CASE REPORT

Birt-Hogg-Dubé syndrome: a rare cause of cystic lung diseases

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SUMMARY

Cystic lung diseases are characterised by multiple intrapulmonary cysts. They can be mimicked by other more common causes of focal parenchymal lucencies such as emphysema, bronchiectasis and honeycombing. The various conditions have differing managements and prognoses, thus correct evaluation is essential. Birt-Hogg-Dubé (BHD) syndrome is an autosomal dominant disorder, that is, a rare cause of cystic lung disease. It is seen in approximately 200 families worldwide. This case describes a 37-year-old woman who presented to a District General Hospital with symptoms of pleuritic chest pain and breathlessness. A CT pulmonary angiogram arranged to assess for pulmonary emboli excluded this but it demonstrated multiple intrapulmonary cysts. After further investigation and subsequent genetic testing this was confirmed to be BHD syndrome.

BACKGROUND

Cystic lung disease encompasses a group of acquired and congenital disorders with distinct features but plenty of overlap among the disease characteristics. Cystic lung disease encompasses four categories of disease: bronchogenic cysts, cystic adenomatoid malformation, lobar emphysema and pulmonary sequestration. The type of cystic lung disease that develops is often contingent upon the timing of the insult during fetal development. Acquired cystic lung disease can arise from trauma to the lungs, as a complication from infection, or from degenerative diseases such as interstitial pulmonary emphysema.

Birt-Hogg-Dubé (BHD) is a rare autosomal dominant disorder, that is, characterised by mutations in the *FLCN* gene,¹ located on the short arm of chromosome 17. They can also occur as a new mutation in an individual with no prior family history. The *FLCN* gene encodes folliculin, which is thought to be a tumour suppressor protein. This protein has been found to be expressed in the normal cells of the skin, kidney, stromal cells and type I pneumocytes of the lung, acinar cells of the pancreas and parotid gland. Mutations in the *FLCN* gene may interfere with the ability of folliculin to restrain cell growth and division, leading to the formation of non-cancerous and cancerous tumours.

The earliest case of possible BHD in the medical literature was published by Burnier and Rejesk in 1927. However, the syndrome was only first well described in 1977. Birt, Hogg and Dubé reported a kindred study of 70 members of three generations, 15 of whom exhibited multiple small skin-coloured

to greyish-white dome-shaped papules distributed over the face, neck and upper trunk.

The syndrome is characterised by the presence of the following clinical triad:^{2,3}

1. Benign skin tumours: most patients develop fibrofolliculomas, which are benign hair follicle tumours after the age of 20 years. They appear as whitish papules.
2. Pulmonary cysts and pneumothorax: the majority individuals (up to 90%) with BHD have multiple cysts in both lungs, detected by chest CT scans. The cysts give rise to an increased risk of pneumothorax and 24% of patients have had one or more episodes of pneumothorax.
3. Renal cell carcinoma: individuals are predisposed to these tumours, which can manifest as various types of renal cell carcinoma. Cases of chromophobe, oncocytic, clear-cell, papillary and hybrid tumours have all been identified in BHD patients.

CASE PRESENTATION

A 37-year-old female patient initially presented to the emergency department with a history of central pleuritic chest pain and acute onset of shortness of breath. She had also been experiencing coryzal symptoms and was expectorating some white sputum. All her observations were stable, her oxygen saturations were 100% and she had no fever. A full examination did not reveal any focal abnormalities. She was treated at that time for a chest infection.

Of note she had a medical history of an atrial-septal defect repair 12 years previously. As part of her investigations for infertility she had been found to have polycystic ovaries. Two years prior to her presentation she had been treated for a skin tag near to her nipple, which was thought to be a papilloma. There was no history of exposure to pneumotoxins and she was a life-long non-smoker. She was originally born in Pakistan but had lived in the UK from the age of 2 years. A travel history demonstrated occasional visits to Pakistan. Her family history only revealed her father and sister to have asthma.

INVESTIGATIONS

On admission, the patient had a routine panel of blood tests and a D-dimer because the differential included pulmonary emboli. The only abnormality was an elevated D-dimer, which prompted a CT pulmonary angiogram, despite the patient having a low Wells score. The scan excluded a pulmonary

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embolism and could have been seen as an overuse of such an investigation. However, it did lead to the discovery of multiple basal intrapulmonary cystic air spaces in both lung fields. This finding prompted a referral to the respiratory outpatient clinic.

