Clinicopathologic Conference

A 26-year-old man with dyspnea and chest pain

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ABSTRACT

A 26-year-old smoker male presented with a history of sudden onset dyspnea and right-sided chest pain. Chest radiograph revealed large right-sided pneumothorax which was managed with tube thoracostomy. High-resolution computed tomography thorax revealed multiple lung cysts, and for a definite diagnosis, a video-assisted thoracoscopic surgery-guided lung biopsy was performed followed by pleurodesis. This clinicopathologic conference discusses the clinical and radiological differential diagnoses, utility of lung biopsy, and management options for patients with such a clinical presentation.

KEY WORDS: Cystic lung disease, pneumothorax, pulmonary Langerhans cell histiocytosis

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PRESENTATION OF THE CASE

Saurabh Mittal

A 26-year-old male presented to the emergency department with a history of shortness of breath and right-sided chest pain. Shortness of breath was of sudden onset, was present at rest, and was associated with sharp pleuritic right-sided chest pain. There was no history of respiratory symptoms before this episode. The patient was a smoker for the past 4 years and used to smoke 3–4 cigarettes per day. There was no significant past and family history. On examination, the patient appeared anxious, respiratory rate was 26/min, heart rate was 110 beats/min, and oxygen saturation on room air was 91%. On respiratory system examination, breath sounds were absent on the right side with hyperresonant note on percussion. There were no features to suggest marfanoid habitus. Rest of the physical examination was unremarkable.

Posteroanterior chest radiograph demonstrated large right-sided pneumothorax [Figure 1a], for which intercostal drain insertion was performed following which there was complete expansion of the lung [Figure 1b]. Following chest drain insertion, there was no air leak. Routine investigations including hemogram and liver and kidney function tests were normal. Sputum examination for acid-fast bacilli was negative on two occasions and sputum culture was sterile. Hepatitis B surface antigen was positive. High-resolution computed tomography (HRCT) scan of the thorax revealed variably sized cysts in both lungs. There was no significant mediastinal lymph node enlargement, and the lung parenchyma intervening between the cysts was normal [Figure 2]. Pulmonary function tests demonstrated very severe restrictive abnormality with a marked reduction in the diffusing capacity (41% of predicted). For a definitive diagnosis of the underlying cause of the cystic lung disease, a video-assisted thoracoscopic surgery (VATS)-guided biopsy was performed. Mechanical pleurodesis was performed following lung biopsy.
DIFFERENTIAL DIAGNOSIS

Important features of the case
Karan Madan
This patient is a young smoker who presented with a large spontaneous pneumothorax. The list of differential diagnoses in individuals with spontaneous pneumothorax is long and includes common disorders such as chronic obstructive pulmonary disease and interstitial lung disease (ILD).[^1] When no underlying lung disease is apparently present, it is termed as primary spontaneous pneumothorax (PSP). The first clinical differential in this patient is PSP. However, as the HRCT thorax demonstrated features of an underlying cystic lung disease, some common cystic lung diseases which may present as spontaneous pneumothorax need to be considered as important differential diagnoses and are subsequently discussed.

Pulmonary Langerhans cell histiocytosis
It is a rare disorder characterized by accumulation of histiocytes in lungs particularly in small airways leading to the formation of inflammatory nodules.[^5] It is common in young adults between the age of 20 and 40 years with a history of smoking.[^1] The presentation of pulmonary Langerhans cell histiocytosis (PLCH) is variable. Most of the patients (two-thirds) present with dry cough and dyspnea while up to 25% of patients are asymptomatic and are detected on routine chest radiographs. Spontaneous pneumothorax and chest pain are seen in the remaining 10–20% of cases. Extrapulmonary involvement is seen in up to 15% of cases where bone pain due to bone cysts (18%), rash (13%), and polyuria due to diabetes insipidus (5%) are the most common manifestations. It is postulated that in response to smoke, proliferation of Langerhans cells in the bronchiolar and bronchial epithelium forms granulomas that result in nodule formation. As the disease progresses, these nodules undergo cavitation to form stable, thin-walled cysts with an end result of nodulocystic pattern.[^4] Thus, depending on the stage of the disease, one may find different patterns on radiology, earliest being the bilateral reticulonodular pattern, especially involving upper and mid zones.[^5] The lung bases are often spared. Lung volumes are generally preserved, and reduced lung volumes are uncommon and are seen only in end-stage fibrotic cases. Hyperinflation of chest can be seen; however, lymph node enlargement is usually rare.

