Respiratory Medicine Case Reports 19 (2016) 106–108

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case report

Recurrent spontaneous pneumothoraces and bullous emphysema. A novel mutation causing Birt-Hogg-Dube syndrome

Andrew Burkett [a, *], Niamh Coffey [b], Eva Tomiak [c], Nha Voduc [a]

[a] University of Ottawa, The Ottawa Hospital, Division of Respiratory Medicine, Canada
[b] University of Ottawa, The Ottawa Hospital, Department of Medical Imaging, Canada
[c] University of Ottawa, Children's Hospital of Eastern Ontario, Department of Genetics, Canada

ARTICLE INFO

Article history:
Received 2 February 2016
Received in revised form
14 August 2016
Accepted 21 August 2016

Keywords:
Interstitial lung disease
Birt-Hogg-Dube
Cystic lung disease

ABSTRACT

Birt-Hogg-Dube syndrome (BHDS) is a rare form of classically cystic lung disease that may present with spontaneous pneumothorax. The associated skin manifestations (fibrofolliculomas) are not always present. This article describes a case of spontaneous pneumothorax secondary to bullous emphysema in an otherwise healthy gentleman caused by a novel mutation in the folliculin (*FLCN*) gene.

1. Case presentation

In November 2012, a 46 year old man was referred for assessment of spontaneous pneumothoraces pending an upcoming bullectomy by thoracic surgery. This gentleman had a past medical history of recurrent pneumothoracies, asthma diagnosed in childhood, eczema, depression and anxiety. His only current medication was duloxetine 30mg daily. His pneumothoraces began 24 years ago, the first of which was a tension pneumothorax he developed after contact in a rugby game at the age of 22. He has had 7 spontaneous pneumothoraces in total, 3 of which were treated with a chest tube. He underwent a right bullectomy in 1996 and, after being assessed in our clinic, proceeded with left bullectomy with subtotal parietal pleurectomy later in November 2012. At time of assessment, he was asymptomatic. He had no cough, dyspnea, chest pain, or exercise limitations.

He is a lifelong non-smoker and has no work place or hobby exposures. His family history is positive for a mother with colon cancer diagnosed at the age of 45 and a sister with spontaneous pneumothoraces. There was no history of renal neoplasms in the family.

His physical exam was normal with no evidence of skin lesions, abdominal masses, or hypertension.

Pulmonary investigations included pulmonary function tests (PFTs), thoracic computed tomography (CT), and surgical lung biopsy. PFTs demonstrated a total lung capacity of 6.65 L (93% predicted), a reduced forced vital capacity (FVC) of 3.44 L (68% of predicted [normal ≥80%]), and a reduced forced expiratory volume in 1s (FEV1) of 1.96 L (49% of predicted [normal ≥80%]); there was evidence of airflow obstruction, with a FEV_1/FVC ratio of 57% (normal ≥70%). Post bronchodilator, his FEV1 improved to 2.70 L (67% predicted) which is a 38% improvement. His diffusing capacity for carbon monoxide (DLCO) was normal at 74% predicted.

A CT scan showed multiple, bilateral cysts in varying sizes and shapes with the largest measuring 10 cm within the left lower lobe (Fig. 1). With regards to craniocaudal distribution, there was a basal predominance. With regards to axial distribution, the cysts were diffuse with no central or peripheral predominance. The cysts demonstrated variable morphology with many of the larger supleural cysts within the lower lobes demonstrating lobulated, septated appearance. Intervening parenchyma appeared unremarkable without nodules, ground glass, septal thickening or honeycombing.

The patient was diagnosed with asthma and started on budesonide/formoterol fumarate turbuhaler 200/6 mcg 2 inhalations twice daily, sent for asthma education, and referred to a Geneticist. The patient was counselled that his uncontrolled asthma may be contributing to bullae enlarging and risk of spontaneous pneumothorax. Pathological samples of lung tissue obtained during his left bullectomy showed benign lung parenchyma with subpleural

* Corresponding author.
E-mail address: aburkett@toh.ca (A. Burkett).

