Birt-Hogg-Dubé Syndrome presenting with chronic progressive dyspnea

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1. Case report

A 42-year-old female never smoker, with past medical history notable for asthma, obstructive sleep apnea (OSA), and gastroesophageal reflux disease (GERD) presented to our institution following a diagnosis of bullous emphysema made one week prior at an outside emergency department (ED).

At that time, she reported wheezing and dyspnea which she attributed to an asthma exacerbation unresponsive to her current treatment regimen. Computed tomography (CT) of the chest revealed DCLD, for which she received a presumptive diagnosis of bullous emphysema.

On follow-up, her age and lack of smoking history prompted a more thorough investigation to explain her symptoms and imaging. Additional history revealed six months of progressively worsening dyspnea. Family history was notable for emphysema in both parents, who were smokers. Her sister experienced a pulmonary embolism (PE) at the age of 42 years. Review of systems was unremarkable except for heartburn and nausea.

Vital signs were within normal limits with an oxygen saturation averaging 97% on room air. Physical exam was notable only for innumerable skin-colored to hypopigmented papules involving the face, frontal scalp, and neckline (Image 1).

High-Resolution CT (HRCT) of the chest demonstrated numerous
lower lung predominant, thin-walled unilocular, multilocular and septated subpleural, paramediastinal and peribronchovascular cysts with round, oval, and lentiform morphology, ranging in size from 3 to 60 mm (Image 2). Pulmonary function testing (PFT) demonstrated normal lung volumes, normal diffusion capacity for carbon monoxide (DLCO), and no evidence of restriction or obstruction. Echocardiography was normal. Laboratory testing was unremarkable with normal complete blood count and negative autoimmune serologic testing. A month into her work-up she returned to the ED with dyspnea and a mildly elevated D-Dimer prompting a CT angiogram of the chest which revealed no PE.

The syndromic findings of lung cysts and cutaneous lesions raised the possibility of a genodermatosis, and subsequent skin biopsy was consistent with fibrofolliculomas (Image 3).

A workup for less common causes of DCLD revealed a normal alpha-1-antitrypsin (AAT) phenotype (M1M1), tuberous sclerosis complexes 1 and 2 (TSC1 and TSC2), vascular endothelial growth factor-D (VEGF-D) and a negative serum immunofixation. Analysis of the Folliculin (FLCN) gene revealed a heterozygous truncating mutation, confirming the diagnosis of BHDS.

The patient continued to experience dyspnea despite an optimized asthma treatment regimen. Esophagogastroduodenoscopy (EGD) revealed gastroparesis, hiatal hernia, and evidence of severe esophagitis. The clinical picture was consistent with chronic micro-aspiration causing recurrent progressive dyspnea. A polysomnogram confirmed mild OSA (apnea/hypopnea index (AHI) of 12 events/hour) and a shared decision to start continuous positive airway pressure (CPAP) was made with the patient being informed of the theoretically increased risk of pneumothorax with cystic lung disease. The small risk of pneumothorax was not felt to outweigh the benefit of avoiding the complications of untreated OSA and judicious CPAP use was prescribed with detailed precautions regarding the symptoms of pneumothorax and indications for immediate medical attention. MRI surveillance for renal carcinoma revealed an 8-mm simple renal cyst with no suspicious solid or cystic lesions.

2. Discussion

Birt-Hogg-Dubé Syndrome (BHDS) represents a rare and likely under-recognized disease process. To date, only 663 BHDS families have been identified worldwide [6] Although the overall incidence of FLCN mutations in these families is high (88% in one study) with a relatively high disease penetrance among carriers, the true global prevalence remains unknown [7].

Although disease penetrance among carriers is high, there is also a large range in the extent of phenotypic expression, which can make presentation highly variable [7]. For example, cutaneous hamartomas (fibrofolliculomas and trichodiscomas) are the only visible manifestation of BHDS and are present in over 90% of cases, but phenotypic expression ranges in severity from nearly imperceptible to extensive papules, comedones and cysts affecting the upper body [7,8].

