Pulmonary Lymphangiomyomatosis*

Follow-up and Long-Term Outcome with Antiestrogen Therapy; A Report of Eight Cases

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Lymphangiomyomatosis is a rare disease which affects young women of childbearing age. Eight women with pulmonary LAM were treated with antiestrogen therapy and were monitored by blood estrogen measurements along with clinical hypoestrogenic symptoms. Treatment ranged from three to nine years. The response to therapy was evaluated by the clinical course, chest x-ray films, pulmonary function tests and overall long-term outcome. Three patients died of respiratory failure after three, five and nine years of treatment. Of the five patients remaining alive, respiratory function deteriorated in four cases, after a transient period of mild improvement lasting three years in two cases. The last patient appeared stable after three years of follow-up. Time course ranged from 4 to 17 years. However, without a control group, we cannot determine whether or not the apparent improvement of the natural course was due to the hormonal treatment.

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CT = computed tomography; LAM = lymphangiomyomatosis

Pulmonary LAM results from the proliferation of immature smooth muscle cells in the peribronchial, perivascular and perilymphatic areas of the lung, without any inflammatory cells or organized fibrosis.1,2,4 The disease primarily affects women of childbearing age who have progressive breathlessness, spontaneous and recurrent episodes of pneumothorax, chylous effusion and hemoptysis.1,5,6 Most patients die from progressive failure of their respiratory function. The radiologic signs are characteristic although not specific. The lesions appear as fine reticulonodular interstitial infiltrates predominantly basal, which progress to a pattern of small cystic changes and honeycombing, with progressively increasing lung volume.5,8 They may be associated with pneumothorax or pleural effusion. The CT scan may provide useful information about the natural history and progression of LAM.9-11 The obstructive airflow limitation with considerable air trapping is responsible for most of the pulmonary symptoms.2,5,6,8 Functional changes of the restrictive defect also may develop, such as muscular proliferation, pleural effusion, pneumothorax, and pleuropneumonia, contributing to the reduction of lung volumes. Renal or perirenal angiomyolipomas also can occur, as in tuberous sclerosis.

Previous attempts to treat LAM by x-ray irradiation,7,12-14 or chemotherapy with cyclophosphamide or steroids,7,15,16 have been unsuccessful. Dietary fat restriction, Le Veen's peritoneal-jugular shunt,13,17,18 pleurectomy and sclerosing agents in pleura to minimize chylous effusions frequently are doomed to failure. Thoracic duct ligation may be dangerous.

The pathogenesis of the atypical smooth muscle proliferation is incompletely understood but steroid metabolism may play a major role. The relationship to estrogen is inferred because LAM almost exclusively affects women of reproductive age, except for some cases of tuberous sclerosis in males, if LAM is considered to be an incomplete form of tuberous sclerosis. Lymphangiomyomatosis tends to increase during pregnancy,19 with use of oral contraceptives20-22 and during menses.23 Moreover some authors have detected estrogen or progestin receptors in the lungs of patients with LAM.24-26 Estrogen sensitivity of smooth muscle with increased glycogen has been studied.27 Glycogen has been found in excess in proliferating cells of patients with LAM.26 On the other hand, uterine leiomyomas are more frequent than usually observed in women of childbearing age, suggesting a possible relationship between atypical smooth muscle hyperplasia and estrogen. These observations suggest an opportunity to treat LAM via hormonal manipulation. Several trials of antiestrogen therapy have been carried out with a marked heterogeneity among the reported cases. Unfortunately, the use of oophorectomy,2,17,19,25,29-32 progestosterone,11,20,25,26,29,31,33,34 and tamoxifen11,34,35 has yielded variable results. A recent attempt of metaanalysis concluded on the possible success of oophorectomy and progestin treatment, but this study is difficult to

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Pulmonary Lymphangiomyomatosis (Urban et al)
Table 1—Clinical Data in Eight Patients with Lymphangioleiomyomatosis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>39</td>
<td>29</td>
<td>47</td>
<td>31</td>
<td>30</td>
<td>34</td>
<td>46</td>
<td>27</td>
</tr>
<tr>
<td>Presenting symptom</td>
<td>PNT SOB PNT PNT SOB CT + PNT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>+ + + + + + + + + +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>+ + + + + + + + + +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chylothorax</td>
<td>- - - - - - - - - -</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiomyolipoma</td>
<td>- - - - + - - - -</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine leiomyoma</td>
<td>+ - + + + + + + - -</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung disease</td>
<td>- + - + + + + + +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of total course</td>
<td>7 14 4 17 12 9 9 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SOB = shortness of breath; PNT = pneumothorax; + = present; - = absent; ? = unknown; CT = chylothorax

interpret because of the heterogeneity of the cases.36

A recent review of 32 patients reports a better average survival than expected, with no conclusions concerning the role of hormonal manipulation and its relationship with this improvement.37

In an effort to clarify the role of hormonal therapy in LAM, we report the follow-up and outcome of eight patients with LAM treated with antiestrogen therapy.

