LYMPHANGIOLEIOMYOMATOSIS - TREATMENT WITH PROGESTERONE

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ABSTRACT

Lymphangioleiomyomatosis is a rare devastating disease affecting women mostly of child-bearing age. It presents with spontaneous pneumothorax, chylous effusions, hemoptysis and progressive breathlessness. Most patients die from respiratory failure within 10 years. There are no controlled studies on the efficacy of various treatment regimens. We report our experience with progesterone therapy in three patients. Two failed to respond, one died about 11 years after presentation and another after 5 1/2 years. The third patient has survived 11 years after onset of disease.

Keywords: lymphangioleiomyomatosis, female patients, pneumothorax, respiratory failure, progesterone therapy

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INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a rare pulmonary disease which presents only in women, usually of child bearing age with spontaneous pneumothorax, chylous effusions, hemoptysis and slowly progressive dyspnoea. It has characteristic radiological, pulmonary physiological and pathological patterns[1,2] and appears to deteriorate rapidly during pregnancy[3-5]. Reports of disease onset in the post menopausal years are very rare[6-8]. The signs and symptoms result from the proliferation of smooth muscle around the airways, blood vessels and lymphatic vessels. Gross examination of a cut lung specimen shows cysts throughout the lungs. Most patients die from respiratory failure within ten years from the onset of symptoms[1].

Attempts to treat this disease with gluco-corticoids, surgery, radiation therapy and conventional chemotherapy have not shown to affect the course of the disease. Because LAM occurs almost exclusively during the child bearing years, with exacerbations with menses and during pregnancy, it has long been suspected that there is some degree of hormonal influence. Reports of treatment through sex hormonal manipulation, such as administration of androgens[2,9], discontinuation of exogenous oestrogens[10], tamoxifen therapy[2,11-15,32], oophorectomy[10,16-20,32] and progesterone therapy,[5,12-14,21-32] indicate both success and failure. Due to the rarity of the disease, no controlled studies on the efficacy of the various treatment regimens have been performed.

We report our experience with progesterone therapy in three patients.

CASE REPORTS

Case 1

This patient has been described previously[3]. This 34 year old Chinese woman first presented in August 1974 when she was two months pregnant with bilateral pneumothorax. She improved with bilateral intercostal tube drainage. She had a recurrence of bilateral pneumothorax in September 1975 which failed to resolve with conservative treatment. A right open pleurodesis and lung biopsy was done and the diagnosis of LAM confirmed. She remained relatively well except for breathlessness on exertion between December 1975 and September 1981. In April 1979 a shallow left pneumothorax was noted on her chest radiograph which resolved spontaneously. She was given a six month trial of medroxyprogesterone acetate (MPA) (400 mg. intramuscularly per month) from September 1981. There was no symptomatic or functional improvement (Table I). MPA was stopped in March 1982. Her condition continued to deteriorate gradually; she died of increasing respiratory failure and cor pulmonale in September 1985.

Table I
Pulmonary Function Studies - Case 1

Index	Time after Therapy		% Change
	0 Month	6 Month	
VC (litres)	1.83 (67)	1.76 (64)	-3.8
FEV_1 (litres)	0.86 (34)	0.72 (28)	-16.3
MMFR (litres/sec)	0.42 (13)	0.34 (11)	-19.0
TLC (litres)	3.91 (95)	3.52 (85)	-9.9
D_LCO (ml/min/mmHg)	3.5 (21)	3.50 (21)	0

Numbers in parentheses indicate percentage of predicted normal

Case 2

This 26 year old Chinese woman complained of blood streaked sputum in January 1980. She was found to have a loculated right pneumothorax which resolved spontaneously. She remained well until October 1980 when she was admitted to hospital for sudden onset of breathlessness and bilateral upper chest pain. A chest radiograph revealed a left pneumothorax and a right hydropneumothorax. Aspiration of the fluid in the right pleural cavity showed a chylous effusion. She failed to respond to intercostal tube drainage. A left open pleurodesis and lung biopsy was done followed by a right open pleurodesis. Histology revealed LAM. Her condition improved post

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operatively. In April 1981 she had a recurrent small left pneumothorax which resolved spontaneously. She also noted some blood staining of her sputum. A six month trial of intramuscular MPA (400 mg. per month) was started in July 1981. She showed no symptomatic or functional improvement (Table II). MPA was stopped in January 1982. She was re-admitted three months later for right sided chest pain associated with a recurrence of right chylothorax. She responded to conservative treatment and remained fairly well for the next two years except for occasional episodes of blood streaked sputum and increasing breathlessness. She died from respiratory failure and cor pulmonale in July 1985.

