

## The Lungs in Tuberos Sclerosis Complex A Case Report

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### ABSTRACT

*Tuberous sclerosis complex manifests predominantly as a neurocutaneous disorder. Lung involvement was considered rare. Lymphangioliomyomatosis which occurs mainly in women of childbearing age is the major pulmonary disorder seen in tuberous sclerosis. Multifocal micronodular pneumocyte hyperplasia has also been described in tuberous sclerosis. The case of a 51-year old female diagnosed with tuberous sclerosis is described after she presented with progressive shortness of breath and was found to have interstitial lung disease. Tuberous sclerosis should be considered as a differential in patients with interstitial lung disease especially in association with cutaneous lesions.*

## Los Pulmones en el Complejo de Esclerosis Tuberosa Reporte de un Caso

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### RESUMEN

*El complejo de esclerosis tuberosa se manifiesta predominantemente como un desorden neurocutáneo. El compromiso pulmonar era considerado raro. La linfangioliomiomatosis que se presenta principalmente en mujeres en estado de gestación, es el principal trastorno observado en la esclerosis tuberosa. La hiperplasia micronodular pneumocítica ha sido también descrita en la esclerosis tuberosa. Se describe el caso de una mujer de 51 años a quien se le diagnosticó esclerosis tuberosa, luego de que se presentara con disnea y se hallara que padecía la enfermedad intersticial del pulmón. La esclerosis tuberosa deber ser considerada como un diagnóstico diferencial en pacientes con la enfermedad intersticial del pulmón, especialmente cuando se encuentra asociada con lesiones cutáneas.*

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### Case Report

A 51-year old female was referred to Peebles hospital Tortola, British Virgin Islands, by her private physician with a history of shortness of breath of unclear duration that got progressively worse over the last two weeks. She also complained of unproductive cough but denied a history of chest pain and haemoptysis. She did not complain of fever, leg swelling, calf pain or weight loss. She denied any gastrointestinal and urinary symptoms. She had no history of hypertension or diabetes mellitus but had had facial rash

since childhood. She had visited many physicians in the past for this but was not given any specific diagnosis. She neither smoked cigarettes nor drank alcohol. Family history was significant as there was a similar facial rash in her mother and one of her sisters. Additionally, her sister had seizure disorder. She had no children and had myomectomy in 1984 and total abdominal hysterectomy with bilateral salpingo-oophorectomy in 1994. She had not been on any hormonal replacement therapy.

Physical examination revealed a middle aged female in severe cardiopulmonary distress with a respiratory rate of 40 breaths/minute, temperature 37.78°C, pulse 102 beats/minute, blood pressure 140/75 mmHg and oxygen saturation of 80% while breathing ambient air. Multiple nodular brownish lesions (angiofibromas) were noted on her face and

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forehead (Fig. 1a). A flesh coloured nodular lesion was noted in her right fourth finger (Fig. 1b). She also had two plaques at the lumbosacral region (Shagreen patches – Fig. 1c). She



Fig. 1a: Facial angiofibroma.

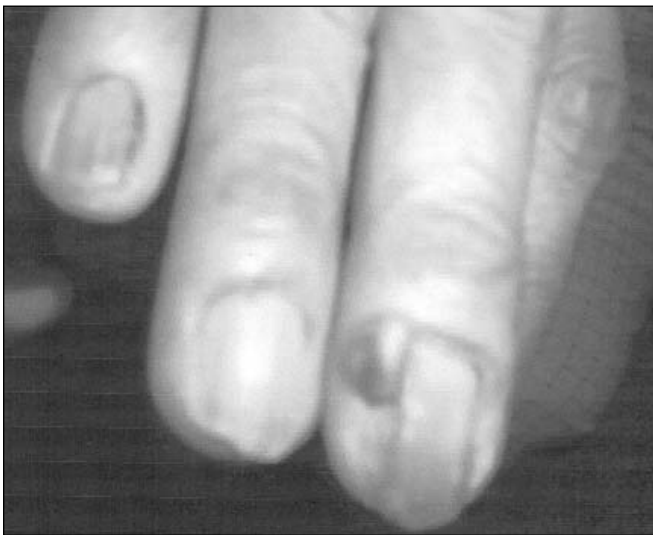


Fig. 1b: Ungual fibroma.



