# Tuberous Sclerosis with Recurrent Pneumothoraces and Lung Transplantation — A Case Report

Chia-Cheng Tseng, Chao-Chien Wu, Meng-Chih Lin, Ming-Jang Hsieh*

Tuberous sclerosis with lung involvement is very rare. We report herein a case of tuberous sclerosis with recurrent spontaneous pneumothraces, for which lung transplantation was ultimately performed due to refractory cor pulmonale. A 23- year-old woman with tuberous sclerosis presented with recurrent pneumothoraces at our hospital. She had had a past history of right renal angiomyolipoma, and since childhood, she had been noted to have skin lesions with angiofibromas on both cheeks and in the lumbosacral area. With the assistance of sonography, she was also found to have hepatic tumors that had not grown for several years, indicating they were benign. These findings confirmed our diagnosis of tuberous sclerosis. As the disease progressed, chest radiographs revealed more interstitial lung infiltration and honeycombing change. Her pulmonary function also deteriorated progressively. Chronic respiratory failure began in 1999. Although she underwent lung transplantation, she died one year later due to severe infection and malignant lymphomas.

To date, no one has reported an effective treatment for tuberous sclerosis. Although oophorectomy and treatment with progestational agents have been reported to provide improvement or stabilization of the disease in a subset of patients, only lung transplantation, which is an option for some patients, offers the possibility for cure. ***(Thorac Med 2004; 19: 145-151)***

Key words: tuberous sclerosis, recurrent pneumothoraces, lung transplantation, lymphagioleiomyomatosis

## Introduction

Tuberous sclerosis is a systemic disease with a clinical triad of mental retardation, epilepsy, and dermal angiofibroma (adenoma sebaceum). Systemic manifestations include calcified cerebral and paraventricular harmatomas, renal angiolipomas, cardiac rhabdomyomas, and periungual fibromas [1]. Patients with this multi-system disease most commonly present with skin lesions and benign tumors of the central nervous system. Renal involvement is common, with angiomyolipomas, usually bilateral, being the most frequent abnormality. Renal cysts, which may also be present, can give an appearance similar to that of autosomal dominant polycystic kidney disease [2]. Heart rhabdomyomas, probably hamartomatous growths, occur in multiples in 90% of the cases. Mortality with cardiac abnormalities is usually due to intramural rhabdomyomas, which affect 30% of individuals

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with tuberous sclerosis, resulting in death during the first year of life [3]. Patients inheriting the tuberous sclerosis gene are at an increased risk of developing ependymomas and childhood astrocytomas, more than 90% of which are sub-ependymal giant cell astrocytomas. These are benign neoplasms that may develop in the retina or along the border of the lateral ventricles, and may obstruct the foramen of Monro and produce hydrocephalus [4]. Death, usually from neurologic complications, occurs in more than 75% of affected individuals by age 20.

Tuberous sclerosis involving the lungs is pathologically identical to lymphangioleiomyomatosis (LAM) and, therefore, presents a similar clinical, radiographic, and physiologic picture. However, pulmonary disease is rare, appearing in 1% and only in female patients who survive to adulthood. The onset of dyspnea usually occurs during the third decade. As in LAM, progressive dyspnea, recurrent spontaneous pneumothoraces, and hemoptysis are to be expected. Herein, we present a 23-year-old patient with recurrent spontaneous pneumothoraces who was finally diagnosed as having tuberous sclerosis.

## Case Report

In June 1990, a 23-year-old Taiwanese woman visited our emergency room. She complained of right chest pain that suddenly began at 5 a.m. The pain was sharp and worsened if she breathed deeply. A raised erythematous facial rash was noted on examination. She was afebrile, normotensive, and had a normal peripheral pulse. A percussion examination of her chest revealed decreased breathing sounds and hyper-resonance in the right lung field. The chest radiograph revealed pneumothorax in the right lung (Figure. 1). She first underwent tube thoracostomy, and then later was admitted to our chest ward.