Table II
Pulmonary Function Studies - Case 2

Index	Time after Therapy		% Change
	0 Month	6 Month	
VC (litres)	1.56 (58)	1.49 (55)	-4.5
FEV_1 (litres)	1.24 (49)	1.12 (44)	-9.7
MMFR (litres/sec)	1.32 (41)	1.00 (28)	-24.2
TLC (litres)	2.67 (67)	2.52 (63)	-5.6
D_LCO (ml/min/mmHg)	5.5 (31)	5.0 (27)	-9.1
	At Rest / After Exercise*	At Rest / After Exercise	
PaO_2 (mmHg)	79 / 82	72 / 57	
$PaCO_2$ (mmHg)	32 / 30	29 / 31	
pH	7.39 / 7.35	7.40 / 7.32	

Numbers in parentheses indicate percentage of predicted normal

*Maximum Exercise at 400 kpM/min.

Case 3

This 33 year old Chinese woman first presented to hospital in January 1980 for right sided chest pain and breathlessness due to a right spontaneous pneumothorax. This resolved with intercostal tube drainage. She was re-admitted five months later with a left pneumothorax which again resolved with chest tube drainage. In February 1981 she had a bout of severe coughing followed by chest discomfort and breathlessness. A chest radiograph showed bilateral pneumothorax. Bilateral open pleurodesis was done; a lung biopsy confirmed the diagnosis of LAM. Her condition improved post operatively and she was discharged from the hospital in March 1981. In February 1982 she was started on a six month trial of MPA intramuscularly (400 mg. per month). She improved symptomatically, being less breathless on exertion. This was accompanied by objective improvement in the flow rates, diffusing capacity and arterial blood gases (Table III). MPA therapy was withheld from August 1982 to February 1985 during which period she remained well except for breathlessness on exertion. MPA therapy was reinstituted in February 1985 when the pulmonary function tests showed deterioration. Her respiratory status and pulmonary function again improved with reinstitution of the injections. MPA has been continued till the present. She has remained well except for two episodes of pneumothorax in April 1987 and June 1988 which resolved spontaneously. Her serial pulmonary function tests over the past ten years are shown in Fig 1. Fig 2 shows the classic chest CT scan.

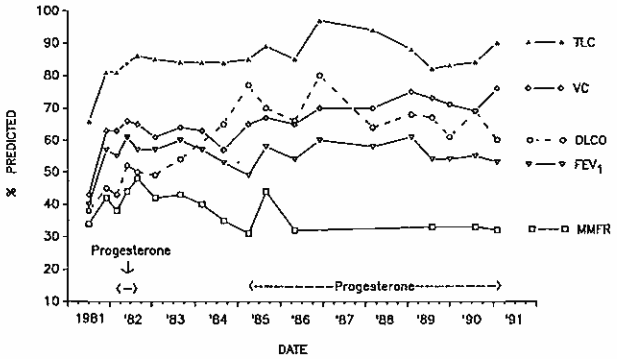
Table III
Pulmonary Function Studies - Case 3

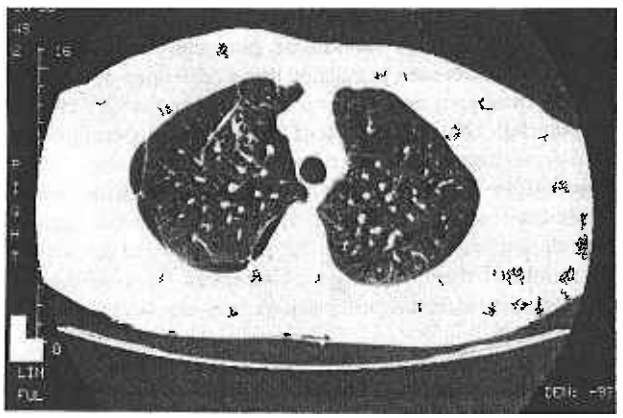
Index	Time after Therapy		% Change
	0 Month	6 Month	
VC (litres)	1.66 (63)	1.70 (65)	2.4
FEV_1 (litres)	1.32 (55)	1.39 (57)	5.3
MMFR (litres/sec)	1.22 (38)	1.55 (48)	27.0
TLC (litres)	3.16 (81)	3.34 (86)	3.2
D_LCO (ml/min/mmHg)	7.0 (43)	8.1 (50)	15.7
	At Rest / After Exercise*	At Rest / After Exercise	
PaO_2 (mmHg)	93 / 103	99 / 116	
$PaCO_2$ (mmHg)	31 / 32	28 / 27	
pH	7.41 / 7.28	7.42 / 7.31	

Numbers in parentheses indicate percentage of predicted normal

* Maximum Exercise at 450 kpM/min.