Fig. 1c: Shagreen's Patch.

had bilateral varicose veins and a chronic venous leg ulcer on the lower third of the left leg. Bilateral basal crackles were heard on chest examination with no clinical evidence of pneumothorax. The kidneys were not balloted. Cardiovascular and neurological examinations were unremarkable. She had a mini mental status examination score of 24/30.

Her complete blood count and complete metabolic panels were within normal limits. She had positive D-dimer (1096 microgram/ml) but bilateral venous doppler showed no evidence of deep vein thrombosis but revealed a narrow left common femoral vein. Chest X-ray showed bilateral reticulonodular densities with honey combing appearance most marked at the bases. Chest computed tomography (CT) showed similar findings, with cystic lesions in both lungs (Fig. 1d). Ultrasound and CT of the abdomen showed bila-

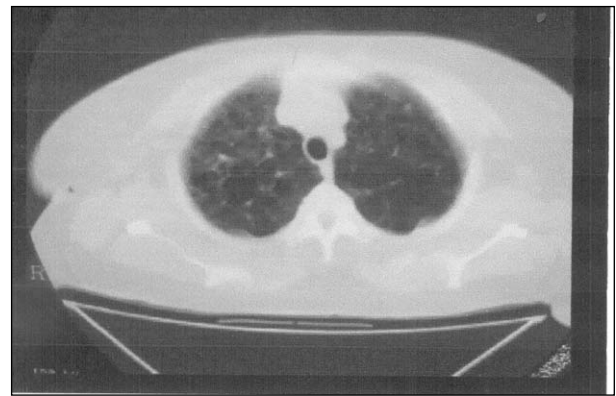


Fig. 1d: Computed tomography of the chest showing cystic lesions.

teral multiple cysts and huge angiomyolipoma of the left kidney (Fig. 1e). Computed tomography of the brain was not



Fig. 1e: Computed tomography of the abdomen showing renal angiomyolipoma.

done because of the cost. Lung biopsy was not done. Ventilation/perfusion scan and spiral CT were not available locally. Electrocardiogram showed sinus tachycardia.

With skin and imaging findings, the index case satisfied the criteria for the diagnosis of tuberous sclerosis (Table 1) and thus was diagnosed with familial tuberous

Table 1: Major and minor diagnostic criteria of tuberous sclerosis complex

Major Criteria	Minor Criteria
Facial angiofibroma or forehead plaques	Multiple dental pits
Ungula fibroma	Hamartomatous rectal polyps
Three or more hypomelanotic macules	Bone cysts
Shagreen patch	Cerebral white matter radial migration lines
Multiple retinal nodular hamartomas	Gingival fibromas
Cortical tubers	Nonrenal hamartoma
Subependymal nodule	Achromic patch
Subependymal giant cell astrocytoma	“Confetti” skin lesions
Cardiac rhabdomyoma	Multiple renal cysts
Lymphangioliomyomatosis	
Renal angiomyolipoma	

sclerosis and lymphangioliomyomatosis. She was treated with supplemental oxygen and antibiotics for presumed superadded infection. She was also started on prednisone and anticoagulation. She improved and was discharged from hospital with discharge oxygen saturation of 93% on ambient air. She was also referred to a urologist for evaluation of her renal angiomyolipoma because of its large size and the risk of bleeding.

## DISCUSSION

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by the development of benign neoplasms (hamartomas) of the skin and the internal organs (1, 2). Inactivating mutations in either of two genes—TSC1 on chromosome 9 and TSC2 on chromosome 16 constitute the genetic basis for this disorder (3). Prevalence of TSC is estimated at 1:10 000. About two-thirds of the cases are sporadic. Familial cases which account for a third of all cases were first reported in 1910 whereas the autosomal pattern of inheritance was established in 1935 (4).

The major clinical features of TSC are neurocutaneous involvement. Skin involvement, which occurs in 95% of cases, includes facial angiofibromas, hypomelanotic macules, ungula fibroma and shagreen patches (4). Seizure occurs in about 85% of cases. All types of seizures have been described in TSC, except absence seizures (4). Mental subnormality, autism and learning disorders are other neurological manifestations of TSC. Renal cysts and angiomyolipoma occur in 60%. The brain, eyes and heart may also be involved.

