

# Pulmonary manifestations of tuberous sclerosis in first degree relatives

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**ABSTRACT** In a family with tuberous sclerosis affecting four generations a mother and daughter had the rare pulmonary manifestations of the disease. Pathologically the pulmonary disease may be the same as pulmonary lymphangioleiomyomatosis.

## Introduction

Tuberous sclerosis is associated with the development of multiple tumours of ectodermal and mesodermal origin. These have been described in the retina, brain, skin, gingiva, heart, thyroid, pancreas, ovaries, uterus, spleen, and kidneys. The incidence of tuberous sclerosis is 1/100 000–1/150 000 live births<sup>1,2</sup> but only 0.1–1.0% of patients have pulmonary manifestations.<sup>3–5</sup> We report a mother and daughter who both had tuberous sclerosis complicated by pulmonary disease.

## Case reports

### DAUGHTER

Tuberous sclerosis was diagnosed in the daughter during childhood, when she presented with adenoma sebaceum and grand mal and petit mal seizures. She was of low normal intelligence and completed elementary school with difficulty. Ovarian cysts were diagnosed at the age of 22, and at 23 she underwent hysterectomy for uterine leiomyoma. She had many episodes of bilateral flank pain accompanied intermittently by gross haematuria.

Exertional dyspnoea was noted when she was 21 and progressed thereafter. She was admitted to hospital four years later (1982) because of haemoptysis and at this time a microreticulonodular infiltrate was noted on her chest radiograph, predominantly in the lower lung fields peripherally. At this time the bronchoalveolar lavage cell profile showed 77% macrophages, 11% lymphocytes, and 12% polymorpho-

nuclear leucocytes. Lung function tests showed normal volumes with moderate airways obstruction, a substantial reduction in transfer factor for carbon monoxide, and arterial hypoxaemia (table). An open lung biopsy showed considerable smooth muscle proliferation in the interstitium, related particularly to lymphatics and small airways.

Over the following 18 months she became progressively more disabled and had frequent lower respiratory tract infections with haemoptysis. When reviewed at the age of 26 (1983) she had cutaneous manifestations of tuberous sclerosis (adenoma sebaceum, peau chagrine on the left forehead, numerous filiform papillomas, bilateral periungual fibromas, and subcutaneous fibrotic nodules over the lumbar region). Fundoscopy showed a right sided hyperpigmented plaque but no retinal tumours. Examination of the chest indicated mild hyperinflation and intercostal indrawing. The liver was slightly tender and the right kidney was ballotable and tender. The haemoglobin concentration was 11.3 g/dl with microcytosis, and all biochemical tests gave normal results apart from a creatinine clearance of 0.7 (normal 1.58–2.16) ml/s. Computed tomography of the brain showed multiple periventricular calcifications and the electroencephalogram was abnormal, showing a diffuse slow wave pattern. Computed tomography of the abdomen confirmed the presence of renal tumours (renal ultrasound and intravenous pyelography had previously disclosed the pathognomonic cysts and densities of renal angiomyolipomas) and showed a 4.5 cm right sided ovarian cyst and mild hepatosplenomegaly.

A chest radiograph showed no change from that of 1982. She had arterial hypoxaemia while breathing air (table), and ear oximetry showed a resting arterial oxygen saturation (SaO<sub>2</sub>) of 92% when breathing oxygen at 4 l/min through nasal cannulas and desaturation to 83% during exercise after the oxygen

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Pulmonary function studies

	Daughter			Mother	
	Mar 1982	Nov 1983	Jan 1985	Mar 1982	Mar 1983
TLC (l)	4.0	4.5	4.6	5.0	4.9
VC (l)	3.2	2.9	1.3	3.2	3.1
FEV <sub>1</sub> (l)	1.9	0.8	0.4	2.5	2.0
TLCO (%pred)	26	24	9	92	63
<i>Arterial blood gases</i>					
pH	7.46	7.41	7.43	7.39	—
PCO <sub>2</sub> (mm Hg)	28	36	56	37	—
Po <sub>2</sub> (mm Hg)	64	44	31	71	—
HCO <sub>3</sub> <sup>-</sup> (mmol/l)	20	21	37	22	—

TLC—total lung capacity; VC—vital capacity; FEV<sub>1</sub>—forced expired volume in one second; TLCO—single breath carbon monoxide transfer factor; PCO<sub>2</sub>—partial pressure of carbon dioxide; Po<sub>2</sub>—partial pressure of oxygen; HCO<sub>3</sub><sup>-</sup>—serum bicarbonate. Conversion: 1 mm Hg ≈ 0.133 kPa.

flow rate had been increased to 6 l/min. The results of lung function tests had deteriorated, showing more severe airways obstruction, air trapping, and impaired carbon monoxide transfer factor (table). The static pressure-volume curve of the lung showed some loss of lung recoil pressure.