Lymphangioleiomyomatosis
Lymphangioleiomyomatosis (LAM) can occur sporadically or may be associated with tuberous sclerosis (TS). Sporadic LAM almost always occurs in females (of childbearing age) and is much more severe than that seen in association with TS. Common presenting features include dyspnea, hemoptysis, pneumothorax, and chylothorax.[^6] Risk of spontaneous pneumothorax increases during pregnancy. Associated renal angiomyolipomas may be seen in patients with TS. Most common HRCT finding is multiple thin-walled cysts with a normal intervening lung parenchyma. These cysts usually have a uniform distribution throughout the lungs unlike PLCH.[^5] It may show the presence of pneumothorax or chylothorax. On histopathological examination, airways, alveoli, and lymphatics are seen infiltrated with smooth muscle cells known as LAM cells. They are spindle-shaped cells with eosinophilic cytoplasm and stain positive for HM B-45.

The treatment of LAM used to be mainly supportive, but recent studies with mammalian target of rapamycin inhibitor sirolimus have shown good results, and the drug is currently recommended for therapy in LAM.[^7]

Birt–Hogg–Dube syndrome
It is a rare disorder characterized by lung cysts, spontaneous pneumothorax, renal tumors, and skin fibrofolliculomas.[^8] Spontaneous pneumothorax occurs in a quarter of these patients, but the risk of recurrence is very high. HRCT shows multiple thin-walled cysts mainly in periphery of lung in bases as well as in areas along the mediastinum.[^5] A confident diagnosis can be established with supporting clinicoradiological findings.

Lymphocytic interstitial pneumonia
Lymphocytic interstitial pneumonia (LIP) is characterized by lymphocytic infiltration of alveolar and interlobular...
septa. It is more common in females.\[9\] It is seen more commonly in association with Sjogren's syndrome, and idiopathic LIP is rare. HRCT usually shows diffuse ground-glass opacities (GGOs), ill-defined centrilobular nodules, and perilymphatic nodular thickening. These nodules later on progress to multiple thin-walled cysts which usually involve <10% of lung parenchyma.\[10\]

**Desquamative interstitial pneumonia**

It commonly occurs between the ages of 40 and 60 years and is commonly associated with heavy smoking. Sometimes, exposure to inhalational agents such as paints or substance abuse, connective tissue diseases, and sirolimus therapy may lead to desquamative interstitial pneumonia (DIP).\[11\] The characteristic CT findings in DIP are the presence of GGOs commonly in lower lung zones along with cysts having imperceptible walls. The fibrosis is minimal and traction bronchiectasis is rare. The presence of cysts with GGOs is a unique feature of DIP.

**Tracheobronchial papillomatosis**

Lung involvement may occur in this disorder in the form of multiple lung nodules which can progress to cavitation and small cysts are finally formed.\[12\] They are usually randomly distributed throughout the lungs. Associated tracheal or laryngeal papillomas are key to establishing the diagnosis.

**Cystic metastasis**

Cystic metastases are rare, but the presence of lung cysts in a patient with a history of malignancy should raise the suspicion of cystic metastasis. They occur more commonly in squamous cell cancers and rare in adenocarcinoma.\[13\]

**Amyloidosis**

Pulmonary involvement in amyloidosis is uncommon and may have various forms. The nodular forms of amyloidosis can have multiple subpleural nodules which can later cavitate. It can have multiple large cysts with internal septations which are more common in periphery of the lung and in lower lobes.\[14\]

**Infections**

Infections including tuberculosis, hydatidosis, paragonimiasis, histoplasmosis, and posttuberculosis sequelae can present as spontaneous pneumothorax. Pneumocystis jiroveci pneumonia (PJP) can have cyst formation in up to one-third patients leading to spontaneous pneumothorax and cysts are more common in upper lobes.\[15\] Treatment with inhaled pentamidine is a risk factor of pneumothorax in PJP.

