

Case of Tuberous Sclerosis with Pulmonary Involvement

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Abstract: Tuberous sclerosis is a rare genetic disorder. The diagnosis of tuberous sclerosis requires the presence of two major or one major and two minor features. Pulmonary involvement has been reported to occur in less than 1% in patients and carries a poor prognosis. We present a female tuberous sclerosis patient with pulmonary involvement, evaluated for a positive PPD reaction.

Key Words: Tuberous sclerosis, pulmonary involvement, LAM, kidney, radiology

Pulmoner Tutulumla Seyreden Tuberoskleroz Olgusu

Özet: Tuberoskleroz nadir rastlanan genetik bir hastalıktır. Tuberoskleroz tanısı iki major veya bir major iki minor bulgunun varlığı ile konur.

Pulmoner tutulum % 1 den daha az hastada görülür ve kötü prognoz kriteri olarak raporlanmaktadır.

PPD pozitifliği nedeniyle araştırılan pulmoner tutulumu olan bir bayan hastayı sunmayı uygun gördük.

Anahtar Sözcükler: Tuberoskleroz, pulmoner tutulum, LAM, böbrek, radyoloji

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Introduction

Tuberous sclerosis (TS) is an autosomal dominant genetic disorder with a reported incidence of approximately 1 in 5,000-10,000 live births (1,2). Although it is a genetic disorder, only one-third of cases are familial. The criteria for diagnosis of TS were defined at a consensus conference in 1998. According to these criteria, diagnosis requires the presence of two major features, or one major and two minor features (Table 1) (3).

Table 1. Tuberous sclerosis criteria.

| Major | Minor |
|---|---|
| facial angiofibromas or forehead plaque | multiple randomly distributed pits in dental enamel |
| no traumatic ungula or periungual fibroma | rectal hamartomatous polyps |
| hypomelanotic macules (three or more) | bone cysts |
| shagreen patch (connective tissue nevus) | cerebral white matter radial migration lines |
| multiple retinal nodular hamartomas | gingival fibromas |
| brain cortical tuber | nonrenal hamartomas |
| subependymal nodules | retinal achromic patch |
| subependymal giant cell astrocytoma | confetti skin lesions |
| cardiac rhabdomyoma | multiple renal cysts |
| pulmonary LAM | |
| renal AML | |

LAM: Lymphangioleiomyomatosis. AML: Angiomyolipoma.

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Case Report

A 57-year-old female patient was admitted to the hospital for evaluation of a positive PPD. She had no respiratory complaints and had never smoked.

Complete blood count, routine biochemical analysis and urine analysis were normal. The posteroanterior chest radiograph was reported to show a right paraspinal mass in the lower zone (Figure 1). Computed tomography (CT) scan of the chest was obtained. It confirmed that the mass represented a large intrathoracic hiatal hernia. Representative CT images of the lung showed multiple thin-walled lung cysts (Figures 2a, 2b).

The upper abdominal CT scan showed multiple bilateral renal masses, some of which contained fat (Figures 3a, 3b).

The patient had a clinical history of TS with facial angiofibromas, mental retardation and seizures for a long period. The previous brain CT demonstrated characteristic periventricular subependymal calcifications. On the basis of the above findings, the diagnosis of TS was made.

Discussion

Tuberous sclerosis (TS) is an uncommon autosomal dominant genetic disorder. Some studies have established

