LONG TERM SURVIVAL IN A PATIENT WITH PULMONARY LYMPHANGIOLEIOMYOMATOSIS

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CASE REPORT

A patient with pulmonary lymphangioleiomyomatosis was diagnosed more than 22 years after the onset of symptoms by a thoracoscopic lung biopsy, after a high resolution computerized tomogram of the chest was highly suggestive of the disease. After nearly 30 years since the onset of her symptoms, the patient leads a relatively normal life with only mildly abnormal lung function and has minimal reduction in her exercise tolerance. There have been few reports of patients surviving for such a long time after the onset of this disease; the literature suggests that most patients die within 15 years of symptom onset.

Key Words: Angiomyolipoma; Pulmonary lymphangioleiomyomatosis

Pulmonary lymphangioleiomyomatosis (LAM) is a rare condition that exclusively affects women, predominantly of childbearing age (1-4), with onset usually occurring early in the fourth decade of life (1-3,5). The most common clinical presentations are dyspnea (2-4,6) and pneumothorax (2-4,6-8). Other common findings are cough, hemoptysis and chylous pleural effusions (1-6,9). Nonpulmonary manifestations may also occur, and include renal angiomyolipoma (1,4,7,10) and chylous ascites (1-5,9). Because of its predilection for women of childbearing age and reports of the disease worsening with pregnancy (1,6,11-14), LAM is believed to be stimulated by estrogen. Traditionally, the prognosis has been grim, with death from respiratory failure commonly occurring within 10 years of symptom onset (2,4). However, a few case reports of patients who have survived longer have suggested that the prognosis may be better in some patients (2,4,6,15). We present the case of a patient who was diagnosed at least 22 years after the onset of symptoms and maintains a good functional status with mildly abnormal lung function more than 27 years after symptom onset.

CASE PRESENTATION

The case of a female patient, born in 1953, who had never smoked and who began experiencing cough, intermittent left-sided shortness of breath and chest pain at about the time of her first pregnancy in 1974 is presented. These symp-
toms persisted after her delivery, and during a hospital admission for a urological procedure in 1976, she was incidentally found to have a left-sided pneumothorax. This was successfully treated with tube thoracostomy. She experienced two symptomatic recurrences over the next year, and in 1977, she underwent surgical pleural stripping. At the time of thoracotomy, her pleural surface was noted to have multiple blebs.

Her symptoms were minimal for several years, but by 1989, she was complaining of a bothersome cough, for which she was referred to the respiratory service. Her chest radiograph at the time showed no abnormalities other than residual scarring on the left side from her previous surgery. Her pulmonary function tests showed borderline mild restriction, which was thought to be from her previous thoracic surgery. Her expiratory airflow was mildly reduced, and her diffusing capacity was moderately decreased. Allergen skin prick testing showed no reaction to common environmental allergens. Her cough improved with a treatment trial of inhaled beta-agonists and inhaled steroids, and she was diagnosed with cough-variant asthma. In 1991, she became pregnant for the second time, and was rerefereed to the respiratory clinic because of increasing cough and dyspnea. Her pulmonary function tests were unchanged, and no radiograph was performed because of the pregnancy. Later in the pregnancy, she developed a large retroperitoneal hemorrhage. An abdominal computed tomography (CT) scan showed a renal angiomyolipoma. She was managed conservatively throughout the pregnancy and delivered a healthy child later that year. The angiomyolipoma was resected shortly after.

She was referred again to the respiratory clinic in 1996 because of persistent cough and exertional dyspnea that limited her exercise tolerance to walking one block. Her lung function was mildly abnormal and not significantly changed from 1989. A plain chest radiograph was completed, and the results were interpreted as normal. A radionuclide lung scan was ordered because of unexplained dyspnea with decreased carbon monoxide diffusing capacity of the lungs and showed low probability for thromboembolic disease. An echocardiogram showed normal left ventricular function, with no evidence of valvular disease. Cardiopulmonary exercise testing showed a mild decrease in exercise tolerance, with no arterial oxygen desaturation and no exercise-induced bronchospasms. A high-resolution CT (HRCT) scan was performed in 1997 and showed multiple thin-walled cysts, which is characteristic of LAM (Figure 1).

A review of the abdominal CT scan completed in 1991 (Figure 2) showed parenchymal cysts in the lung bases.

A thoracoscopic lung biopsy was performed in 1997 (by the same surgeon who performed the pleurodesis in 1977), and the histological examination (Figure 3) confirmed the radiographic diagnosis of LAM. The lung biopsy showed the characteristic lacy pattern of smooth muscle proliferation within the interstitium, and around the bronchioles and vessels, which is associated with focal cystic change. Although the biopsy showed a predominantly cystic type of LAM (approximately 10% of the biopsy tissue was affected by cystic lesions and 5% by abnormal smooth muscle cells), the total percentage of lung tissue involvement by both the smooth muscle and cystic components was estimated to be less than 25% (LAM histological score [LHS] 1) (8). The maximal cyst size was measured to be between 3 and 5 mm. The smooth muscle cells stained positively with antibodies to estrogen and progesterone receptors, and melanoma antigen HMB45. The intervening lung was relatively normal except for foci of hemosiderin-filled macrophages. The degree of accumulation of hemosiderin-laden macrophages was regarded to be mild (seen focally in less than 5% of the overall tissue) (8). A photograph of the pleural surface taken from the video of the thoracoscopy is shown in Figure 4; by the surgeon’s own account, the pleural surface appeared to be similar to that seen in 1977.
She was started on intramuscular depoprogesterone injections every three months, with a resulting dramatic decrease in dyspnea and cough, and improved exercise tolerance. These injections were later increased to every six weeks. She experienced symptomatic improvement from this therapy. Because her lung function was only minimally abnormal, no appreciable change in objective testing was seen with progesterone therapy. The patient continues to be relatively stable on depoprogesterone and inhaled fluticasone for ‘steroid-responsive’ cough, and is able to walk 20 to 30 blocks without stopping. Her most recent pulmonary function tests show mild expiratory airflow obstruction and a moderate decrease in the carbon monoxide diffusing capacity of the lungs. Table 1 shows her most recent pulmonary function tests, as well as those from 1997, just before initiation of progesterone therapy.

