Differentiating pulmonary lymphangioleiomyomatosis from pulmonary langerhans cell histiocytosis and Birt-Hogg-Dube syndrome

Sir,

We read with great interest the pictorial quiz case reported by Singh and Singh[1] describing a patient of pulmonary lymphangioleiomyomatosis (LAM) in association with tuberous sclerosis complex (TSC) presenting with pneumothorax, cystic lung lesions, and characteristic dermatological findings. The authors have discussed some important causes of cystic lung lesions in the discussion which included pulmonary Langerhans cell histiocytosis (PLCH) with the special mention of 'bizarre' shape of lung cysts seen in this disorder. Through this letter, we want to briefly discuss a patient of PLCH managed in our institute with a specific focus on the salient differences in the radiological and clinical finding in these two disease entities, both of which are considered as important differential diagnoses of cystic lung diseases. We also want to briefly mention one another important and rare genetic cause of cystic lung diseases known as 'Birt-Hogg-Dube (BHD) Syndrome' which shares multiple clinical features with LAM. BHD was not discussed as a differential diagnosis by the authors in the original report.

A 28-year-old Caucasian female with 20 pack year smoking history presented to our chest medicine clinic with 3 months history of nonproductive cough and exertional dyspnea. There was no history of any chronic pulmonary diseases in both paternal and maternal sides of her family. Only significant finding on the physical examination was presence of bibasal expirational crackles on lung auscultation. Pulmonary function tests were normal. Chest radiograph did not show any abnormal findings. We obtained a high resolution computed tomography (CT) scan of the chest which revealed multiple bizarre shaped lung parenchymal cysts mostly involving the upper lobes of the lungs and sparing the bases [Figure 1, Panel A and B]. Based on these characteristic findings a diagnosis of PLCH was made and patient was strongly advised against smoking and was prescribed some over-the-counter cough suppressants for symptomatic relief. Patient successfully quit smoking and over next 1 year her symptom improved greatly.

PLCH, formally known as histiocytosis X, is a rare interstitial lung disease characterized by abnormal proliferation and accumulation of Langerhans-type histiocytic cells in the lung parenchyma resulting in the formation characteristic cystic and nodular lung parenchymal lesions. This disease mostly occurs in the age group 20-40 years and there's a very strong association with smoking with more than 95% of patients having history of current or past smoking.[2] The exact prevalence and incidence of this disease is unknown because a vast majority of patients remain asymptomatic. The pathogenesis behind the development of PLCH remains largely unknown. Role of smoking induced proliferation of Langerhans cells beneath the epithelium of tracheobronchial tree has been implicated.[3] Some authors have also proposed the role of several inflammatory cytokines, specifically interleukin (IL)-17.[4] Another hypotheses has looked at the association of PLCH and smoking with observation of increased expression of proinflammatory glycoprotein osteopontin in PLCH lesion.[5] Pathologically, PLCH lesions are characterized by abundance of langerhans cells which

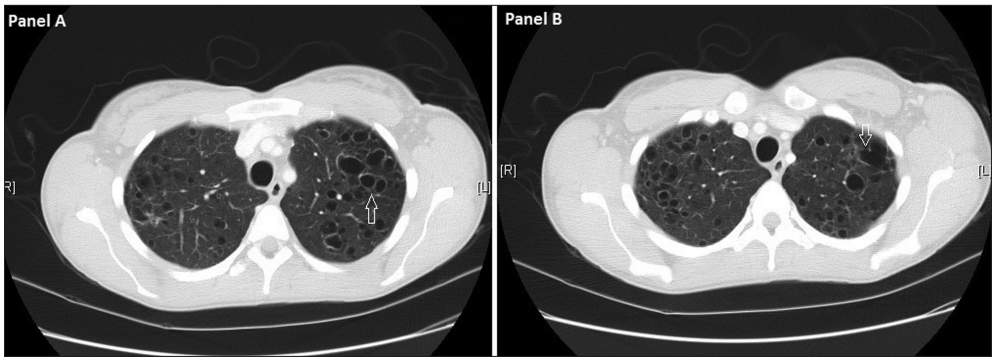

Figure 1: (Panel A) High resolution computed tomography (CT) scan of the chest showing irregular, bizarre shaped lung parenchymal cysts in bilateral upper lobe. A bilobed cyst in left upper lobe is marked (arrow). (Panel B) Another section of CT scan of the same patient at different anatomic level showing almost clover leaf-shaped cavity (arrow)

