Progressive Dyspnea in a 49-Year-Old Woman With Long-standing Epilepsy*

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(Author's note: This is a case report discussing a 49-year-old woman presenting with progressive breathlessness on exertion and occasional hemoptysis. She had a history of intermittent pleuritic pain and was being treated for epilepsy with lamotrigine and sodium valproate. On admission, she had a raised erythematous facial rash and was afebrile, normotensive, and had a normal peripheral pulse. Examination of her chest revealed no abnormality.

ECG findings were normal. Arterial blood gas indexes on room air were as follows: pH, 7.39; Pco₂, 34 mm Hg; Po₂, 90 mm Hg; HCO₃, 25.6 mmol/L; hemoglobin, 9.0 g/dL; WBC count, 13.7 × 10⁹ g/dL; and platelets, 1,158 × 10⁹/L. Urea and electrolyte levels were normal.

A chest radiograph showed a left pneumothorax. There was reticulation in both lungs without loss of lung volume. There was sclerosis of the upper thoracic vertebrae (Fig 1). High-resolution CT (HRCT) of the lungs (Fig 2, top) showed well-defined, thin-walled cysts in both lungs. The intervening lung parenchyma was normal. A view of the upper abdomen with soft-tissue settings (Fig 2, bottom) showed huge masses composed of fat and soft tissue replacing both kidneys. A large high-attenuation area occupied the right kidney. Results of a ventilation perfusion lung scan were unremarkable.

What is the diagnosis? What nonpulmonary complication has occurred?)
Figure 1. Sclerosis of upper thoracic vertebrae seen on chest radiograph.

Figure 2. Top: HRCT reveals well-defined thin-walled cysts. Bottom: Masses of fat and soft tissue replaced kidneys.
Diagnosis: Lymphangioleiomyomatosis as part of tuberous sclerosis complex.
Complication: Spontaneous right renal hematoma

The presence of multiple well-defined pulmonary cysts, bilateral fatty renal tumors, and bony sclerosis is pathognomonic of tuberous sclerosis complex.

Tuberous sclerosis complex (TSC) is an autosomal-dominant, neurocutaneous disorder involving the brain, skin, kidneys, bones, heart, and lungs. Many other sites may be involved, including the liver, pancreas, and retroperitoneal and mediastinal lymph nodes. Clinically, TSC is characterized by the triad of mental retardation, seizures, and adenoma sebaceum. Not all of these features may be present, and because of this, imaging may disclose features of this condition that are clinically silent. TSC has an incidence of 1 in 10,000 to 1 in 100,000. The disease is dominantly inherited; however, sporadic cases are very frequent, representing 80 to 90% of index cases. This could be due to the fact that the gene is passed on by asymptomatic individuals or as a result of new mutation. Recently, there has been great interest in the genetic basis of the disease. Two responsible mutations have been identified; TSC1, which is located on chromosome 9q34 (cloned in 1997), and TSC2, located on chromosome 16p13 (cloned in 1993). Both genes seem to code for proteins that have a tumor suppressor activity.1

The clinical, radiologic, and histologic features of pulmonary involvement in TSC are indistinguishable from lymphangioleiomyomatosis (LAM). Pulmonary involvement is said to occur in 1 to 2.3% of patients with TSC.2,3 Although TSC affects both sexes equally, pulmonary involvement, like LAM, almost exclusively affects women of childbearing age. There is a lower incidence of epilepsy and mental retardation in patients with pulmonary involvement compared with other patients with TSC.4 Both pulmonary TSC and LAM are characterized by hamartomatous proliferation of smooth muscle in the walls of airways, venules, and lymph vessels within the lung.5

Involvement of airways results in narrowing, obstruction, and air trapping. Damaged alveoli coalesce, eventually leading to cyst formation. Cysts may rupture resulting in pneumothorax, a feature in 40 to 80% of patients with LAM.5,6 Owing to degeneration of elastic fibers in the wall of the alveolus, affected lungs have reduced elastic recoil. This may be a further mechanism for the development of lung cysts.7 Lung volumes are typically normal or increased. Obstruction of venous flow in the lungs results in venous distension, pulmonary venous hypertension, and hemoptysis, a feature in 40% of patients.8 Lymphatic obstruction leads to chylothorax in 80% of patients,9 a complication that is said to occur more commonly with LAM than TSC.9 Infra-diaphragmatic lymphatic obstruction may result in retroperitoneal cystic masses.