The pulmonary disease failed to respond to corticosteroid and progesterone treatment and she died in 1985 of respiratory failure with cor pulmonale.

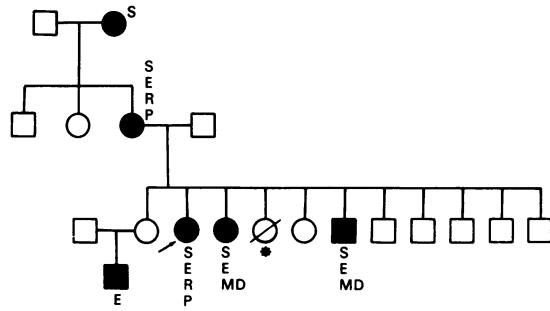
MOTHER

The mother of this patient was a 45 year old housewife when first seen. Tuberous sclerosis was diagnosed from adenoma sebaceum, childhood epilepsy, and renal angiomyolipomas in 1969, when a left nephrectomy for a 16 cm tumour was necessary. She required a hysterectomy for uterine leiomyomas in 1970 and a partial right nephrectomy for excision of angiomyolipomas in 1982.

At this time (1982) she complained of mild exertional dyspnoea, though clinical examination of her chest and chest radiography showed nothing abnormal. She had arterial hypoxaemia, however (table). Her bronchoalveolar lavage cell profile was: 93% macrophages, 6% lymphocytes, 1% polymorphonuclear leucocytes. Over the next two years she developed increasing dyspnoea, recurrent lower respiratory tract infection, and haemoptysis; and bilateral diffuse reticulonodular infiltrates were noted on her chest radiograph.

Discussion

In this family lung disease occurred in two of four generations affected by tuberous sclerosis (figure). Tuberous sclerosis has an autosomal dominant inheritance with variable penetrance.<sup>2-6-8</sup> An unlinked autosomal dominant gene modifying the expression of



Family tree of the two patients, showing tuberous sclerosis affecting four generations. → *proposita*; *S*—adenoma sebaceum; *E*—epilepsy; *R*—renal angiomyolipomas; *P*—pulmonary manifestations; *MD*—mental deficiency; \* *infant death*.

the tuberous sclerosis gene may explain the occurrence of “skip” generations—in this family, for example, the grandson of the mother described above has tuberous sclerosis but an unaffected mother.<sup>7</sup>

The sex incidence of tuberous sclerosis is approximately equal, but pulmonary manifestations are more frequent in females.<sup>14-19</sup> Intellectual impairment and seizures are less common in patients with than without pulmonary disease (46% and 20% respectively versus 62% and 93%).<sup>14</sup> Progressive dyspnoea often begins in the second and third decades, with an incidence of pneumothorax of up to 50%.<sup>14-11</sup> Chronic dry cough and haemoptysis are frequent, and death often occurs within four or five years of presentation as a result of cor pulmonale and respiratory failure.

Chest radiographs generally show a diffuse microreticulonodular pattern, predominantly in the lower lobes. Pulmonary function tests usually indicate airways obstruction with gas trapping, as illustrated by the daughter in this family.<sup>12</sup> Decreased transfer factor for carbon monoxide, as seen in the daughter, has also been reported previously.<sup>3,9-13</sup> Extensive leiomyomatous disease of the small airway walls and encroachment of air spaces by emphysematous, cyst like spaces account for the decreased capacity for gas exchange. A decrease in elastic recoil was expected in the daughter, though this is the first case in which it has been demonstrated.<sup>3</sup> The steady progression of respiratory disease seen in the daughter is typical of lung disease in tuberous sclerosis.

The relation of pulmonary tuberous sclerosis to pulmonary lymphangioleiomyomatosis is not clear.<sup>10-14-17</sup> Pulmonary tuberous sclerosis occurs predominantly in women and lymphangioleiomyomatosis has never been recorded in men. Both show exacerbation during pregnancy and hormonal manipulation may be effective treatment.<sup>18-21</sup> The clinical, radiographic, and histopathological features of lymphangioleiomyomatosis bear a striking resemblance

to those of tuberous sclerosis. These similarities and the occurrence of renal angiomyolipomas in pulmonary lymphangioliomyomatosis suggests that this and pulmonary tuberous sclerosis may be the same pathologically, the former being a forme fruste of the latter.<sup>13</sup>

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