http://dx.doi.org/10.1016/j.rmcr.2016.08.006

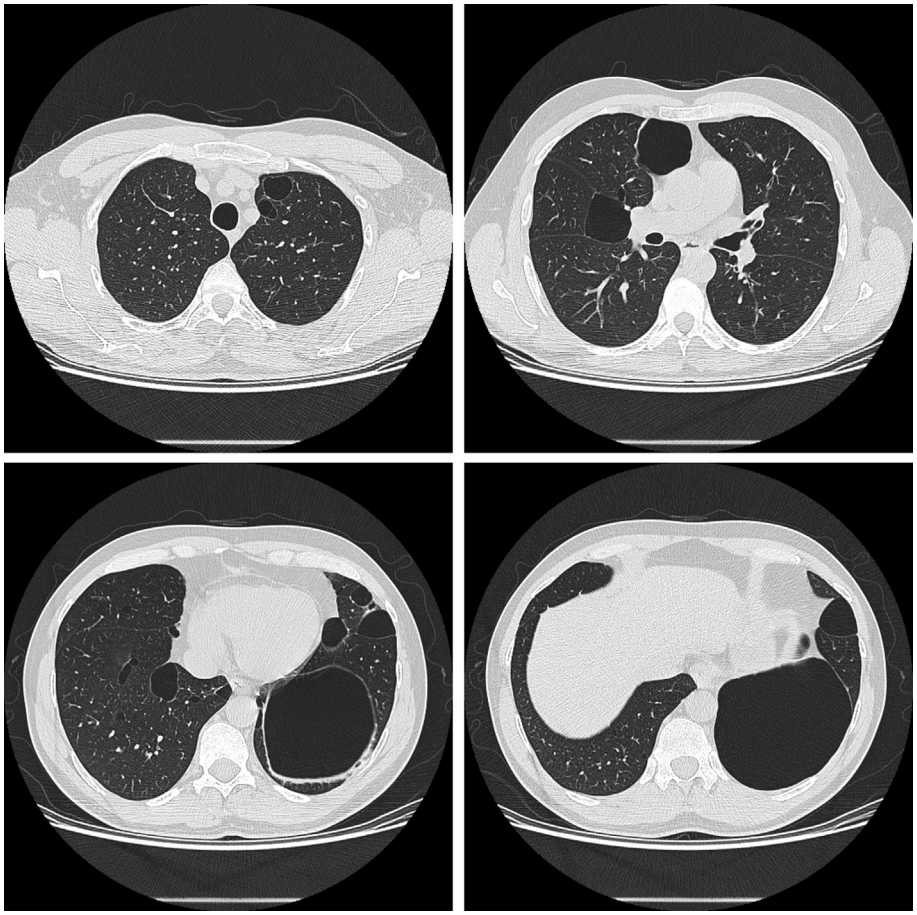

Fig. 1. Patient's presenting CT scan of the thorax demonstrating multiple, lobulated, septated bilateral cysts in varying sizes and shapes with a basal predominance.

bulla and benign pleural tissue with evidence of chronic inflammation. No cystic lesions were identified despite two large samples being obtained from the left upper and lower lobes.

Based on the clinical presentation, family history, and CT results, the patient's diagnosis was most compatible with Birt-Hogg-Dube syndrome (BHDS) syndrome. Genetic testing revealed a deleterious mutation (c.1219delA) in his folliculin (*FLCN*) gene. He has had no post-surgical complications and abdominal CT showed normal sized kidneys with no renal lesions. His immediate family members were referred to a Geneticist for consideration of screening.

2. Discussion

BHDS is a rare autosomal dominant genodermatosis that described in 1977 as the triad of multifocal kidney cancer, pulmonary cysts, and fibrofolliculomas by three Canadian physicians [1]. While the fibrofolliculomas are classical of BHDS, only two thirds of BHDS patients will develop these lesions [2]. Lung involvement is seen in 80% of BHDS patients and spontaneous pneumothorax is the presenting feature in 25% of patients [3]. Renal cancer has variable penetrance in BHDS with 30% of patients developing solitary or multi-focal lesions [4]. Although not classically described in the triad, the original case reports of a BHDS like syndrome included generalized fibrofolliculomas and colonic polyps [5,6] and one case series found an incidence of colonic lesions (polyps or GI cancer) in 30% of BHDS patients [2].

The radiological lung findings in classical BHDS vary in severity but, if present, may show lentiform-shaped cysts that predominate in the lung bases and periphery and abut or include the proximal portions of the lower lobe pulmonary arteries and veins [7,8]. In the absence of extra-pulmonary manifestations that may help confirm BHDS, the lower zone location of cysts abuting vessels, lentiform cysts with or without septae, and absence of emphysema strongly suggest BHDS [7]. A family history of spontaneous pneumothorax should also raise strong suspicion for BHDS among the other causes of familial spontaneous pneumothorax which include Marfan syndrome, Homocystinuria, Ehlers–Danlos syndrome, and α1-Antitrypsin deficiency [9]. This patient had multiple large bullae with septae in addition to smaller, more typical, cysts and we hypothesized that his untreated airflow obstruction from asthma predisposed bullae formation. Regardless of etiology, the pleuroulomonary pathology of multiple pleural blebs and large subpleural bullae with pleural changes consistent with pneumothorax has been described [10] and, while not specific, these changes are rare in the absence of emphysematous changes outside of BHDS.