**DISCUSSION**

LAM is a non-neoplastic proliferation of atypical smooth muscle cells that infiltrate the peribronchial, perivascular and perilymphatic structures of the lung. Symptoms usually precede any abnormal findings on objective testing, and the diagnosis is usually delayed for several years after symptom onset (1-3). Pulmonary function tests may be normal early in the disease, but eventually show expiratory airflow limitation and hyperinflation (3). The chest radiograph may also

<table>
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<th>Test</th>
<th>1997 best measurement</th>
<th>2001 best measurement</th>
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<tbody>
<tr>
<td>FVC (L) (% predicted)</td>
<td>2.61 (78)</td>
<td>2.68 (83)</td>
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<td>FEV₁ (L) (% predicted)</td>
<td>1.70 (66)</td>
<td>1.62 (65)</td>
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<tr>
<td>FEV₁/FVC</td>
<td>65</td>
<td>60</td>
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<tr>
<td>TLC (L) (% predicted)</td>
<td>3.74 (78)</td>
<td>4.60 (96)</td>
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<tr>
<td>RV (L) (% predicted)</td>
<td>1.13 (70)</td>
<td>1.93 (116)</td>
</tr>
<tr>
<td>D_{L}CO (mL/mmHg/min) (% predicted)</td>
<td>15.3 (58)</td>
<td>11.5 (45)</td>
</tr>
<tr>
<td>D_{L}CO/VA (mL/mmHg/min/L) (% predicted)</td>
<td>4.23 (76)</td>
<td>3.12 (78)</td>
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<tr>
<td>Pulse oximetry (at rest)</td>
<td>97%</td>
<td>96%</td>
</tr>
<tr>
<td>Pulse oximetry (exercise)</td>
<td>93%</td>
<td>91%</td>
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$D_{L}CO$ Carbon monoxide diffusing capacity of the lungs; FEV₁, Forced expiratory volume in 1 s; FVC Forced vital capacity; RV Residual volume; TLC Total lung capacity; VA Alveolar volume.
Long term survival with pulmonary lymphangioleiomyomatosis

Although the percentage of the lung biopsy affected by cystic lesions alone also showed a correlation with the overall survival of the patients in their study. There was also a correlation between the maximal size of the cysts and patient survival, which was very close to being statistically significant. Accumulation of hemosiderin in lung macrophages was associated with both higher LHS and increased mortality. Although the present patient had predominantly cystic disease on biopsy, the LHS was graded as 1, because the percentage of the total area of lung biopsy affected by cystic lesions and abnormal smooth muscle cells was less than 25%; the degree of hemosiderosis was mild. In the study by Matsui et al (8), the category of patients with an LHS of 1 identified a group of patients who did not die or did not undergo lung transplantation. Our case supports their observation that the histological findings of a low LHS and mild hemosiderosis are associated with a relatively mild clinical course.

The present patient is notable not only for her long term survival, but also her relatively preserved lung function and exercise capacity nearly 30 years after symptom onset (the first 25 years of which she received no specific therapy). Although she was not definitively diagnosed until 1997, the appearance of her pleura at thoracotomy in 1977 is convincing evidence that her disease was present at that time and was responsible for her recurrent pneumothoraces. Furthermore, her left-sided chest pain in 1974 is suspicious of an undiagnosed pneumothorax at that time.

CONCLUSIONS

We present the case of a patient who was definitively diagnosed with pulmonary LAM more than 22 years after the onset of her symptoms. Her clinical course included two pregnancies (the first of which was complicated by a pneumothorax and the second by a retroperitoneal hemorrhage due to an angiomyolipoma), recurrent pneumothoraces, an angiomyolipoma and persistent exertional dyspnea with cough. She is now managed with intermittent medroxyprogesterone therapy, and has enjoyed clinical stability and a relatively normal exercise tolerance for nearly 30 years after symptom onset. This is exceptional, because the literature reveals only a few reports of patients with this disease living for such a long period of time after symptom onset. The present case supports the recent report by Matsui et al (8) that states that the histological findings of a low LHS and mild hemosiderosis are associated with a relatively mild clinical course in patients with LAM.

ACKNOWLEDGEMENTS: Dr Cockcroft is a Saskatchewan Lung Association Research Professor. Dr Reid was sponsored by the Moorhead Foundation Research Fellowship.

REFERENCES
3. Taylor JR, Ryu J, Colby T, Raffin T. Lymphangioleiomyomatosis:
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