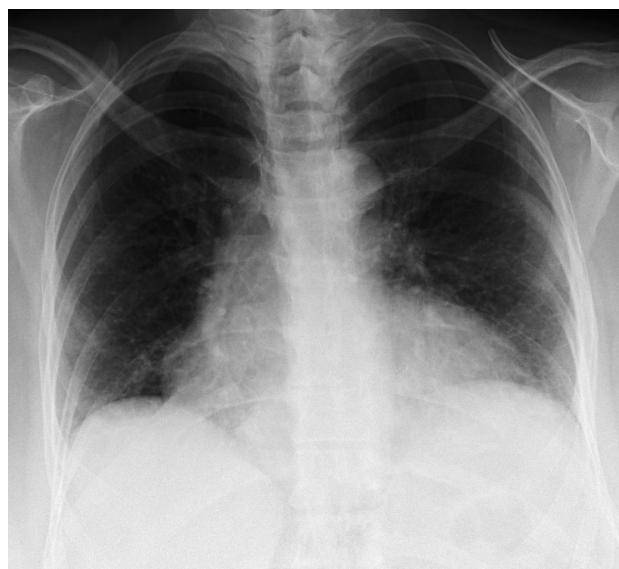
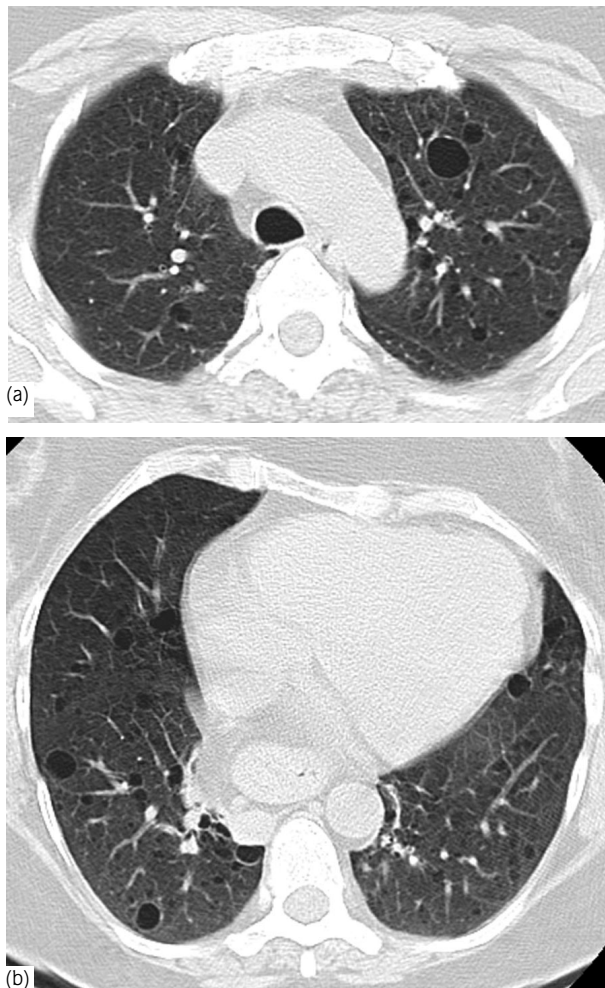


Figure 1. Chest radiograph showing a soft tissue abnormality in the lower right paraspinal region at the right lung base.

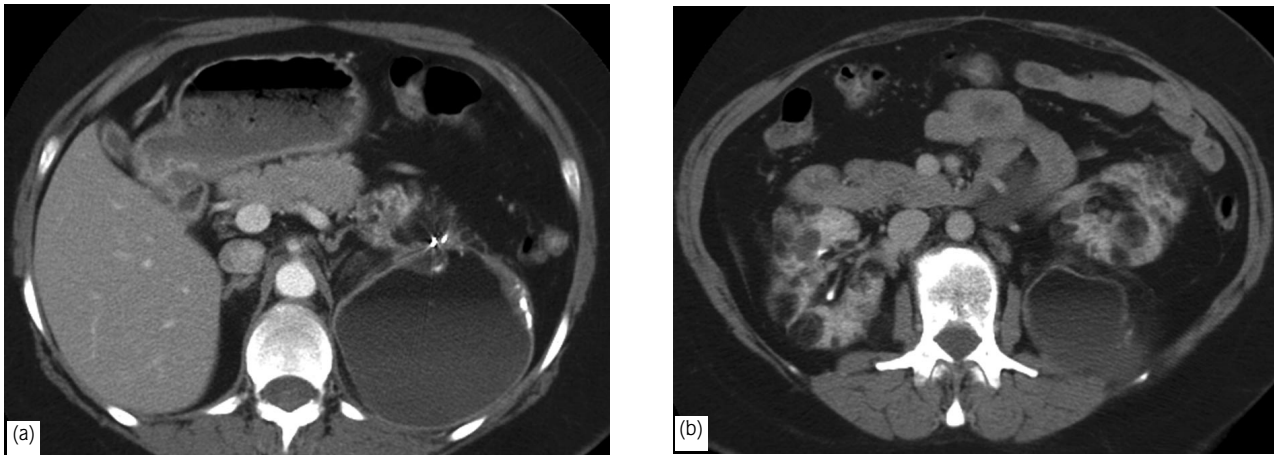


Figures 2. Axial CT images of the lungs obtained at the levels of the aortic arch (2a) and lung bases (2b) showing cystic lung disease. The right paraspinal abnormality on the chest radiograph is explained by a large hiatal hernia.

a direct relationship with mutations in two genes, TSC1 on chromosome 9q 34 and TSC2 on chromosome 16p13 (4).

Tuberous sclerosis is characterized by multiple hamartomas in one or many organs, particularly the skin (adenoma sebaceum, angiofibromas, pigmented lesions), central nervous system (periventricular tubers, subependymal calcifications), retina, and kidneys (angiomyolipomas, AML) (5). These hamartomas are composed of varying amounts of mature adipose tissue, smooth muscle, and blood vessels (6).

The classic clinical triad for TS consists of seizures, mental retardation, and facial angiofibromas. This classic triad occurs in fewer than 50% of patients with TS (3).



Figures 3. (a) Contrast enhanced axial CT image of the upper abdomen at the level of liver and body of pancreas. There is a cystic mass in the left upper quadrant showing a fluid-fluid level.
 (b) Contrast enhanced axial CT image of the upper abdomen obtained at the level of kidneys.