Materials and Methods

The patient group consisted of eight women with biopsy-proven LAM. The diagnosis of LAM was established on the basis of previously published reports. Characteristic biopsy specimens and a clinical course consistent with LAM (pneumothorax, chylothorax, angiomyolipoma or uterine leiomyoma) and without symptoms of tuberous sclerosis were required in all cases. The clinical onset of pulmonary LAM was defined as the time of onset of pulmonary symptoms probably attributed to this disease. The following features were reviewed: age at onset, methods of diagnosis, clinical and radiologic presentation, associated diseases, clinical course, serial pulmonary function tests, hormonal therapy, response and long-term outcome.

The age at the onset of disease ranged from 27 to 47 years, with an average age of 35 ± 7 years (mean ± standard error of the mean). None of the patients had a history of epilepsy or mental retardation or skin lesions. The major presenting symptoms were progressive breathlessness (three cases), pneumothorax (four cases), chylos pleural effusion (one case) or an interstitial lung pattern on chest x-ray films without clinical symptoms (one case) (Table 1).

Pneumothorax, frequently recurrent, occurred in seven women; chylos effusions were found in three cases. The review of chest x-ray films demonstrated several distinct patterns with progression from linear reticulonodular diffuse opacities to small cysts or bullae or honeycombing and increased lung volumes. One patient had a renal tumor which proved to be an angiomyolipoma when surgical lombotomy was performed. Renal arteriography (three cases), tomography (one case) or CT scan (two cases) were performed in five other patients looking for a renal tumor without success. Other findings included uterine leiomyoma in five of seven cases (Table 1). Initial pulmonary function tests are listed in Table 2.

Hormonal antiestrogen therapy was performed in all patients. Antiestrogen therapy trials varied in the 17 years during which the series was studied: bilateral oophorectomy; medroxyprogesterone acetate; combination of lynestrenol and tamoxifen. Dosages were adjusted to hypoestrogenic symptoms and blood estrogen measurements. Treatment regimens are listed in Table 3. Usual doses were: medroxyprogesterone acetate, 500 mg per month, intramuscularly; lynestrenol, 5 to 10 mg per day; tamoxifen, 10 mg per day.

The response to treatment was evaluated on physical examination, intensity of dyspnea, x-ray film studies, measurements of pulmonary function tests and long-term outcome.

Results

Time course from the first pulmonary symptom ranged from 4 to 17 years (mean, 10 ± 4 years). Time of treatment ranged from 3 to 9 years with an average of 5 ± 2 years.

Serial pulmonary function values before and after starting therapy are listed in Table 2.

Patients 6, 7 and 8 died of respiratory failure after 5, 9 and 3 years of treatment, respectively. Of the five patients remaining alive, respiratory function deteriorated in four (patients 1, 2, 4 and 5) after a transient period of mild improvement lasting three years in two cases. The last patient (No. 3) appeared to be stable after three years of follow-up (Table 3).

Bilateral oophorectomy was performed in patients 6 and 7: alone in case 7; and with medroxyprogesterone acetate, then lynestrenol and tamoxifen in case 6. None of the patients were improved after treatment.

Table 2—Serial Pulmonary Function Values Before and After Treatment in the Five Deceased Patients

<table>
<thead>
<tr>
<th>Case No</th>
<th>Dates of studies</th>
<th>Treatment</th>
<th>Lung volumes (% pred)</th>
<th>FEV VC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7/84</td>
<td>Yes</td>
<td>92</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>7/86</td>
<td>Yes</td>
<td>98</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>10/83</td>
<td>No</td>
<td>98</td>
<td>109</td>
</tr>
<tr>
<td></td>
<td>3/89</td>
<td>Yes</td>
<td>88</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>4/86</td>
<td>No</td>
<td>85</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>6/89</td>
<td>Yes</td>
<td>95</td>
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<tr>
<td>4</td>
<td>1/83</td>
<td>No</td>
<td>91</td>
<td>93</td>
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<td></td>
<td>1/88</td>
<td>Yes</td>
<td>105</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>12/82</td>
<td>No</td>
<td>111</td>
<td>63</td>
</tr>
</tbody>
</table>

TLC = total lung capacity; VC = vital capacity; RV = residual volume; FEV = forced expiratory volume
Table 3—Evolution and Outcome of Eight Women with Lymphangiomyomatosis

<table>
<thead>
<tr>
<th>Case No</th>
<th>Length of Treatment</th>
<th>Type of Treatment</th>
<th>Outcome</th>
<th>Time Course (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 years</td>
<td>LT</td>
<td>Temporary stabilization then aggravation; alive</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>5 years</td>
<td>LT</td>
<td>Moderate aggravation; alive</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>3 years</td>
<td>LT</td>
<td>Durable stabilization; alive</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>6 years</td>
<td>LT</td>
<td>Aggravation; alive</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>4 years</td>
<td>OPT-MPA LT</td>
<td>Temporary stabilization then aggravation; alive</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>5 years</td>
<td>MPA-T LT</td>
<td>Temporary stabilization, then died</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>9 years</td>
<td>OPT</td>
<td>Died</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>3 years</td>
<td>MPA</td>
<td>Died</td>
<td>11</td>
</tr>
</tbody>
</table>

LT = lynestrenol-tamoxifen; MPA = medroxyprogesterone-acetate; OPT = oophorectomy

The sixth patient remained stable for three years; then her condition deteriorated and she died. The time course was nine years for these patients.

