Irish Medical Journal
Established 1867

Issue: Ir Med J; Vol 114; No. 8; P445

Birt-Hogg-Dubé Syndrome: From a Skin Tissue to a Multi-Visceral Issue

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Abstract

Presentation

A 39-year-old woman noticed subtle skin changes on her face.

Diagnosis

Skin biopsy revealed fibrofolliculomas, a hallmark of Birt-Hogg Dubé syndrome (BHDs). Molecular genetic testing for the folliculin gene identified a pathogenic in-frame deletion mutation and imaging yielded multiple bilateral thin-walled lung cysts and an indeterminate renal lesion questionable for neoplasm.

Treatment

The patient was educated about possible complications and referred for genetic counselling as well as respiratory, renal, and dermatological services for appropriate specialist surveillance.

Conclusion

Birt-Hogg-Dubé syndrome is a rare genetic disease characterized by benign skin lesions, thin-walled pulmonary cysts, spontaneous pneumothorax, and renal tumours. Clinical features are easily under-recognized. A multidisciplinary specialist approach along with vigilant screening and genetic counselling are integral to management.

Introduction

Birt-Hogg-Dubé syndrome, a rare autosomal dominant disease affecting approximately 200 families worldwide, is linked to a mutation in the folliculin gene which encodes the protein folliculin (*FLCN*). [1,2,4]

Folliculin's function is largely unknown yet studies have shown it is naturally expressed in multiple tissues, alteration of which leads to formation of cystic structures in certain tissues and tumour suppression in others.

To elaborate more on this, the *BHD* gene also known as tumour suppressor gene *Folliculin* (*FLCN)* which is expressed in multiple tissues including the skin, lungs, and kidneys codes for the protein folliculin. Folliculin has been shown to have a role in tumor suppression exercising an inhibitory effect on the growth-promoting mammalian target of rapamycin (mTOR) pathway. [7,8]

Mutations and therefore modifications observed within the *FLCN* gene in BHDs lead to the expression of indolent or ineffective folliculin, subsequently activating the mTOR pathway. This in turn promotes cell growth and proliferation eventually resulting in tumour pathogenesis. The clinical expression of which typically includes cutaneous fibrofolliculomas and renal tumours of various histological types. [7,8]

A wide range of phenotype heterogeneity exists in families with Birt-Hogg-Dubé Syndrome despite sharing the same folliculin mutation.[3]

Diseases characteristics include multiple benign skin lesions (fibrofolliculomas and trichodisomas), thin-walled pulmonary cysts, spontaneous pneumothorax (89%), and sevenfold increased risk for renal tumours. [1,5]

Identification and treatment of complications, genetic counselling and appropriate surveillance are the cornerstones of management.

Case Report

A 39-year-old woman with a history of treated superficial spreading malignant melanoma attended for routine skin surveillance where she drew attention to new flesh-like bumps on her face (Figure 1)

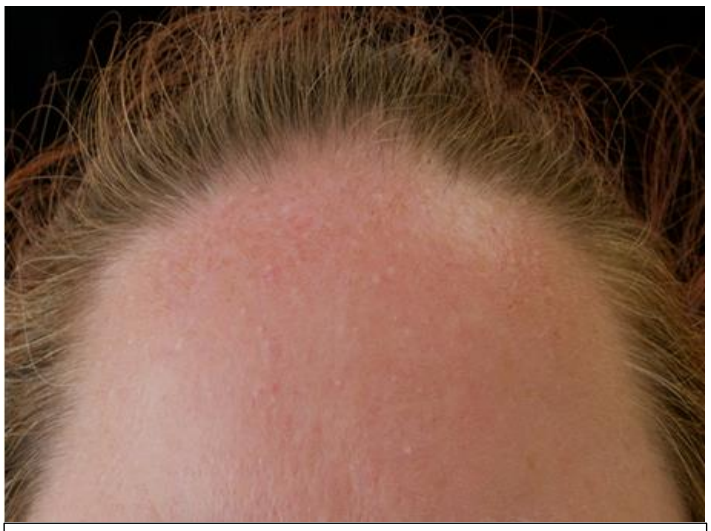

Figure 1: Forehead image showing small discrete subtle white to flesh coloured smooth dome shaped papules. These discrete papules appear clinically indistinguishable.