Tracing her history, we found that she had experienced two episodes of pneumothoraces, one in the right lung in 1986, and the other in the left lung in February 1990. At that time, she had right flank pain. When searching for the source of that pain, we found a huge right renal tumor, which was removed with a right nephrectomy in January 1990. Pathology revealed an angiomyolipoma, 3.2 kg in weight.

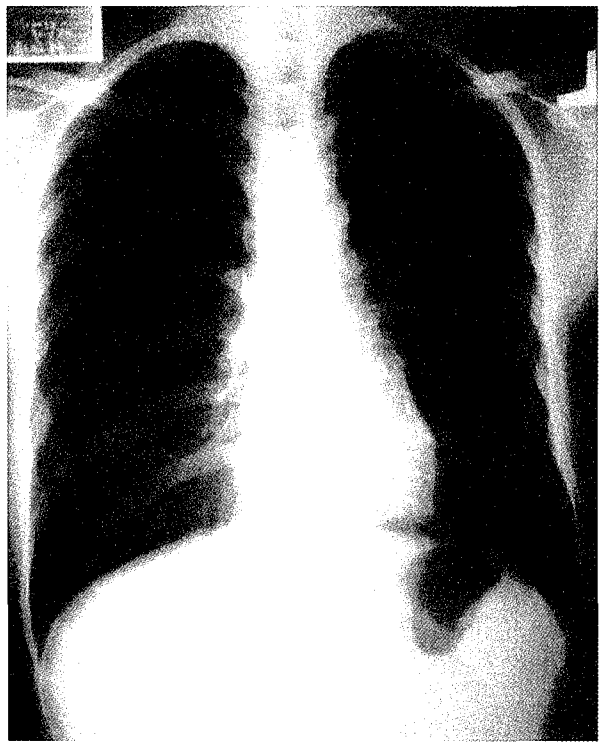

**Fig. 1.** Chest radiograph reveals pneumothorax in the right lung with mild interstitial infiltration in the bilateral lower lung field.

The patient presented a sporadic case with no family history of the disease. She had normal development of intelligence and no history of seizures. No history of trauma or medical history could add any more to our clinical findings.

Since childhood she had been noted to have skin lesions with erythematous papules on both cheeks and leaf-shaped plaque on the skin of her buttocks. A biopsy of the skin lesions revealed angiofibroma. The patient's presumptive diagnosis was tuberous sclerosis, based on the findings of facial angiofibroma, renal angiomyolipoma, and recurrent spontaneous pneumothoraces. These findings were compatible with Gomez's inclusion criteria for tuberous sclerosis.

At admission, surgery was indicated to treat the

recurrent spontaneous pneumothoraces. During the operation, she was found to have numerous generalized blebs and spots with pigmentation throughout the lung. Pathology reported harmatomatous proliferation. Sonographic findings also revealed her liver to have multiple hyperechogenic lesions, compatible with vascular tumors. These liver lesions had been found much earlier and were followed up by sonography 6 and 9 years after they were first discovered, but no increase in size was noted, strongly suggesting that they were benign.

However, another episode of left spontaneous pneumothorax occurred in December 1990. A left thoracotomy with repair of air leaking blebs and pleurodesis were both performed.

After discharge, the patient seemed quite well and had no specific complaint related to lung disease. A pulmonary function test that was done at that time showed FVC to be 70% and $FEV_1$ to be normal, which meant she could be considered as having only a mild restrictive ventilatory impairment. In June 1995, she complained of dyspnea on exertion and occasional hemoptysis episodes. She was observed to have wheezing and moderate obstructive ventilatory impairment. She was prescribed a bronchodilator and inhaled corticosteroid. Polyvalent pneumococcal vaccine and annual influenza vaccinations were also given. With these medications, the patient could initially tolerate her symptoms, but, starting in April 1997, she experienced more profound dyspnea on exertion and hemoptysis. She was found by spirometry to have moderate to severe obstructive and restrictive ventilatory impairment.