on electronic microscopy show classic pentalaminar cytoplasmic inclusions also known as Birbeck granules. These cells are positive for S-100 protein and CD1a antigen on immunohistochemial staining. In PLCH, if clinical characteristics are well correlated with imaging findings, disease can be confirmed without lung biopsy. However, this typical finding is relatively uncommon, so in numerous cases lung biopsy is needed for final diagnosis, to exclude other conditions presenting as cystic lung diseases. Around one-third of PLCH patients are asymptomatic at the time of diagnosis and in symptomatic patients, most common symptoms include dyspnea and nonproductive cough. About 15% of patients of PLCH develop spontaneous pneumothorax which can be recurrent like LAM patients.

Radiological findings, specifically high resolution chest CT scan findings are pathognomonic in PLCH and also help in differentiating PLCH from LAM. Majority of PLCH patients have nodules and/or cysts or combination of both on CT scan of the chest. Both PLCH and LAM patients have lung parenchymal cysts, but they are uniform and rather round shaped in LAM, in contrast PLCH cysts are often irregular, bilobed, cloverleaf-shaped, or bizarre shapes [Figure 1, Panel A and B]. Another differentiating feature is the predominance of cysts in the upper and middle lung zones and sparing of lower lung zones and costophrenic areas in PLCH.[6] As mentioned by author, presence of thicker cyst walls and the presence of nodules in the intervening lung parenchyma between the cysts in PLCH is one more radiological differentiating feature.

One more genetic lung disorder known for the presence of cystic lung lesions and recurrent pneumothoraces, just like PLCH and LAM is Birt-Hogg-Dube (BHD) syndrome. It is a rare autosomal dominant genetic disorder caused by germline mutations in FLCN gene on chromosome 17p11.2 which codes for a tumor suppressor protein called folliculin.[7] Described first in 1977 by Birt, Hogg, and Dube; BHD is characterized by combination of skin fibrofolliculomas (hamartoma of the hair follicle), multiple lung cysts, recurrent pneumothoraces, and renal cancers. LAM associated with TSC also shares significant clinical involvement with BHD in the form of presence of skin involvement with angiofibromas and renal involvement with angiomyolipomas, thus making BHD an important differential diagnosis of LAM. Around 25% of carriers of BHD do not have skin lesions and BHD is known to show heterogeneity of penetrance in mutation carriers. Some patients can have isolated skin lesions or isolated lung cyst, or isolated renal tumor. The definite diagnosis is based on DNA testing for FLCN mutation. Some genetic studies have even suggested the role of similar common genetic pathway known as mTOR pathway in the pathogenesis of both LAM and BHD.[8] Few of the differentiating features between these two disorders include, almost exclusive involvement of females only in LAM. Not only LAM associated with TSC, but also LAM without TSC is almost exclusively found in women of child-bearing age. In contrast, BHD can be found in male subjects due to autosomal dominant inheritance, and for this reason, it is very important to carefully investigate family history (for male sex involvement) in the patients of cystic lung diseases. Another contrasting feature between LAM and BHD is the propensity of cystic lung involvement in basilar and peripheral areas in the BHD patients. Occasional chylous pleural effusions seen in LAM only and subpleural lentiform cysts seen in BHD only are few more differentiating features.

In conclusion, we have described PLCH and BHD syndrome as two most important differential diagnoses of LAM. Although all these three clinical disorders share multiple clinical features, characteristic clinical features and radiological findings described above can be very helpful in differentiating one disorder from other, thus avoiding invasive testing.

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