The differential diagnosis for a 42-year-old female with dyspnea should of course first exclude the usual suspects. This patient suffered from asthma for many years, and although she denied new potential exacerbating exposures or any accidental or purposeful reduction in medication use, the workup was first directed at excluding asthma as the singular cause of her symptoms. PFTs demonstrated no significant obstructive or restrictive process, and after reviewing and optimizing
her treatment regimen without a subsequent change in her symptoms it was felt that asthma alone could not explain her presentation.

When the finding of DCLD is added to the symptom of dyspnea a more interesting, and somewhat narrowed differential may be established. Some entities to consider include chronic obstructive pulmonary disease (COPD), alpha-1-antitrypsin (AAT) deficiency, pulmonary Langerhans cell histiocytosis (PLCH), lymphoctic interstitial pneumonia (LIP) and sporadic or tuberous sclerosis complex associated lymphangioleiomyomatosis (S-LAM/TSC-LAM).

The typical patient with AAT-deficiency emphysema presents with dyspnea, cough, wheezing and obstructive PFTs beginning in the fourth or fifth decade [9]. HRCT demonstrates bilateral predominant panlobular emphysema, and in a smaller subgroup, airway thickening, bronchiectasis and bullous disease [10]. As in this case, the diagnosis may be excluded by targeted genotyping of the alpha-1 protease inhibitor locus demonstrating a normal M1/M1 phenotype.

Although the association between PLCH and smoking exceeds 95%, cases in non-smokers have been described. In adults, onset is typically in the third to fourth decades with two-thirds presenting with dyspnea and a non-productive cough. PFTs demonstrate impaired DLCO in 70% of patients, with an otherwise non-specific pattern of restriction and/or obstruction. HRCT shows upper lung predominant reticulonodular and cystic changes with characteristic sparing of the lung bases and costophrenic recesses [11]. In our patient, a normal DLCO, inconsistent imaging findings, and lack of smoking history makes PLCH unlikely.

The underlying cause of LIP remains unknown but is commonly associated with immune dysfunction (e.g. HIV infection and Sjögren syndrome). There is a female predominance, with most patients presenting with dyspnea and dry cough in their fifth to eight decades [12]. The imaging features of LIP include areas of ground glass attenuation, centrilobular nodules and peribronchovascular and interlobular septal thickening [13]. These findings were notably lacking in this patient, making the diagnosis unlikely.

A tempting alternative to BHDS is LAM, which may arise spontaneously (S-LAM), or as part of the tuberous sclerosis complex (TSC-LAM). S-LAM occurs nearly exclusively in women during their childbearing years. Greater than 70% present with dyspnea and an obstructive PFT pattern. HRCT shows diffuse, thin-walled, round cysts ranging in size from 2 to 40 mm with no regional predilection. Chylothorax is also a characteristic CT feature of LAM [14–16]. Like BHDS, both presentations of LAM are associated with renal tumors, though unlike the malignant cancers typical of BHDS, the angiomylipomas of LAM have a low malignant potential. Early manifestations of tuberous sclerosis and subsequent genetic testing usually prelude a diagnosis of TSC-LAM, but S-LAM may go unrecognized into adulthood [17].

The first step in accurately diagnosing this patient was to identify the incongruity of bullous emphysema in a young, never smoker. Although COPD occurs in non-smokers, it is rare, rarer still in the young, and features more prominent PFT abnormalities and less conspicuous structural disease [18]. The second step was to separate the presenting symptom of dyspnea from the finding of DCLD.

Lung cysts affect 84% of BHDS patients starting in the fourth and fifth decades [7,19]. The cysts of BHDS are thin-walled, variable in size and morphology (round, oval, irregular, and lenticular), and occasionally multi-septate [20,21]. However, these features overlap with those of LIP and LAM. A recent study aimed to distinguish the cysts of LIP, LAM and BHDS on the basis of HRCT characteristics, concluding that a lower lung predominance, a greater number of paramedial cysts, and cysts with an elliptical or lenticular morphology provided a strong degree of confidence for BHDS [22].