Over time, her condition deteriorated. PFT showed severe obstructive ventilatory impairment and a resting oxygen saturation below 90%, so she began receiving oxygen therapy in January 1999. The chest radiograph and computed tomography (CT) showed more interstitial lung infiltrations and honeycombing lesions than she had had nine years before (Figure 2, 3). Anti-estrogen therapy with tamoxifen had been tried for one month in 1999, to no benefit.

Despite all efforts, medical management of her symptoms was failing and her condition deteriorated rapidly. She underwent a lung transplantation due to chronic respiratory failure in June 2001.

Although she received regular immunosup-

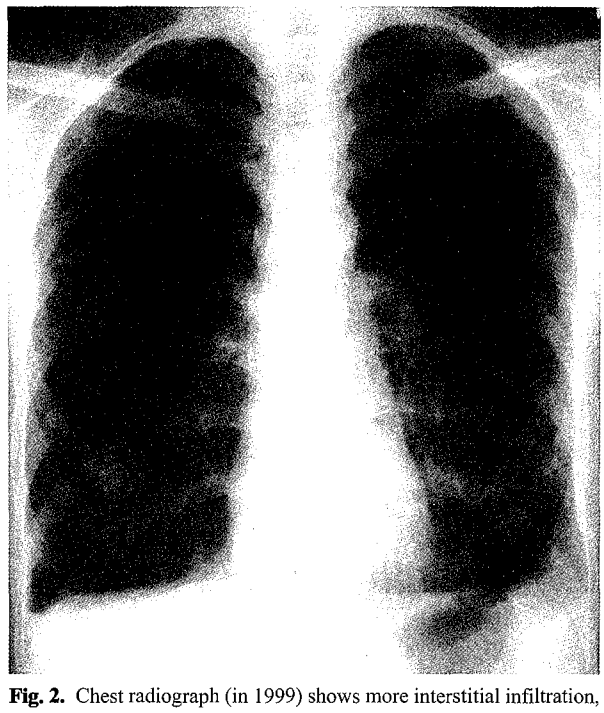

**Fig. 2.** Chest radiograph (in 1999) shows more interstitial infiltration, honeycomb lesions, and hyperinflation compared to that of Figure 1 (in 1990); bilateral pleural thickness is also noted.

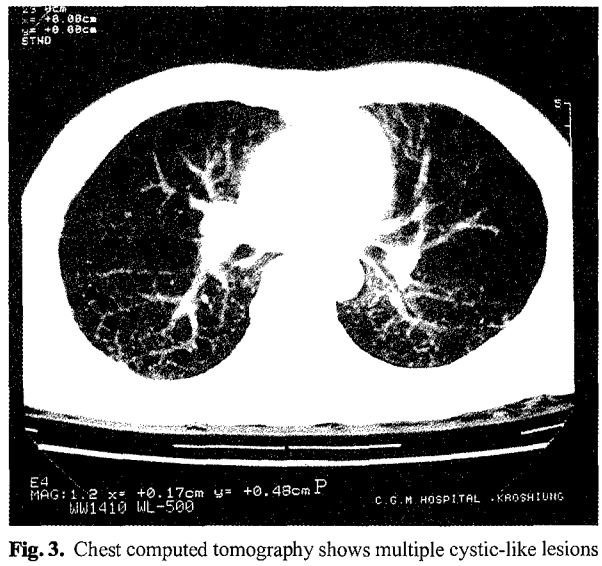


**Fig. 3.** Chest computed tomography shows multiple cystic-like lesions permeating the entire lung parenchyma.

pressant medication after lung transplantation, the continuing dyspnea negatively affected her quality of life, especially when she came down with a common cold. One year after lung transplantation, the patient died due to severe infection and malignant lymphomas.