Diagnosis of definite TSC requires the presence of two major criteria or one major and two minor; probable TSC requires one major and one minor or two minor criteria, whereas possible TSC requires two or more minor criteria (Table 1). The index case had four major criteria (facial angiomias, ungual fibroma, shagreen's patches and pulmon-

ary lymphangioliomyomatosis) (PLAM) and one minor (multiple renal cysts). Therefore, with this constellation of pathognomonic clinical and imaging features, the authors were confident of the diagnosis of TSC even in the absence of genotyping.

Pulmonary lymphangioliomyomatosis is the major lung disease associated with TSC. It was initially thought to be rare in TSC. Earlier studies estimated it to occur in 2–3% of TSC patients (5). However, in a recent survey of 38 female patients with TSC, Moss *et al* reported a high prevalence of 34 % (6). Similarly, in a recent review of 78 female patients with definite TSC, Costello *et al* reported that evidence of PLAM was found in 20 (26%) of the patients (7).

Pulmonary lymphangioliomyomatosis is characterized by unrelenting interstitial lung injury as a result of diffuse proliferation of abnormal smooth muscles (8, 9). Bronchovascular smooth muscle proliferation results in alveolar destruction and cystic parenchymal damage. Pulmonary lymphangioliomyomatosis mainly affects females of reproductive age with dyspnoea and pneumothorax as the commonest clinical presentations. In a comprehensive evaluation of 35 patients with PLAM, Chu *et al* noted dyspnoea in 83%, while 69% presented with spontaneous pneumothorax (10). Other clinical manifestations of PLAM include non-productive cough, haemoptysis, chylous pleural effusion and chylous ascites (10).

There is a close association of PLAM and renal angiomyolipoma (AML). Indeed, AML represents the commonest extrapulmonary manifestation of PLAM and occurs in 32–60% of cases (11). AML can present with flank pain, haematuria, retroperitoneal bleeding and recurrent pyelonephritis. Risk of bleeding increases sharply when the size is more than 4 cm and such patients should be referred for arterial embolization or nephron sparing surgery (11).

Idiopathic PLAM is a rare sporadic disease that occurs in patients without tuberous sclerosis (5, 8, 9). With or without TSC, PLAM is seen almost exclusively in women of childbearing age, though there are a few reports of PLAM in postmenopausal women (12) and even fewer reports in males (13). Pregnancy and exogenous oestrogen seem to exacerbate PLAM (14,15). The epidemiological, clinical, radiological and histological similarities between idiopathic PLAM and PLAM in TSC raise the possibility of idiopathic PLAM being a *forme fruste* of TSC (16). PLAM has also been reported in association with Langerhan's histiocytosis, alpha-1 antitrypsin deficiency, bronchoalveolar carcinoma and thyroid carcinoma (4, 5, 17).

Survival in PLAM was thought to be bleak with death occurring from progressive pulmonary insufficiency within 10 years of diagnosis. However, in a review of 72 patients with PLAM, Johnson *et al* reported a 10-year survival of 91 % from onset of symptoms (18).

Hormonal manipulation, which includes progesterone, tamoxifen, oophorectomy and irradiation of the ovaries have

all been tried, with variable efficacy (19, 20). The index patient was started on steroids because of the suspicion of interstitial lung disease. However, review of the literature did not indicate a role for steroids. The clinical improvement noted in the index case could be attributed to antibiotics. On the other hand, could steroids have played any part? Perhaps a well designed randomized trial is needed to define the role of steroids in PLAM. Lung transplantation has emerged as a viable option and is now considered in PLAM patients with progressive pulmonary insufficiency (21).

Multifocal micronodular pneumocyte hyperplasia (MMPH) is a less common pulmonary feature of TSC occurring in both sexes. It is characterized by hyperplasia of type 2 pneumocytes resulting in alveolar destruction without cystic changes. It is thus considered distinct from PLAM (22).

History of shortness of breath or chest pain in a female particularly of child bearing age with skin lesion should alert physicians to the possibility of tuberous sclerosis.

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