The most common pulmonary symptoms in patients with pulmonary TSC are dyspnea on exertion (68%), spontaneous pneumothorax (50%), cough (27%), and hemoptysis (27%).2 Pulmonary function test results in patients with LAM and pulmonary TSC reveal airflow obstruction and reduced gas transfer.3 Furthermore, restrictive lung defects may be encountered in the presence of pleural effusions or surgery. The majority of patients with respiratory symptoms will have radiologic manifestations of pulmonary TSC at presentation. The chest radiographic finding may be normal or may show diffuse reticulation throughout all lung zones. Reticulation is due to summation of numerous pulmonary cysts.9 Typically, lung volumes are preserved or increased. Another important cause of this pattern on the chest radiograph is Langerhans’ cell histiocytosis (LCH), from which LAM must be distinguished. In the latter condition, a chylos pleural effusion or pneumothorax may also be present. Thin-section CT is superior to plain radiography,9–12 and often reveals cysts in the lung parenchyma even when the chest radiographic findings are normal. Classically, in the early stages of the disease, there are well-defined, uniformly distributed, thin-walled cysts throughout all zones of the lung with relative apical sparing.9 The intervening lung parenchyma is normal. With disease progression, cysts enlarge and may coalesce, causing architectural distortion. The main CT differential diagnosis is between LCH and emphysema. In LCH, nodules are a prominent feature and cyst walls are of variable thickness unlike in LAM.9 LCH is predominantly mid-zone and upper-zone predominant, sparing the costophrenic angles.11 Unlike LAM, emphysema is associated with preservation of the central arterial core of the secondary pulmonary lobule.

The diagnosis of TSC is usually made clinically by recognition of the somatic features. Imaging plays a pivotal role in detection of associated pulmonary or extrapulmonary pathology. The presence of dyspnea and airflow obstruction in a female nonsmoking patient should prompt a search for LAM, whether or not she is known to have TSC. Open-lung biopsy and histologic examination using the monoclonal antibody HMB 45, which specifically stains LAM smooth-muscle cells,13 is considered the diagnostic “gold standard.” Although the HRCT appearances in LAM are highly specific,9,11 biopsy confirmation is required, as these patients are often considered for lung transplantation.14

Airflow obstruction is managed with β2-agonists.15 A pneumothorax is managed in the usual way with the insertion of intercostal tube. As pneumothoraces
may be recurrent, mechanical or chemical pleurode-
sis may be necessary; while these procedures do not
rule out future lung transplantation, they may make
such a procedure more hazardous.16

The extrapulmonary features of TSC are well
documented and are readily demonstrated using
imaging.17 In this patient, bony sclerosis was evident
in the neural arches of vertebrae and in the ribs.
Classically, bony sclerosis is patchy and dense and is
due to periosteal thickening. Bilateral renal angio-
myolipomata, a hallmark of TSC, were evident on
abdominal CT. These are hamartomatous lesions
and contain an abundance of fat, muscle, and blood
vessels. The latter are prone to rupture, accounting
for the spontaneous hematoma in the right kidney.
Interestingly, patients with LAM have a higher
prevalence of associated renal angiomylipomata
than the general population. The clinical features
and treatment response in LAM and pulmonary TSC
are so similar that some authors3,18 have been prompted
to consider these disorders part of the same condition.

LAM and pulmonary TSC may be treated simply
with inhaled β-agonists in an attempt to reverse
airway obstruction. A pneumothorax should be man-
aged in the usual way, but an early surgical opinion
should be sought since this complication tends to be
recurrent. However, it should be remembered that
future lung transplantation may prove difficult once
the patient has embarked on surgical procedures of
the pleura.16 As LAM and pulmonary TSC are hormonally dependent, the purpose of drug therapy
is to induce a low estrogen state. Therefore, progesterone and surgical oophorectomy are the most
commonly used treatments. In a retrospective study,
Johnson et al19 found that the mean decline in FEV1
was less in patients receiving progesterone than in
patients receiving no treatment. Single-lung transplan-
tation is reserved for patients with end-stage LAM.14
The main complications of this treatment are hemor-
hage and, in the native lung, chylothorax and pneu-
mothorax. LAM may develop in the transplanted lung.

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