The 1-3mm flesh-coloured dome-shaped papules were spread across her forehead and cheeks and slowly multiplying in previous months to years. Skin biopsy was sought and a histopathological diagnosis of 'fibrofolliculoma' was made, a hallmark of Birt-Hogg-Dubé Syndrome.

Molecular genetic testing for folliculin gene was undertaken. Sequence analysis of the *FLCN* gene identified the pathogenic heterozygous variant c.1522_1524delAAG, p.(Lys508del). Full blood count, renal, liver, bone, and autoimmune profiles were normal.

High resolution CT Thorax revealed multiple bilateral thin-walled lung cysts with no pneumothorax (Figure 2). Contrast MRI kidney identified an isolated 13 mm T2 hypointense endophytic lesion in the interpolar region of the right kidney which could represent renal malignancy.

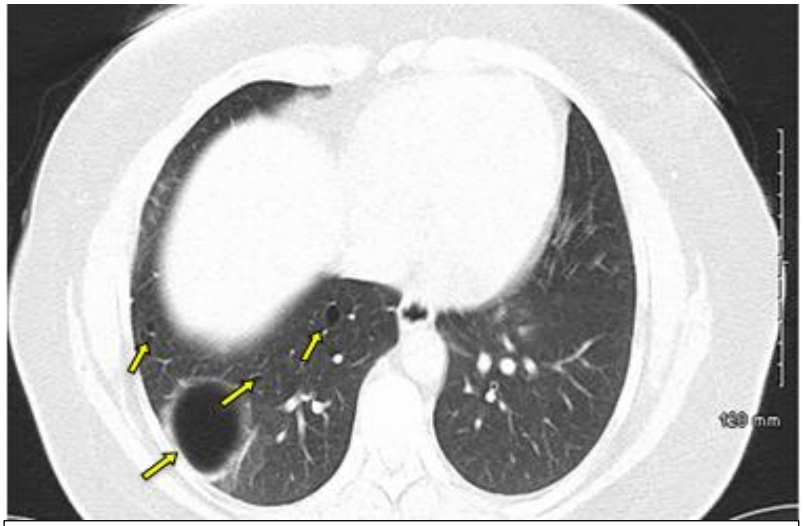

Figure 2: Chest CT showing multiple bilateral thin-walled lung cysts (arrows) consistent with the diagnosis of Birt-Hogg-Dubé syndrome the largest of these is in the posterior basal right lower lobe and measures 5.8 cm in diameter.

The combination of fibrofolliculomas, lung cysts, suspicious MRI kidney findings along with the positive pathogenic variant on genetic testing consolidated a diagnosis of Birt-Hogg-Dubé Syndrome.

Fibrofolliculomas are benign. Conventional cosmetic treatments were offered which our patient did not pursue.

There is currently no specific therapy/follow-up strategy of lung cysts associated with Birt-Hogg-Dubé Syndrome. Treatment strategies are based on education and management of complications.[7] Given the 50-fold increased risk of pneumothorax, counselling was given on avoidance of precipitants such as smoking and diving.[9] Respiratory specialist involvement ensured close outpatient surveillance.

The role of close respiratory outpatient follow up centres around preventing and treating pneumothoraces. It is recommended to repeatedly remind patients about the risk and symptoms of pneumothorax, and to recommend medical assessment in case of new respiratory symptoms such as dyspnoea or chest pain because of the high recurrence rate of pneumothorax in BHD. Furthermore, it is recommended to consider pleurodesis after the first episode of spontaneous pneumothorax. Moreover, periodic pulmonary function testing should be provided to patients with impaired lung function at baseline and those with extensive cystic lung disease.[7,9]

Annual MRI surveillance of the renal lesion was recommended with follow-up approach dictated by size and nature of tumour progression. Renal specialist involvement was organized. Expert recommendations suggest 36 monthly abdominal imaging in patients without evidence of renal lesions on baseline imaging.[6]

Given the 50% inheritance risk, this woman opted for genetic counselling and her family were subsequently screened. She had a family history of paternal colon cancer in his fifth decade; however, she did not know of any previous family members to suffer pneumothoraces or renal tumours.

