A 34-year-old woman presented with slowly progressive exertional dyspnea of over 3 years’ duration. She was a nonsmoker and worked 3 days per week packaging. She had noted blood-streaked sputum twice in the past year. The patient's desire to become pregnant worried her parents. Current medications included diphenylhydantoin, phenobarbital, carbamazepine, and thioridazine.

**Physical Examination**

Vital signs: normal. Chest: minimal crackles midlung. Neurologic: absent deep tendon reflex in knees and ankles; tandem gait impaired. Skin: healed dermabrasion scars on face; nodular lesions on fingers (Fig 1); hypomelanotic patches over thorax.

**Laboratory Findings**

Hemoglobin, 13.2 g/dl; WBC, 4,300 µl; urinalysis, normal; serum creatinine, 1.1 mg/dl; PPD, neg; ECG: right axis deviation. Arterial blood gas analysis on room air: pH, 7.42; PCO₂, 32 mm Hg; P O₂, 54 mm Hg; Arterial blood gas analysis after 2.2 min of exercise: pH, 7.47; PCO₂, 28 mm Hg; P O₂, 37 mm Hg

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**Figure 1.** Nodular lesions on fingers.

**Figure 2.** Chest radiograph shows interstitial infiltrates.

Hg. Pulmonary function tests: forced vital capacity (FVC), 3.6 L (88 percent predicted); FEV₁, 1.3 L (39 percent); FEV₁/FVC, 37 percent; FEF₂₅₋₇₅, 0.5 L/s, (15 percent); total lung capacity, 6.8 (120 percent); residual volume, 3.1 L (206 percent); maximal voluntary ventilation, 52 L/min (43 percent); DCO, 5 (19 percent). Chest radiograph: interstitial infiltrates (Fig 2).

What additional study would confirm your diagnosis? What is your advice regarding pregnancy?
**Diagnosis:** *Pulmonary tuberous sclerosis*

The resemblance of the grossly nodular and indurated cerebral convolutions to tubers prompted Bourneville to use the term "tuberous sclerosis of the cerebral convolutions" in the first (1880) detailed report of neuropathologic findings in this disease. Since Vogt established the classic clinical triad for the diagnosis—mental retardation, seizures, and "adenomus sebaceum"—additional hamartomatous lesions of virtually every organ system have been described in various combinations and severity.

Although the numerical risk for each child of either sex born to an affected parent is 50 percent in this autosomal dominant disorder, the degree of expression is extremely variable in terms of organs involved (pleiotropic effect) as well as severity. Incomplete penetrance and even new mutations also complicate tracing the manifestations of tuberous sclerosis (TS) in families. Estimation of its prevalence in more recent literature (1 in 9,500 persons) suggests that for each recognized patient there must be many unsuspected, asymptomatic cases. Fewer than 1 percent of all cases have pulmonary involvement.

The clinical, radiographic, and pathologic findings of pulmonary involvement in TS are virtually indistinguishable from pulmonary lymphangioleiomyomatosis (LAM) and most consider the latter a *forme fruste* of TS. Almost all TS patients with pulmonary involvement are women. They usually present with exertional dyspnea and frequently present with pneumothorax, hemoptysis, or chylous effusion. Proliferations of immature-appearing smooth muscle cells along bronchioles is associated with air trapping, cystic air spaces, and pneumothorax, and similar proliferation in pulmonary veins and lymphatics may lead to hemoptysis and chylous effusions, respectively.

Typically, the chest radiograph reveals a diffuse interstitial pattern (Fig 2) associated with normal volume or even somewhat hyperinflated chest, in contrast to most patients with chronic diffuse interstitial infiltrates, who have low lung volumes. Pulmonary function testing most often reveals airway obstruction with a reduced diffusing capacity and PaO₂.

Thus, a patient (usually a woman in her early 30s) with the above symptoms and findings should strongly suggest the diagnosis. Even without a history of seizures or mental retardation, finding hypomelanotic macules, angiofibroma of the face (adenoma sebaceum) or fingers (Fig 1), or a shagreen patch on the trunk allows the diagnosis to be made without lung biopsy. The chest computed tomographic (CT) scan (Fig 3) appearance of randomly disseminated pulmonary cysts in all lung zones (in contrast to predominant upper lobe distribution in histiocytosis X) is characteristic and identical in TS and LAM. Indeed, CT scan of the chest and abdomen or head can be used to secure the diagnosis of TS when associated with hamartomatous lesions (eg, bilateral renal angiomylipoma, cardiac rhabdomyoma, cerebral or cerebellar tubers, or subependymal nodules).

Patients with TS with pulmonary involvement have an average survival of 3 to 5 years following their diagnosis. The rarity of this condition has not allowed the accumulation of meaningful data regarding therapy. Observations that pulmonary LAM may respond to hormonal manipulation (eg, by oophorectomy or administration of medroxyprogesterone) has led to some limited success in several patients with LAM and one patient with TS who had associated chylous effusion. Several reports suggest that pulmonary LAM and presumably TS may be exacerbated by pregnancy even in the absence of severe respiratory impairment. These considerations led to our recommendation to this woman that she undergo total hysterectomy.

**Clinical Pearls**

1. Radiographic findings of diffuse interstitial infiltrates and airway obstruction with normal or increased lung volumes in a young woman with chronic dyspnea suggests the diagnosis of pulmonary TS or LAM.

2. Any patient with a diagnosis of LAM with extrapulmonary features, such as skin lesions, mental retardation, or seizures, almost certainly has TS.

3. Careful inspection of the skin may detect other significant lesions, even in the absence of classic adenoma sebaceum, that would help distinguish TS from LAM; chest CT scan findings of diffuse random cystic disease obviate lung biopsy.

4. The limited survival of women with pulmonary TS, the 50 percent risk that the child may be affected, and the likelihood that hormonal influences of pregnancy could accelerate progression of the disease must be discussed with the patient. Indeed, hysterectomy and oophorectomy with other hormonal manipulation may be helpful in slowing progression.
Suggested Readings


