lineage Commitment. *Immunity* 2009; 30(6): 832-844. doi:10.1016/j.immuni.2009.04.014.
15. Moller DR. Cells and cytokines involved in the pathogenesis of sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1999; 16(1): 24-31.