**CLINICAL DIAGNOSIS**

In this patient, in view of the younger age, strong history of smoking, and the radiological distribution pattern of cysts, we would like to consider PLCH presenting with spontaneous pneumothorax as the first differential diagnosis.
Saurabh Mittal: Should all patients with spontaneous pneumothorax undergo HRCT chest to look for underlying lung disease?

Randeep Guleria: It is of utmost importance to diagnose secondary causes in patients with spontaneous pneumothorax to differentiate it from secondary spontaneous pneumothorax. Patients with LAM who develop pneumothorax have a 73% chances of recurrence while about one-fourth individuals with Birt–Hogg–Dube syndrome have a recurrent pneumothorax.[20] In patients who do not have underlying cystic lung disease, pneumothorax may be managed with drainage only, but in individuals with underlying diffuse lung disease, pleurodesis is generally recommended to prevent recurrence. HRCT screening in patients with spontaneous pneumothorax may be cost-effective in evaluation of underlying cystic lung disease.[21]

Saurabh Mittal: How should a patient with PLCH having isolated lung involvement be investigated to diagnose systemic disease?

Anant Mohan: Pulmonary involvement commonly occurs in LCH, but isolated PLCH is a well-known entity. It is important to determine the extent of disease when a diagnosis of PLCH is made. Obtaining a detailed history and complete physical examination is essential to look for extrapulmonary features of LCH. All patients should have a complete blood count and liver and kidney function tests supplemented by C-reactive protein level to look for systemic disease. A skeletal survey consisting of anteroposterior and lateral views of the skull and spine, as well as radiographs of the ribs, pelvis, and upper and lower limbs, is also recommended.[22] In our patient, blood investigations were normal and skeletal survey did not reveal any lytic lesions.

Saurabh Mittal: What are the therapeutic options for patients with PLCH?

Vijay Hadda: Smoking is the most important known risk factor for the development of PLCH. Smoking cessation is the first step in the treatment of PLCH. Smoking cessation itself may lead to disease remission or may halt disease progression. However, disease recurrence may occur despite smoking cessation. Patients who develop remission after smoking cessation should be kept under follow-up to assess for any disease recurrence. All adult patients with severe disease or with progressive decline in lung function despite smoking cessation should be considered for immunosuppressive therapy. Corticosteroids (usually prednisolone in a dose of 0.5–1 mg/kg) are commonly used for the treatment as first-line therapy, but the utility is unclear.[23,24] Other immunosuppressive agents such as cladribine, methotrexate, and cyclophosphamide have been used with variable success. Cladribine is a purine nucleoside analog which has direct toxic effects on monocytes. It has been shown to improve lung function and dyspnea in many case reports and case series.[25,26] Currently, it is being investigated in a multicenter trial (www.clinicaltrials.gov, NCT01473797). Lung transplant is considered in patients with progressive disease despite medical therapy and smoking cessation. Prior pleurodesis is not a contraindication to lung transplant in patients with a history of pneumothorax. The outcomes of lung transplant are similar to those due to other indications including cystic fibrosis and emphysema.

Saurabh Mittal: What are the common complications of the disease and how to manage them?

Karan Madan: Spontaneous pneumothorax and pulmonary hypertension are two common complications. Pulmonary hypertension occurs more commonly than other chronic diseases such as idiopathic pulmonary fibrosis. It is associated with poor prognosis and is related to primary pulmonary vasculopathy manifested by intimal fibrosis and vessel wall remodeling. Diagnosis is achieved by echocardiography followed by right heart catheterization. Treatment with newer vasodilators (including phosphodiesterase inhibitors and endothelin antagonists) may be helpful, but prostacyclin therapy should be used cautiously due to high incidence of veno-occlusive disease[27] and may lead to acute pulmonary edema.

Saurabh Mittal: What is the prognosis in these patients?

Karan Madan: The disease can be progressive, stable, or improving and has variable prognosis even with smoking cessation and medical therapy.[31] PLCH has relatively good prognosis with a 5-year survival of about 75%. Certain poor prognostic factors include old age, prolonged constitutional symptoms, extensive cysts formation, and presence of pulmonary hypertension.

**SUMMARY**

Our case highlights the importance of HRCT in a patient with spontaneous pneumothorax and knowledge of various radiological patterns of cystic lung diseases can lead to a correct diagnosis.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.
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Conflicts of interest
There are no conflicts of interest.

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