## Discussion

Tuberous sclerosis (Bourneville's disease) is a rare autosomal dominant disorder, with a prevalence varying from 1/27,000 to 1/100,000 population. Family history may be negative, and it is estimated that up to 68% of cases is caused by new mutations [5]. There are distinctive differences in age, sex, and presenting symptoms in tuberous sclerosis patients with lung involvement and those without (Table 1).

Kidney involvement, especially cysts and angiomyolipomas, is common. Renal angiomyolipomas have been reported to be one of the most important extrapulmonary complications of tuberous sclerosis, and often occur multiply and bilaterally. They are reported in up to 60% of the patients with LAM [6]. Massive bleeding, a major complication of renal angiomyolipomas [6-8], may cause symptoms of shock. In mild cases, angiomyolipomas result in intratumoral hemorrhage or cause chronic flank pain.

Although the association of tuberous sclerosis and renal angiomyolipomas is well established, the occurrence of hepatic benign tumors in this disease is less well documented. Pathologically, intrahepatic angiomyolipomas, lipomas, and hemangiomas have been reported. Until now, approximately 100 cases of hepatic counterparts have been reported since they were first described by Ishak in 1976, though hepatic angiomyolipomas do not necessarily always occur with tuberous sclerosis [9-10]. Multiple hepatic angiomyolipomas are extremely rare. Only six cases have been reported, and most of them (5/6) have been associated with tuberous sclerosis [9].

The pulmonary manifestations of tuberous sclerosis are indistinguishable from those of LAM. The onset of lung involvement generally occurs during the third to fourth decade of life; it rarely occurs before age 20. When pulmonary involvement is present, there is a marked female predominance, especially in those of childbearing age [11], though the complete clinical triad described is rarely found. Most patients with lung involvement will present dyspnea, but about one-third will have the onset of the disease marked by recurrent spontaneous pneumothoraces [12]. Hemoptysis and chest pain are also important clinical features, but chylothorax is rare [13]. The dyspnea is usually progressive, leading to respiratory failure, and cor pulmonale, which may be fatal. The rapidity of progression of this airflow obstruction is highly variable among patients.

Possible radiographic findings of tuberous sclerosis include interstitial opacities, honeycomb changes, and hyperinflation, although the radiograph may be normal early in the course of the disease [14]. As the disease progresses, cysts enlarge, ranging in diameter from a few millimeters to several centimeters, and may coalesce, causing architectural distortion. Thin-section CT is superior to plain radiography, and often reveals cysts in the lung parenchyma even when the chest radiographic finding is normal at the early stage [7,14-5]. Although these findings are very useful in establishing the diagnosis of LAM, they are not pathognomonic of

**Table 1.** Comparison of tuberous sclerosis with and without lung involvement.

| Features | Without lung involvement | With lung involvement |
|---|---|---|
| Age at onset | <20 years old | 20-35 years old |
| Presenting symptoms | CNS disorder | Dyspnea |
| Male: Female | 1:1 | 1:5 |
| Mental retardation (%) | 60% | 40% |
| Epilepsy (%) | 80% | 20% |

the disease. Similar cysts can be seen, for instance, in Langerhans' cell histiocytosis and emphysema. It is desirable to perform a lung biopsy for histologic confirmation of the diagnosis. Pulmonary function studies often reveal evidence of gas trapping and demonstrate obstruction to airflow and reduced single breath diffusing capacity, but otherwise, spirometric indexes are normal.

Pulmonary tuberous sclerosis or LAM is characterized by a hamartomatous proliferation of smooth muscles in the walls of the airways, venules, and lymph vessels in the lung. The involvement of airways results in narrowing, obstruction, and air trapping. Damaged alveoli coalesce, eventually leading to a cystic formation, which may rupture, resulting in pneumothorax [15]. Obstruction of the venous flow in the lung results in venous distension, pulmonary venous hypertension, and hemoptysis. Lymphatic obstruction leads to chylothorax, a complication that appears more commonly in LAM than in tuberous sclerosis. Infradiaphragmatic lymphatic obstruction may result in retroperitoneal cystic masses [15].