Pulmonary involvement has been reported to occur in less than 1% of patients. The histological appearance of pulmonary involvement in TS is identical to pulmonary lymphangiomyomatosis (LAM) (5). There is diffuse parenchymal smooth muscle infiltration, which results in destruction of alveolar septa and formation of pulmonary cysts. This similar histology has led to the speculation that LAM may be a *forme fruste* of TS (6,7).

The onset of pulmonary involvement with TS is rare before the fourth decade of life and occurs more commonly in females with TS. Pulmonary TS may present clinically with progressive dyspnea, spontaneous pneumothorax, chest pain, and rarely hemoptysis (8).

The proliferation of smooth muscle can also involve the lymphatics in the chest and abdomen. This can result in lymph node enlargement and lymphatic obstruction with resultant chylothorax or chylous ascites (9).

In cases of mild pulmonary TS, the patient may be completely asymptomatic and the chest radiograph can appear normal. In more severe cases, the cystic nature of the disease may be apparent, producing a honeycomb pattern on chest radiographs. The pulmonary cysts are usually much easier to identify and characterize by CT scanning. The characteristic CT appearance is cystic airspaces of variable sizes. The walls of the cysts are usually very thin and sharply defined (Figures 2a, 2b). The CT appearances of TS cysts are identical to pulmonary LAM, and are also very similar to the cystic lung disease in Langerhans histiocytosis (LH). The cysts in LAM and TS do not typically have the upper zone

predilection (at least in early disease) or the more bizarre shapes that tend to occur with LH (4).

Distinction between LH cystic lung disease and the cysts occurring in LAM and TS is often not possible based on CT appearance alone. The chest imaging findings in TS, when combined with clinical history and physical findings, will usually establish the correct diagnosis without the need for a lung biopsy. Pulmonary function testing (PFT) is usually abnormal in cases with significant pulmonary involvement. The most common PFT abnormalities are impaired gas transfer and obstruction. Pulmonary involvement can cause progressive dyspnea, respiratory failure, cor pulmonale, and death (9). Renal hamartomas (AML) occur in 40-80% of patients with TS (10).

The contrast enhanced CT scan of the upper abdomen in the present case (Figure 3b) showed multiple bilateral renal masses, some of which contained fat. The fat component in these renal masses is apparent on the CT images when the low-density components of the masses are visually compared to subcutaneous and retroperitoneal fat. CT region of interest (ROI) measurements confirmed the presence of fat in these renal masses. Spontaneous hemorrhage is a common and potentially life-threatening complication of renal AMLs (9).

A fluid-fluid level was present in one of the large renal AMLs arising in the upper pole of the left kidney (Figure 3a), indicating a resolving recently contained bleeding with the characteristic CT appearance of a fluid-fluid level related to the different CT attenuations of different blood

products. Because of the high incidence of renal involvement in patients with TS, it is important to recognize and manage the bleeding complications of AMLs. Common clinical symptoms of bleeding in AMLs include flank pain, retroperitoneal signs, hematuria, and symptoms similar to pyelonephritis. Most cases of renal AMLs are detected incidentally during abdominal imaging examinations. The CT appearance of AMLs is usually diagnostic with single or multiple renal masses containing fat densities, as was present in our patient. These lesions can range in size from a few millimeters to over 10 cm (9).

It is now recognized that some women with LAM also have renal AMLs, but have no other TS features. Women with LAM and only renal AMLs do not have an increased risk of having children with TS involvement (11).

The identification of a renal AML in a woman with LAM is insufficient for a clinical diagnosis of TS without other diagnostic criteria of TS (7). The exact relationship between LAM and TS remains uncertain. The renal AMLs occurring in association with LAM are usually solitary, and abdominal CT is currently the best imaging modality for screening patients with LAM for the presence of renal AMLs. Renal biopsy is usually unnecessary since the CT appearance is almost always diagnostic (9).

Patients with TS have a decreased survival with renal disease and brain tumors as the most common causes of death (12).

Small (<4 cm) asymptomatic renal AMLs usually do not require treatment, and can be followed by serial imaging. Intervention (selective arterial embolization or conservative partial nephrectomy) may be considered for larger AMLs (>4 cm) or AMLs that grow. Treatment should be directed to preserving renal function and avoiding nephrectomy if at all possible (12).

Pulmonary involvement in TS usually carries a poor prognosis, with progression of lung disease being common (13).

There is currently no effective treatment. Because of its similarity to LAM, treatment with progesterone, luteinizing hormone-releasing hormone (LHRH) analogs, and/or oophorectomy have been tried in women with progressive pulmonary TS. Lung transplantation could be an alternative option in some patients (14).

In conclusion, this case report reviews the characteristic imaging findings of pulmonary involvement in TS, and shows the similarity in the radiological features of pulmonary TS and LAM.

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