

Pulmonary tuberous sclerosis treated with tamoxifen and progesterone

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Tuberous sclerosis is a rare disease and pulmonary manifestations are extremely rare. Like pulmonary lymphangiomyomatosis, tuberous sclerosis of the lung affects only women of childbearing age and carries a very poor prognosis. The radiological and pathological features of the two conditions in the lung are indistinguishable and some authors therefore consider lymphangiomyomatosis to be a forme fruste of tuberous sclerosis,¹ although others believe that the relationship is unclear.²

In pulmonary lymphangiomyomatosis bilateral oophorectomy and high dose progesterone have sometimes been beneficial,²⁻⁴ and antioestrogens have been advocated on theoretical grounds.⁵ In this report we describe two patients with pulmonary tuberous sclerosis; both were treated with tamoxifen and progesterone.

Case reports

PATIENT 1

Patient 1 was a white woman of average intelligence, born in 1959. She had had childhood epilepsy, smoked 20 cigarettes daily until 1981, and had no pulmonary complaints before 1976. In 1976 she had a left nephroureterectomy because of an angiomyolipoma and after this suffered her first pneumothorax. Other pneumothoraces followed and were treated by chemical pleurodesis. In 1977 she was referred to our hospital with bilateral pneumothoraces (her seventh and eighth) and was again treated with chemical pleurodesis. In 1978 she had an abortion and in 1979 she was delivered of a normal child by caesarean section, at which time no tumour was palpable in the abdomen, although chest radiography showed diffuse interstitial opacities. In 1980 pleuroctomy was performed because of the tenth pneumothorax; the lung was covered by numerous blebs and bullae (3-20 mm). Examination of material obtained at biopsy showed emphysematous spaces associated with fibromuscular hyperplasia, compatible with either lymphangiomyomatosis or tuberous sclerosis of the lung. Subsequently a discrete facial angiofibroma was found and subependymal calcifications were identified on computed tomography of the brain. There was no retinal phakoma.

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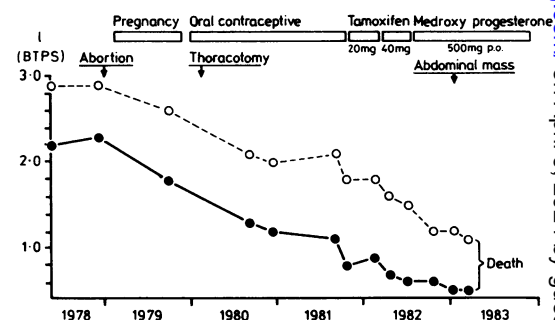
Although the family history was negative, tuberous sclerosis with pulmonary manifestations was diagnosed.

There was progressive deterioration of pulmonary function despite treatment with tamoxifen and later medroxyprogesterone acetate until her death (fig). In January 1983 computed tomography showed enlargement of the spleen, liver, and right kidney. In July she had her twelfth pneumothorax, and in September retroperitoneal bleeding. She died of respiratory failure in November 1983.

Necropsy showed multiple emphysematous spaces in the lung with proliferation of smooth muscle cells in the walls of these spaces. Angiomyolipomas were present in the kidney, spleen, and liver. Examination of the brain was not permitted.

PATIENT 2

Patient 2 was a white non-smoking woman of average intelligence, born in 1943. Her only pregnancy ended in a stillbirth in 1969. She never used oral contraceptives. In 1979 she was referred to our hospital with a pneumothorax and a two year history of increasing dyspnoea and sporadic haemoptysis. Physical examination showed no abnormalities such as retinal phakoma or facial angiofibroma. The chest radiograph showed bilateral interstitial opacities with honeycombing. Pulmonary function studies showed an inspiratory vital capacity (VC) of 108% and an FEV₁ of 30% of the predicted normal values, after use of a bronchodilator.



Course of pulmonary function of patient 1. ○—○ Inspiratory vital capacity after bronchodilator; ●—● FEV₁ after bronchodilator. The contraceptive comprised levonorgestrel 150 µg, ethinylestradiol 30 µg. Doses are per day.

Because of a second pneumothorax pleurectomy was performed in July 1979. At operation the lung was found to be covered by numerous small blebs. Histological examination showed abnormalities suggestive of pulmonary lymphangioleiomyomatosis. The patient became progressively dyspnoeic. In November 1980 the inspiratory VC was 78% and the FEV₁ 18% of the predicted normal values, after bronchodilatation. Tamoxifen 10 mg twice daily was then prescribed. It was replaced by intramuscular medroxyprogesterone acetate 400 mg once a month in January 1981 and this treatment continued until her death from respiratory insufficiency in June 1982.

At necropsy multiple emphysematous spaces were found in the lungs with proliferation of smooth muscle cells. Lymphangiomyomas were present in the abdominal and mediastinal lymph nodes, and multiple angiomyolipomas were present in both kidneys. There was a giant cell astrocytoma and subependymoma in the brain. The findings permitted a definite diagnosis of tuberous sclerosis, although the family history was negative.

Discussion

Although our patients did not show the typical clinical triad and had a negative family history, both had tuberous sclerosis according to recent criteria.⁶ Whether their disease should be called pulmonary lymphangioleiomyomatosis with the stigmata of tuberous sclerosis or tuberous sclerosis with pulmonary localisation is at present a semantic question. Both diseases carry a poor prognosis despite the use of chemotherapy, corticosteroids treatment, or radiotherapy.

The deterioration of pulmonary function and the beneficial influence of hormonal treatment in some patients with lymphangioleiomyomatosis led us to attempt treatment of both our patients with tamoxifen (at 36 and 10 weeks respectively) and progesterone (at 69 and 71 weeks respectively). Neither patient benefited and both died of respiratory failure. This could be due to the degree of lung destruction at the start of the treatment, although in other patients with similar pulmonary function hormonal treatment seemed at least to arrest progression.^{1,7}

The steady decline of pulmonary function and the development of new angiomyolipomas during treatment suggest a primary hormonal unresponsiveness. Such unresponsiveness could be the result of the absence of sex hormone receptors in the lungs. Progesterone receptors have been demonstrated in the lungs of patients with lymphangioleiomyomatosis, and the most convincing results of progesterone treatment are in

a patient with such receptors.² On the other hand, progesterone has been beneficial in the absence of these receptors,⁸ and has failed despite their presence.^{9,10} Oestrogen receptors have also been found in the lungs of patients with lymphangioleiomyomatosis, but their role has been questioned.⁹ Tamoxifen treatment has failed in this disease,^{4,5} even in the presence of oestrogen receptors.⁹ Nevertheless, it resulted in stabilisation of the disease in another patient with lymphangioleiomyomatosis, who had stigmata of tuberous sclerosis and oestrogen receptors.¹ Regrettably, in our patients sex hormone receptors were not determined, although the assessment of these receptors by current techniques seems at present to have little clinical importance.

Detailed results of pulmonary function tests are available from the authors on request.

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