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CASE STUDY

Progesterone treatment in chylothorax associated with pulmonary tuberous sclerosis

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Progesterone treatment in chylothorax associated with pulmonary tuberous sclerosis. V. Jounieaux, S. Druelle, I. Mayeux, E. Grimault, J-C. Charet. ©ERS Journals 1996.
ABSTRACT: We report the case of a young woman with tuberous sclerosis who developed a chylous pleural effusion after several invasive procedures for treatment of recurring pneumothoraces. Oophorectomy was rejected by the patient and progesterone therapy initiated.

Medroxyprogesterone acetate administration led to a complete disappearance of the chylothorax in 8 months. The patient was kept on therapy, and no recurrence of pleural effusion has been observed up to the present (22 months follow-up). However, a progressive deterioration in pulmonary function was observed, with a significant decrease in pulmonary transfer factor and increase in airway obstruction.

In conclusion, this report demonstrates an objective benefit of progesterone therapy on chylous effusion associated with pulmonary tuberous sclerosis.
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Tuberous sclerosis (TS) is a rare autosomal dominant disease clinically defined by the Vogt's triad: mental retardation, seizures and angiofibroma. TS usually affects several organs but the incomplete penetrance and pleiotropic effect lead to a large clinical variability. Lungs are rarely involved in TS and pulmonary involvement in this disease is found almost exclusively in females of childbearing age. The pathological findings in pulmonary TS are indistinguishable from pulmonary lymphangioleiomyomatosis (LAM). Both in LAM and TS, the proliferation of muscle cells of immature-appearence in the pulmonary lymphatics may lead to chylous effusions being a rare complication. Because a substantial response to hormonal manipulation has been reported in pulmonary LAM, such treatments might be helpful in pulmonary TS. However, due to the small number of cases reported and the variability in regimens, the potential benefits of hormonal treatment remain to be confirmed. We present the case of a young woman with TS, who developed a chylous effusion that responded dramatically to progesterone.

Case report

A 19 year old, nonsmoking, white female presented with complaint of progressive dyspnoea. Since 3 yrs of age, she had documented TS with seizures, facial angiofibroma, subungual fibroma, shagreen patch of the trunk, and some minor degree of mental retardation. Her family history was noncontributory and she had never used oral contraception. At 16 yrs of age, she underwent a right nephrectomy for an acute renal haemorrhage, and the characteristic histological features at microscopic examination (renal angiomyolipoma) confirmed the diagnosis of TS. At this time, a chest radiograph was normal. At 17 yrs of age, a first left pneumothorax was treated with chest tube drainage. Chest radiography remained normal but thoracic computed tomography (CT) scan showed some cystic changes in the lung parenchyma.

At 18 yrs of age, a bilateral pneumothorax was treated with a right chest tube drainage and left pleurectomy. At operation, the lung presented numerous blebs and some peripheral bullae. Histological examination showed a fibromuscular proliferation along the bronchioles and pulmonary veins, associated with cystic spaces. Oestrogen and progesterone receptors were quantified as: 15 and 85%, respectively. On pulmonary function tests, there was no airflow obstruction (forced expiratory volume in one second (FEV_1) 85% of predicted) but air-trapping was observed, with a residual volume (RV) of 145% pred. Total lung capacity (TLC) was normal, 4.6 L (85% pred). The pulmonary transfer factor for carbon monoxide ($T_{L,CO}$) was not measured. Blood gases were normal. At 19 yrs of age, a right pleurectomy was performed for a right recurrent pneumothorax. The patient's pulmonary function was stable and $T_{L,CO}$ was slightly low (70% pred).

Six months later, the patient was referred to our hospital for increasing dyspnoea. Physical examination demonstrated a large right pleural effusion that was confirmed by chest radiography. In addition, bilateral diffuse interstitial infiltrates were present. Pleural aspiration produced 2500 mL of sterile milky fluid (protein 31 $g \cdot L^{-1}$, triglycerides 17 $mmol \cdot L^{-1}$, and cholesterol 2.9 $mmol \cdot L^{-1}$). After thoracocentesis, her dyspnoea disappeared. Oophorectomy was proposed, but the patient refused. The dietetary regimen, containing only medium-chain triglycerides, was not followed by the patient and chylous pleural effusion