Molecular genetic testing for BHDS is the gold standard and can detect 88% of the mutations thought to cause BHDS [11]. Genetic testing to confirm the disease should be considered, even in highly suspicious cases, unless the patient has the other major criteria for diagnosis of BHDS (at least 5 adult onset fibrofolliculomas) [12]. In addition, The European BHDS Consortium suggests it is reasonable to order genetic testing on any patients with characteristic skin lesions, cystic lung disease of no apparent cause, spontaneous pneumothorax, early onset renal cancer, or a first degree relative with any of the prior features. A clinical diagnosis of BHDS can be made if a patient fulfills 1 major or 2 minor criteria from Table 1

Table 1
Criteria to diagnose BHDS [12].

Major criteria
At least five fibrofolliculomas or trichodiscomas, at least one histologically confirmed, of adult onset
Pathologic FLCN germline mutation
Minor Criteria
Multiple lung cysts: bilateral basally located lung cysts with no other apparent cause, with or without spontaneous pneumothorax
Renal cancer: early onset (<50 years) or multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology
A first degree relative with BHDS

A clinical diagnosis can be made of BHDS if a patient fulfills 1 major or 2 minor criteria.

[12].

The pathological findings in BHDS are caused by a loss of function mutation in the tumor suppressor gene *FLCN* which expresses the protein folliculin [13]. Our patient was found to have a novel *FLCN* mutation (c.1219delA) which has not been previously reported. This mutation causes a frameshift starting with codon Serine 407 creating a premature Stop codon at position 61 of the new reading frame (p.Ser407AlafsX61). This mutation is predicted to cause loss of normal protein function, either through protein truncation or nonsense-mediated mRNA decay. Fortunately for our patient, it has been suggested that patients with a C-deleterious mutation maybe have a five-fold less risk of developing a renal neoplasm compared to patients with a C-insertion mutation [14].

Annual screening for renal tumors with ultrasound is common despite evidence that it is not sensitive enough to detect smaller lesions [15]. Although CT is much more sensitive than U/S for detecting lesions 1.5–2cm (100% vs. 58%) [15], the lifetime dose of radiation would be unacceptably high. Therefore, screening with renal MRI is recommended over U/S if it's available [12] although there are no guidelines on the frequency of screening needed. As the mean age of presentation with kidney cancer is 48–51 years in BHDS (standard deviation 11.7 years, range 31–74 years) [14,16], at our center we offer renal MRI screening at the age of 30 and repeat it every 4–5 years in the absence of symptoms. Currently, the recommendation is patients do not need more frequent colon cancer screening than the general population.

An accurate diagnosis of BHDS is important to guide prognosis, management including screening, and family counselling. While there is no current treatment for BHDS, early detection of operable renal cancers remains an important part of surveillance. Animal studies in BHDS knockout mice have shown a survival benefit with treatment using sirolimus [17] and clinical trials using topical sirolimus to treat fibrofolliculomas are underway [18].

3. Conclusion

The present report described an unusual cause of spontaneous pneumothorax in the setting of bullous lung disease caused by BHDS and reports a novel mutation in the *FLCN* gene causing this clinical syndrome. We recommend genetic testing for BHDS in any patient with unexplained lower lobe bullous lung disease even in the absence of cystic lesions on pathological specimen.

Written informed consent was provided by the patient to submit this manuscript and can be provided at the editor's request.

Conflict of interest

None. The authors have no conflicts of interest to declare.

References

[1] A.R. Birt, G.R. Hogg, W.J. Dubé, Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons, Arch. Dermatol. 113 (12) (1977) 1674–1677.

[2] S. Khoo, S. Giraud, K. Kahnoski, Clinical and genetic studies of Birt-Hogg-Dube syndrome, J. Med. Genet. 39 (12) (2002) 906–912.

[3] J.R. Toro, S.E. Pautler, L. Stewart, G.M. Glenn, M. Weinreich, O. Toure, M.-H. Wei, L.S. Schmidt, L. Davis, B. Zbar, P. Choyke, S.M. Steinberg, D.M. Nguyen, W.M. Linehan, Lung cysts, spontaneous pneumothorax, and genetic associations in 89 families with Birt-Hogg-Dubé syndrome, Am. J. Respir. Crit. Care Med. 175 (10) (2007) 1044–1053.