Cysts portend a 50-fold increased risk of spontaneous pneumothorax, with cyst burden directly proportional to risk [7,23,24]. Pneumothorax has been shown to occur in as many as 76% of BHDS cases, with 82% of those cases reporting recurrent episodes. For two-thirds of BHDS patients, acute onset of dyspnea in the setting of a spontaneous pneumothorax is the sentinel event bringing them to medical attention, not the progressive, insidious dyspnea more typical of chronic lung disease, as was demonstrated by this patient [25].

Unlike other entities in the above differential, BHDS is not known for causing pulmonary dysfunction. In 2020, Daccord and colleagues published a retrospective study of lung function in a BHDS cohort, measuring PFTs at baseline and over a 7-year follow-up interval. They demonstrated no significant pulmonary dysfunction at diagnosis, and no decline in function over the study duration [26]. Clinicians may be tempted to reconcile symptoms with a diagnosis that accounts for the simplest possible explanation. However, as we demonstrated, it is critical that BHDS remains on the differential when DCLD is identified, even when the presence of symptomatic pulmonary dysfunction appears inconsistent with the diagnosis. Broadening one’s view of the patient beyond the finding of DCLD to include her medical history and EGD findings brings other explanations for her symptoms into focus – untreated OSA and severe GERD.

Identifying BHDS early can be lifesaving. Although the cutaneous and pulmonary manifestations are generally self-limited, they may be the only clues to the more sinister development of renal carcinoma. As a result, management of BHDS focused on surveillance. Renal tumors develop in 14–34% of FLCN mutation carriers and may present as early as age 20. Types of tumors include oncocytomas (5%) and several histological subtypes of renal cell carcinoma (RCC) (chromophobe [34%], hybrid chromophobe-oncocytomas [50%], clear cell [9%], and papillary [2%]) [19]. Life expectancy in BHDS is most strongly correlated with the presence or absence of RCC, followed by the type and stage at diagnosis. Surveillance with abdominal magnetic resonance imaging (MRI) or CT at least every 36 months is recommended for any individual, or family member of an individual meeting diagnostic criteria for BHDS. MRI or CT are recommended over ultrasound (US) due to US’s low sensitivity for small hybrid chromophobe-oncocytomas. Because lifelong screening is recommended starting at age 20, MRI should be considered over CT when possible to reduce ionizing radiation exposure [27].

A final consideration specific to this patient is the treatment of OSA in BHDS patients with cystic lung disease. There are currently no guidelines addressing pneumotheorax risk with CPAP therapy in BHDS patients, and a paucity of data exists on the safety of CPAP with other DCLDs. Extrapolating from reports of pneumothorax during endotraheal positive pressure ventilation (PPV) in those with underlying pulmonary disease, and anecdotal evidence of an increased incidence of pneumotheorax in BHDS patients following air travel, one might conclude a theoretically increased risk of pneumothorax with PPV does exist [25,28]. This is likely to become a more common clinical dilemma as the recognition of BHDS rises in a population at ever increasing risk of obesity and OSA. Until further research addresses this issue, the small risk of pneumothorax should be weighed against the myriad benefits of CPAP in a shared decision between the patient and a pulmonologist familiar with BHDS, OSA and their complications.

3. Conclusion

BHDS patients benefit from early diagnosis and initiation of screening for RCC to reduce mortality, however, variable phenotypic expression makes late diagnosis or misdiagnosis common. Unlike other conditions frequently considered in the differential for DCLD, BHDS is not known to feature significant symptomatic pulmonary dysfunction. This case underscores the importance of keeping BHDS in the differential even when DCLD is identified in the setting of chronic progressive dyspnea. When the diagnosis of BHDS is made under these circumstances, further investigation into alternate causes of the patient’s symptoms is indicated. Our patient is felt to suffer from severe GERD resulting in reactive airway disease and dyspnea, a presentation which after careful consideration allowed for the potentially lifesaving recognition of BHDS.
Declaration of competing interest
The authors have no conflicts of interest to disclose.

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