In the clinic an autoimmune screen was performed, including antinuclear and antinucleolar antibodies and rheumatoid factor. This was to assess for any collagen vascular diseases or autoimmune conditions. Immunoglobulin levels were measured; these are helpful as a screen to assess for immune deficiency, which together with Sjogren's disease and HIV infection can cause lymphocytic interstitial pneumonia (LIP). A hydatid assay was also performed to exclude parasites as a cause. For this patient all these results were normal except for a slightly raised IgG level.

Lung function testing was arranged to assess for any obstructive or restrictive defects in function and demonstrated: FEV1 1.71 (81% predicted), FVC 2.23 (91%), TLCO 78% predicted with significant postbronchodilator reversibility. An echocardiogram demonstrated a normal left ventricular cavity size and a normal ejection fraction, normal right ventricular size and right ventricular systolic pressure of 24 mm Hg+right atrial pressure. There was no residual shunt.

An expert opinion was obtained from a tertiary centre where the investigations were repeated. In addition a cardiopulmonary exercise test was performed; the patient managed 8 min of the Balke protocol, which terminated due to breathlessness and leg pain. There was no evidence of any deaeration but there was an element of overbreathing with a reduction of the carbon dioxide. At the tertiary centre the CT findings were felt to be consistent with a diagnosis of BHD syndrome. An open lung biopsy was considered but not undertaken due to the stability of the patient's lung function tests. Subsequent genetic testing was performed, which confirmed the diagnosis.

DIFFERENTIAL DIAGNOSIS

It is important to characterise cystic lung diseases as to whether the changes are focal, multifocal, diffuse cystic lung disease and a miscellaneous group including BHD. Owing to patient's age and sex the initial diagnosis was felt to be that of lymphangioleiomyomatosis. However, following review at the tertiary centre and expert radiological advice, the CT scan images were

felt to be most consistent with BHD due to the cysts being predominantly basal. Hence, genetic testing was obtained to confirm the diagnosis.

TREATMENT

She was treated with a combined β -2 agonist and steroid inhaler. The patient later developed recurrent lower respiratory tract infections, for which she required long-term prophylactic antibiotics. Her ongoing symptoms of exertional breathlessness were addressed with a structured exercise programme.

OUTCOME AND FOLLOW-UP

Her disease has been monitored with regular lung function tests and interval CT scans of the chest. Her lung function has remained stable and the cystic changes have not increased. Since genetic confirmation, renal imaging has been organised because of the possible kidney involvement with this syndrome. The patient has also been referred to the local genetic counselling service.

DISCUSSION

Chest CT is the diagnostic modality of choice when assessing for cystic lung diseases (figure 1). It is possible to differentiate between BHD and other cystic lung disease depending on the location of the cysts throughout the lung fields. BHD patients typically have lentiform cysts that are predominantly located in the basal and peripheral parts of the lung and which are often in proximity with the lower lobe pulmonary arteries and veins. Suspected cases of BHD are confirmed by genetic testing to detect mutations in the *FLCN* gene, which are detected by sequencing in 88% of probands with BHD. Hence, some mutations are not currently detectable or the gene is unknown for a minority of BHD patients. Although this is the case, genetic testing is helpful in confirming the clinical diagnosis of BHD and provides a means of determining other at-risk individuals in a family.

Figure 1 Chest CT image at the level of lower lobes shows multiple cysts of varying sizes.

Learning points

- Imaging plays a vital role in obtaining the correct diagnosis for a cystic lung disease. Chest radiography is both insensitive and non-specific in detecting lung cysts and chest CT scan remains the imaging modality of choice.
- High-resolution CT scans of the chest can confidently suggest Birt-Hogg-Dubé (BHD) in most cases obviating the need for lung biopsy.
- Genetic testing is considered not only to be the confirmatory test for BHD, but also helps in identifying family members at risk.
- Atypical cases of cystic lung disease may still require a surgical lung biopsy to confirm the diagnosis of BHD.
- A multidisciplinary approach is essential when managing patients with BHD.

Competing interests None.

Patient consent Obtained.

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REFERENCES

- 1 BHD foundation. Birt-Hogg-Dube Syndrome Research and Support: BHD syndrome literature database.[Online]. <http://www.bhdsyndrome.org/for-researchers/resources/bhd-literature-database/> (accessed 13 Dec 2012).
- 2 Khoo SK, Giraud S, Kahnoski K, *et al.* Clinical and genetic studies of Birt-Hogg-Dubé syndrome. *J Med Genet*[Online] 2002;39:906–12. <http://jmg.bmj.com/content/39/12/906.full.pdf> (accessed 11 Jan 2013).
- 3 Buckley KK, Meffert J. Burt Hogg Dube syndrome[Online]. <http://emedicine.medscape.com/article/1060579-overview> (accessed on 30 Dec 2012).

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