[4] A.C. Houweling, L.M. Gijezen, M.A. Jonker, M.B.A. van Doorn, R.A. Oldenburg, K.Y. van Spaendonck-Zwarts, E.M. Leter, T.A. van Os, N.C.T. van Grieken, E.H. Jaspars, M.M. de Jong, E.M.H.F. Bongers, P.C. Johannesma, P.E. Postmus, R.J.A. van Moorselaar, J.-H. van Waesberghe, T.M. Starink, M.A.M. van Steensel, J.J.P. Gille, et al., Renal cancer and pneumothorax risk in Birt-Hogg-Dubé syndrome; an analysis of 115 FLCN mutation carriers from 35 BHD families, Br. J. Cancer 105 (12) (2011) 1912–1919.

[5] O. Hornstein, M. Knickenberg, Perifollicular fibromatosis cutis with polyps of the colon—a cutaneo-intestinal syndrome sui generis, Arch. Dermatol. Res. 12 (253) (1975) 161–175.

[6] O. Hornstein, Generalized dermal perifollicular fibromas with polyps of the colon, Hum. Genet. 33 (2) (1976) 193–197.

[7] P.P. Agarwal, B.H. Gross, B.J. Holloway, J. Seely, P. Stark, Kazerooni E a. Thoracic CT findings in Birt-Hogg-Dube syndrome, Am. J. Roentgenol. 196 (2) (2011) 349–352.

[8] K. Tobino, Y. Gunji, M. Kurihara, M. Kunogi, K. Koike, N. Tomiyama, T. Johkoh, Y. Kodama, S. Iwakami, M. Kikkawa, K. Takahashi, K. Seyama, Characteristics of pulmonary cysts in Birt-Hogg-Dubé syndrome: thin-section CT findings of the chest in 12 patients, Eur. J. Radiol. 77 (3) (2011) 403–409.

[9] H.T. Chiu, C.K. Garcia, Familial spontaneous pneumothorax, Curr. Opin. Pulm. Med. 12 (4) (2006) 268–272.

[10] K. Butnor, D.G. Guinee Jr., Pleuropulmonary pathology of Birt-Hogg-Dubé syndrome, Am. J. Surg. Pathol. 30 (3) (2006) 395–399.

[11] J.R. Toro, Birt-Hogg-Dubé Syndrome, Feb 27 [Updated 2014 Aug 7], in: R.A. Pagon, M.P. Adam, H.H. Ardinger, et al. (Eds.), GeneReviews® [Internet], University of Washington, Seattle, Seattle (WA), 2006, pp. 1993–2016. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1522/.

[12] F.H. Menko, M.A.M. van Steensel, S. Giraud, L. Friis-Hansen, S. Richard, S. Ungari, M. Nordenskjöld, T.V. Hansen, J. Solly, E.R. Maher, Birt-Hogg-Dubé syndrome: diagnosis and management, Lancet Oncol. 10 (12) (2009) 1199–1206.

[13] J.N. Painter, H. Tapanainen, M. Somer, P. Tukiainen, K.A. Aittomäki, 4-bp deletion in the Birt-Hogg-Dubé gene (FLCN) causes dominantly inherited spontaneous pneumothorax, Am. J. Hum. Genet. 76 (3) (2005) 522–527.

[14] L.S. Schmidt, M.L. Nickerson, M.B. Warren, G.M. Glenn, J.R. Toro, M.J. Merino, M.L. Turner, P.L. Choyke, N. Sharma, J. Peterson, P. Morrison, E.R. Maher, M.M. Walther, B. Zbar, W.M. Linehan, Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dubé syndrome, Am. J. Hum. Genet. 76 (6) (2005) 1023–1033.

[15] P. Choyke, G. Glenn, M. Walther, Hereditary renal cancers, Radiology 226 (2003) 33–46.

[16] C.P. Pavlovich, M.M. Walther, R.A. Eyler, S.M. Hewitt, B. Zbar, W.M. Linehan, M.J. Merino, Renal tumors in the Birt-Hogg-Dubé syndrome, Am. J. Surg. Pathol. 26 (12) (2002) 1542–1552.

[17] M. Baba, M. Furihata, S.-B. Hong, L. Tessarollo, D.C. Haines, E. Southon, V. Patel, P. Igarashi, W.G. Alvord, R. Leighty, M. Yao, M. Bernardo, L. Ileva, P. Choyke, M.B. Warren, B. Zbar, W.M. Linehan, L.S. Schmidt, Kidney-targeted Birt-Hogg-Dube gene inactivation in a mouse model: Erk1/2 and Akt-mTOR activation, cell hyperproliferation, and polycystic kidneys, J. Natl. Cancer Inst. 100 (2) (2008) 140–154.

[18] M.A.M. van Steensel, Topical Rapamycin to Treat Fibrofolliculomas in Birt-hogg-dubé Syndrome (NCT00928798), Available from: http://clinicaltrials.gov/ct2/show/NCT00928798.