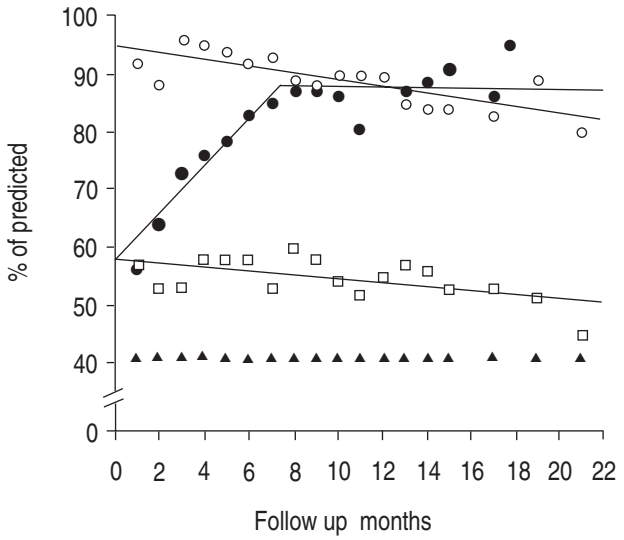

Fig. 1. – Evolution of the patient's spirometric data when treated with medroxyprogesterone acetate (22 months follow-up). ● : vital capacity; ○ : forced expiratory volume in one second as a fraction of vital capacity; □ : transfer factor of the lungs for carbon monoxide. ▲ : intramuscular injection of 400 mg of medroxyprogesterone acetate. Note the significant improvement of vital capacity during the first 8 months of hormonal treatment that was related to a progressive removal of the chylous effusion ($p<0.01$).

soon relapsed. Intramuscular medroxyprogesterone acetate (400 mg once a month) was then initiated and no further thoracocentesis were performed. Progesterone was given in our institution once a month for 15 months and then every two months, and pulmonary function tests were performed at each injection.

The duration of follow-up of the progesterone therapy was 22 months at the time of writing. During the first 8 months a progressive decrease of the chylous effusion was observed resulting in a significant increase in vital capacity (VC) ($p<0.01$, Spearman's rank correlation coefficient (r_s)=-1) (fig. 1). At the same time, TLC and FEV_1 significantly increased ($p<0.03$, r_s=-0.85 and $p<0.01$, r_s= -0.97, respectively) with improvement in exercise performance, whereas RV, FEV_1/VC and $T_{L,CO}$ did not change. After 8 months (*i.e.* when the chylothorax had completely resolved), no significant changes in VC, RV, TLC and FEV_1 were noted but a significant decrease was observed in FEV_1/VC and $T_{L,CO}$ (rs=-0.88 and $p<0.005$, rs=-0.81 and $p<0.005$ respectively) (fig. 1).

Discussion

Pulmonary involvement in TS is very rare, occurring in less than 3% of patients [1]. The clinical, radiographic and pathological findings are similar in pulmonary LAM and pulmonary TS. However, these diseases can be distinguished by features such as seizures or skin lesions, which are usual in TS and always absent in LAM [2] TS affects males and females equally, whereas LAM occurs only in female patients. Pulmonary involvement, which is frequent in LAM, almost always occurs in premenopausal women in TS, and, thus, this condition seems to depend on hormonal influences. In our patient, chylothorax associated with TS responded fully to progesterone therapy. In most reported cases, chylothorax relapsed and required repeated thoracocentesis, chemical pleurodesis or surgical pleurectomy, and a spontaneous improvement of the chylous effusion with time is unlikely. However, the results of hormonal manipulations in chylothorax associated with pulmonary TS [3–5] are not well-documented. In one patient with pulmonary LAM associated with TS and chylothorax, LUNA *et al*. [4] reported that tamoxifen therapy was effective in stopping the progressive course and in controlling the chylothorax but their patient had a tetracycline-pleurodesis prior to the hormonal treatment [4]. MURRAY and O'SULLIVAN [5] reported the case of a woman with chylothorax associated with TS that gradually resolved with medroxyprogesterone over a period of 6 months.

At the present time, there is no successful therapy for pulmonary LAM or TS except for lung transplantation in end-stage disease. Both in pulmonary TS and LAM, the benefits of hormonal manipulations are documented only by means of pulmonary function or blood gas data and not by chest CT data or survival rate. Hormonal treatments have no effect on cystic changes and honeycombing, which are irreversible pulmonary lesions. However, some authors have reported some objective response with hormonal treatments. In patients with pulmonary LAM treated with progesterone alone, URBAN *et al*. [6] observed no response with therapy, whereas ELIASSON *et al*. [7] reported an objective improvement in pulmonary function tests and/or blood gas data in 5 out of 9 patients. TAYLOR *et al*. [8] observed a significant improvement in lung function in two out of 19 patients with pulmonary LAM treated with medroxyprogesterone and a stabilization of functional data in six patients. In the series of CASTRO *et al*., [1] of five patients with pulmonary TS, three patients had a beneficial response (improved oxygenation) to medroxyprogesterone or oophorectomy and two others deteriorated with the hormonal therapy. The mechanisms of these objective responses remain to be elucidated.

In our patient, chylothorax resolved with the hormonal treatment. However, it did not prevent the progressive impairment in airflow obstruction, pulmonary hyperinflation and transfer factor of the lungs. These results suggest an objective action of progesterone on the proliferation of immature cells surrounding the pulmonary or extrapulmonary lymphatics. As the pulmonary lymphatic involvement may differ among patients with TS [9], this could explain the different response rate observed with hormonal treatments: the stronger the pulmonary lymphatic involvement, the better the response to hormonal manipulations. These conclusions remain speculative, as we do not know whether pleural effusion might resolve spontaneously without progesterone therapy. Nevertheless, the appearance of a chylous effusion during the course of TS may be the best indication for hormonal therapy.

As in pulmonary lymphangioleiomyomatosis [10], we recommend treatment with progesterone in chylothorax associated with pulmonary tuberous sclerosis.

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