Discussion

Birt-Hogg-Dubé Syndrome highlights how subtle and inconspicuous skin changes which could be easily overlooked can be the key to a life-changing diagnosis of a potentially very serious genetic condition.

There is not yet enough evidence to prove an association between Melanoma and Birt-Hogg-Dubé Syndrome, but this case raises an interesting consideration given the pathogenesis overlap in some signalling pathways such as mTOR. [10]

We wish to emphasise the importance of thorough skin examination, especially in those with newly identified lung cysts or pneumothoraces.

Due to the Birt-Hogg-Dubé Syndrome's rarity, carcinogenicity, heterogeneity of clinical manifestations, and propensity to mimic other clinical entities, a unifying diagnosis can be very challenging and early recognition, timely diagnosis, and appropriate interventions are key factors influencing survival and prognosis of patients and affected family members.

Patient Consent:
Received.

Declaration of Conflicts of Interest:
No conflicts of interest to be declared.

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References:

1. Dal Sasso AA, Belém LC, Zanetti G, Souza CA, Escuissato DL, Irion KL, et al. Birt-Hogg-Dubé syndrome. State-of-the-art review with emphasis on pulmonary involvement. Respiratory Medicine. 2015 Mar;109(3):289–96.
2. Rehman HU. Birt-Hogg-Dubé Syndrome: Report of a New Mutation. Canadian Respiratory Journal. 2012;19(3):193–5.
3. Schmidt LS, Nickerson ML, Warren MB, Glenn GM, Toro JR, Merino MJ, et al. Germline BHD-Mutation Spectrum and Phenotype Analysis of a Large Cohort of Families with Birt-Hogg-Dubé Syndrome. The American Journal of Human Genetics. 2005 Jun;76(6):1023–33.
4. Toro JR, Wei M-H, Glenn GM, Weinreich M, Toure O, Vocke C, et al. BHD mutations, clinical and molecular genetic investigations of Birt–Hogg–Dubé syndrome: a new series of 50 families and a review of published reports. J Med Genet. 2008 Jun 1;45(6):321.
5. Menko FH, van Steensel MA, Giraud S, Friis-Hansen L, Richard S, Ungari S, et al. Birt-Hogg-Dubé syndrome: diagnosis and management. The Lancet Oncology. 2009 Dec;10(12):1199–206.
6. Stamatakis L, Metwalli AR, Middelton LA, Marston Linehan W. Diagnosis and management of BHD-associated kidney cancer. Familial Cancer. 2013 Sep;12(3):397–402.
7. Ferreira Francisco FA, Soares Souza A, Zanetti G, Marchiori E. Multiple cystic lung disease. Eur Respir Rev. 2015 Dec;24(138):552–64.

8. Cocciolone RA, Crotty KA, Andrews L, Haass NK, Moloney FJ. Multiple Desmoplastic Melanomas in Birt-Hogg-Dubé Syndrome and a Proposed Signaling Link Between Folliculin, the mTOR Pathway, and Melanoma Susceptibility. Arch Dermatol [Internet]. 2010 Nov 1 [cited 2019 Nov 2];146(11). Available from: http://archderm.jamanetwork.com/article.aspx?doi=10.1001/archdermatol.2010.333
9. Zbar B, Alvord WG, Glenn G, Turner M, Pavlovich CP, Schmidt L, et al. Risk of Renal and Colonic Neoplasms and Spontaneous Pneumothorax in the Birt-Hogg-Dubé Syndrome. Cancer Epidemiol Biomarkers Prev. 2002 Apr 1;11(4):393.
10. Sattler EC, Ertl-Wagner B, Pellegrini C, Peris K, Reithmair M, Schädle N, et al. Cutaneous melanoma in Birt-Hogg-Dubé syndrome: part of the clinical spectrum? Br J Dermatol. 2018 Feb;178(2):e132–3.