A combination of lynestrenol and tamoxifen was used in six patients (No. 1 to 6); this therapy was used alone in four cases (No. 1 to 4); after an attempt with medroxyprogesterone acetate in one case (No. 5); and with oophorectomy after an attempt with medroxyprogesterone acetate in case 6. Treatment failed in five cases. The pulmonary function progressively deteriorated in two patients (No. 2 and 4) without any improvement, with a time course of 14 and 17 years. After an improvement of clinical and functional status, the first patient stopped treatment for five months and became more dyspneic; the patient’s functional tests deteriorated, without any improvement after reinstitution of therapy. Pulmonary function tests deteriorated in patient 5 after a temporary stabilization. In only one perimenopausal patient (No. 3) was the disease stabilized during the three years of treatment, with only a four-year follow-up from the first symptoms.

Medroxyprogesterone acetate was used in three cases (No. 5, 6 and 8) and alone in the eighth patient. Two patients died (No. 6 and 8) and the last one deteriorated.

**Discussion**

Clinically the course of the disease in these patients was consistent with LAM with the onset of symptoms during the premenopausal period, except for that in one patient, which took place during the perimenopausal period and with the development of pneumothorax and chyloous pleural effusion. Radiologically, the development of an interstitial pulmonary process with hyperexpansion and destruction with small cysts was characteristic of LAM. Histologic confirmation of LAM was obtained in all cases.

Effectiveness of oophorectomy has been suggested by some authors\(^ {17,19,29,31,32} \) but not by others.\(^ {2,25,30} \) Since the most critical feature is early diagnosis and treatment, bilateral oophorectomy might be more effective when performed early in the course of the disease. However, oophorectomy performed in our patients at a time when x-ray films and functional tests were minimally disturbed was unsuccessful.

Tamoxifen, a competitive estrogen inhibitor, frequently has been associated with lynestrenol, a progestin agent. Several trials with tamoxifen\(^ {11,34,35} \) or progesterone\(^ {11,24-26,29,31,34,36} \) have been carried out with variable results. In our series, the results were subdivided into three groups:

1. In the first group, two patients without any improvement, developed irreversible and progressive respiratory failure despite five and six years of treatment, respectively. Their functional test values were not severely altered when treatment was instituted (Table 3).

2. In the second group, three patients, after a transient stabilization for several years, developed progressive respiratory failure. Without a control group, the role of this treatment and its direct responsibility in the stabilization is uncertain because the natural course of LAM fluctuates according to the variable incidence of pleural involvement or hormonal events such as pregnancy. Two of our patients had an exacerbation during pregnancy, in accordance with previous reports.\(^ {19} \)

3. In the third group consisting of only one patient, a perimenopausal woman experienced stabilization of her disease for the three years of treatment but with only four years of follow-up from the first symptom; once again, menopause usually seems to reduce the activity of LAM.

Mac Carty et al\(^ {20} \) reported the case of a patient treated with medroxyprogesterone acetate, with evidence of clinical and functional improvement. However, the follow-up in terms of pulmonary function tests was only 12 months. While some authors have reported success with this treatment,\(^ {11,29,31,34,36} \) others have not found any evidence of improvement.\(^ {2,25,26,33} \) None of our three patients obtained lasting stabilization of the disease.

Some of our patients with hormonal treatment had a long time course from the first symptom. Neverthe-
less, without a control group, we cannot precisely determine whether this apparent improvement in the time course was due to hormonal treatment or to better supportive care or if it was purely coincidental. For instance, long-term therapy was unable to lastingly stabilize LAM in our study in agreement with some other reports, but in contrast with other previous reports of effectiveness. An insufficient time of follow up in some reports in the literature, an earlier or later diagnosis and treatment, and the fluctuating course of the disease, explain the various conclusions concerning the role of antiestrogen therapy and its relationship with the course of the patient's respiratory function. Similarly, different criteria used to assess the course of respiratory function may explain some discrepancies. In our experience, obstructive airflow limitation and air trapping seem to be the most reliable pulmonary function test. Restrictive limitation also is influenced by pleural involvement.

CONCLUSION

Although some patients had a long time course, all but one of them deteriorated clinically and functionally. Although treatment may have some effectiveness in the short term, it should be initiated as soon as the diagnosis is established to avoid irreversible damage. At the present time in the absence of a control group, no individual treatment can be identified as being really effective. Nevertheless because of the hormonal dependence hypothesis, other attempts with progesterin, antiestrogen agents or other drugs such as danatrol or ketoconazole are currently being evaluated. Response to treatment must be followed by objective measurements such as survival time or obstructive airflow limitation.

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