Fig 1 - Serial pulmonary function tests expressed as percentage of predicted normal. The MMFR values are corrected for changes in FVC. The D_LCO till August 83 are end tidal steady state values; August 84 to January 91 D_LCO values are from single-breath measurements.





DISCUSSION

LAM is an uncommon pulmonary disease. Of unknown aetiology and pathogenesis, it is a condition that affects only

women almost exclusively in the reproductive age. The disease progresses leading to death from respiratory failure usually within ten years.

Due to the rarity of the disease there have been no randomised trials to compare regimes of treatment. In an effort to evaluate the various reports of different hormonal regimens, Eliasson et al[5] subjected them to a meta-analysis. Their comprehensive review of the literature revealed 30 cases of LAM treated with eight regimens of treatment, consisting of progesterone, oophorectomy, tamoxifen and androgen alone or in combination. After meta-analysis only 12 of the 30 cases were judged to be evaluable. The small number of patients in each regimen, however, precluded any differences from reaching statistical significance by X^2 analysis. They concluded that the administration of progesterone or oophorectomy or both were the most effective treatments resulting in improvement or stabilisation of the disease in the majority of cases.

Recently, Taylor et al[32] reviewed the clinical course and response to therapy in 32 patients with LAM - one of the largest series ever reported. Of their 19 patients treated with MPA, two improved, six remained stable and 11 patients deteriorated. Of their nine patients who received antioestrogen therapy with tamoxifen, none improved and six deteriorated. They were of the opinion that tamoxifen should not be used at the present time. Despite the lack of apparent clinical benefit in their 16 patients who underwent oophorectomy, they were of the view that it should be considered as a second line of therapy if patients failed to respond to progesterone.

Of the three patients reported here, two failed to respond to MPA. The third patient showed improvement both clinically and on measurements of pulmonary function. The deterioration in function with stoppage of MPA and improvement again when it was reinstituted strongly support the beneficial effect of MPA. In their report, Eliasson et al[5] in addition to their patient were able to find four other cases out of eight who improved with progesterone treatment alone. If we were to include the two cases from the series of Taylor et al[32] plus our own patient, the total number of reported successful cases treated with progesterone would be eight out of 31, giving a success rate of 26 per cent.

Taylor et al[32] in an analysis of their cases found that the presence of chyle was the only clinical feature that correlated with response to MPA and postulated that chyle indicates a reversible element in LAM. Their review of the literature confirmed that most patients whose condition improved with MPA had either chylous effusion or chylous ascites. However, our patient with chylous effusion failed to improve with MPA whilst the patient who responded did not show any presence of chyle. Although the action of progesterone on LAM is unknown, it has been postulated that a regression of oestrogen dependent myocytes may occur[32]. To help determine the most appropriate therapy, assays of receptors for oestrogen and progesterone have been performed on lung biopsy material[16,21,22,24]. Combining the reported data with those in their own series, Taylor et al[32] could find no apparent correlation between the results of such assays and the response to hormonal therapy. Assays of receptors for oestrogen and progesterone were not performed on lung biopsy material from our patients.

Although it has generally been accepted that most patients with LAM die wthin ten years of the onset of disease[1], Taylor et al[32] found the average survival to be much better, with 78 per cent of their patients alive 8 1/2 years after the onset of disease. Furthermore, they were of the view that "the rate of progression of LAM can vary widely among patients, without apparent regard to type of therapy" and that "the disease can continue to progress after many years and after menopause". One of the patients presenting after the age of 55, described by Bradley et al[7] had two lung biopsies performed with an interval of ten years. Histological examination showed only mild progression of muscular proliferation. Sinclair et al[8] reported on a patient who developed symptoms at the age of 60, five years after oophorectomy who survived for another 12 years. Again muscular proliferation in the lung at autopsy was mild. They suggested that the slow progression of the disease reflected "both its initiation in the perimenopausal period and the reduction of steroid dependent muscle proliferation by oophorectomy".

In a search of published reports of successful therapy with MPA in LAM, the longest duration of treatment we could find was 34 months[21]. Our patient has had MPA for 6 1/2 years without any adverse side effects. The reports of progression of the disease after many years and after menopause would suggest prolonged use of MPA in our patient.

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