Airway obstruction is managed with a bronchodilator. Pneumothorax is managed in the usual way, with the insertion of a chest tube. As pneumothoraces may be recurrent, mechanical or chemical pleurodesis may be necessary; however, these procedures do not rule out future lung transplantation.

Because of the disease's similarity to LAM, which is thought to be brought about in part by female hormones, hormonal manipulation provides the mainstay of treatment [16]. Progesterone, tamoxifen, luteinizing hormone-releasing hormone (LHRH) analogs, and/or oophorectomy, have been used in the treatment of women. Only oophorectomy and treatment with progestational agents, however, have appeared to provide a reliable improvement or stabilization of the disease in a subset of patients [7, 16]. As the disease progresses to the stage of respiratory failure, lung transplantation may offer the only hope for cure. In a retrospective study of 34 cases of lung transplantation for pulmonary LAM, the survival rate was 69% at one year and 58% at 2 years, similar to the post-transplant figures for other lung diseases [16]. The main causes of post-lung transplant death are acute lung injury (early stage), and infection and bronchiolitis obliterans (late stage). Post-transplant lymphoproliferative disorders associated with Epstein-Barr virus occur in 5 to 10% of lung transplant recipients. Nearly all occur within the first year after transplant. Recent data suggest a much higher incidence of this disease in patients who are Epstein-Barr naive and who receive an Epstein-Barr positive graft. Treatment for this disorder, reported to have an approximate 50% survival rate, is usually reduced immunosuppression and antiviral and anti-B lymphocyte drugs. Survivors often develop bronchiolitis obliterans [17].

Patients with tuberous sclerosis have a decreased survival compared to the general population. Renal disease and brain tumors are the most common causes of death [5]. Pulmonary involvement in tuberous sclerosis carries a poor prognosis, with progressive disease being common. Death secondary to respiratory failure often occurs within five years of the onset of symptoms. However, survival time up to 20 years in some cases has been described. In our report, the patient survived 11 years after the symptoms began. The most recent studies report a 10-year survival rate of around 70% to 79% [6]. Long-term survival may occur more frequently today because of improved management for potential complications, especially cor pulmonale and pneumothoraces.

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# 結節性硬化症合併反覆性氣胸及肺移植—一個案例報告

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結節性硬化症合併肺部侵犯是非常罕見的。在這裡我們報導一個反覆性自發性氣胸的案例，最後發生肺心症且內科藥物治療無效而實施肺臟移植。這一個結節性硬化症的23歲女性病患，以反覆性自發性氣胸為其初始症狀，她有右腎血管肌肉脂肪瘤的過去病史，在兩臉頰及腰臀部的皮膚病灶發現血管纖維瘤，皮膚病灶在孩提時即存在。在超音波檢查下也發現肝臟腫瘤且數年之後腫瘤皆無變大的趨向，應是良性腫瘤；這些發現肯定結節性硬化症的診斷。隨著疾病的進展，胸部X光發現更多的間質性浸潤及蜂窩狀的改變，肺功能也逐漸阻塞並惡化，慢性呼吸衰竭及肺心症在十年後發生，肺臟移植在內科藥物治療失效後實施，但病患依然在肺移植一年後因嚴重感染及惡性淋巴瘤死亡。

到今天為止，對於結節性硬化症依然沒有比較有效的治療方法，雖然卵巢切除術及黃體素劑在一些病人身上看到療效，但只有肺臟移植，在一些肺部嚴重侵犯的病人上，是唯一可以治療痊癒的選擇。*(胸腔醫學 2004; 19: 145-151)*

關鍵詞：結節性硬化症，自發性氣胸，肺臟移植，淋巴管平滑肌增生症

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