TEACHING CASE REPORT

A 48-year-old woman with lymphangioleiomyomatosis

The case: A 48-year-old woman visited her family physician because of gradual-onset dyspnea, fatigue and an occasional cough. Dyspnea occurred when the patient walked up stairs, in the cold or against the wind, but it did not occur when she was at rest or lying down. She denied having associated chest pain.

The patient had received a diagnosis of mild asthma at 22 years of age; however, asthma medications had not been required since she was in her early 30s. The patient was a nonsmoker, had a body mass index of 21 kg/m² and, for the past several years, had exercised for 1 hour 3 times per week but reported having decreased exercise tolerance.

On examination, the patient appeared to be well, and her vital signs were normal. A chest examination was unremarkable except for slightly decreased breath sounds at the base of the lungs. A chest radiograph initially appeared to be normal, although on closer review linear bronchial opacities were identified. Results of pulmonary function tests were as follows: forced vital capacity (FVC) 88% predicted, forced expiratory volume in 1 second (FEV_1) 65% predicted and 73% post bronchodilator, FEV_1/FVC 74%, total lung capacity 106% predicted and residual volume 140% predicted. The patient was referred to a respirologist, who diagnosed chronic asthma. Results of a histamine challenge test showed a 38% reduction in FEV_1 at a histamine concentration of 4 mg/mL. Inhaled steroid and salbutamol therapy was prescribed. At a 6-month follow-up visit, the patient reported an improvement in her symptoms and improved exercise tolerance. Her FEV_1 was 60% predicted.

Several months later, after the patient began experiencing increased fatigue and prolonged symptoms of an upper respiratory infection, she visited a second respirologist. Again, results of the clinical examination were normal. Pulmonary function test results revealed a FEV_1 53% predicted and 61% post bronchodilator, and diffusing capacity of the lung for carbon monoxide 46% predicted. Exercise test results showed that oxygen saturation declined from 97% to 90% on exertion. Arterial blood gases revealed partial pressure of oxygen of 66 mm Hg. Results of laboratory tests (including α-1 antitrypsin level) were normal. A chest radiograph revealed nonspecific coarse linear opacities in the base of both lungs, which suggested parenchymal scarring or bronchiectasis.

We made a diagnosis of an obstructive disease that required further investigation. The patient was sent for a high-resolution CT scan which revealed emphysematous and cystic changes in the base of the lungs (Fig. 1). The differential diagnosis included lymphangioleiomyomatosis and eosinophilic granuloma. A bronchoscopy and transbronchial biopsy were recommended but were declined by the patient. A working diagnosis of lymphangioleiomyomatosis was made after an abdominal and pelvic CT scan revealed small renal lesions (4 mm) on both kidneys consistent with angiomyolipoma (Fig. 2) and enlarged retroperitoneal lymph nodes (< 1.5 cm in diameter). An MRI

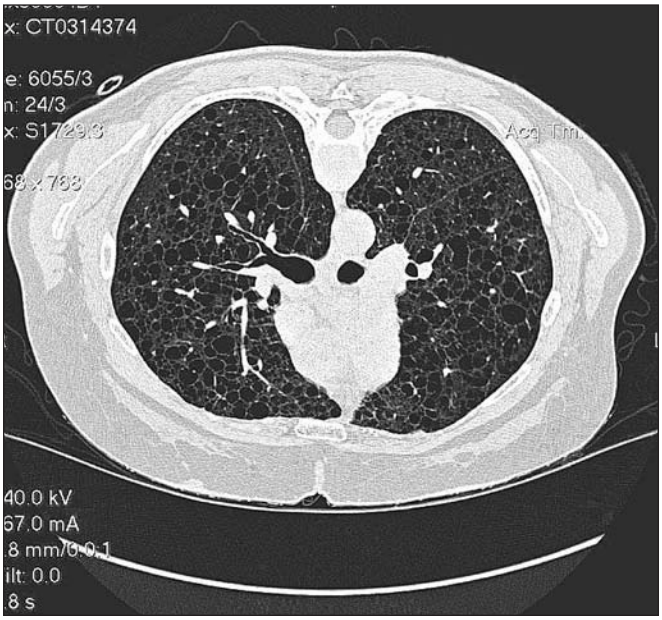

Fig. 1: CT scan of chest showing cystic changes.

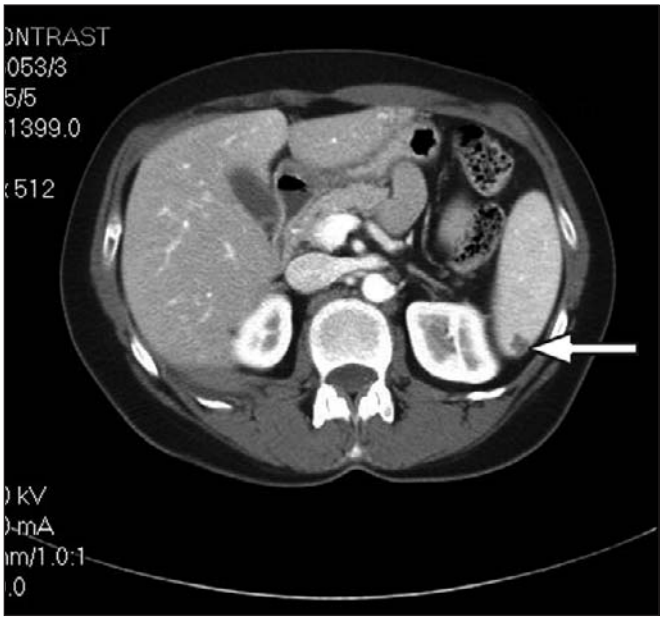

Fig. 2: CT scan of the abdomen showing renal angiolipoma (arrow).

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of the brain ruled out a hamartoma consistent with tuberous sclerosis complex. A course of pulmonary rehabilitation followed; the patient received oxygen therapy (2 L/min, 4 L/min during exercise).

Lymphangioleiomyomatosis is an underdiagnosed, progressive and often fatal lung disease that has an insidious onset. There is currently no treatment or cure. The condition occurs primarily in women between 30 and 49 years of age but has been reported to affect patients as young as 17.[1] There are 2 forms of lymphangioleiomyomatosis: sporadic or associated with tuberous sclerosis complex. Both forms are caused by mutations in tumour suppressor genes: the hamartin gene (*TSC1*) on chromosome 9 (9q34) and the tuberin gene locus (*TSC2*) on chromosome 16 (16p13.3). Estimates from lymphangioleiomyomatosis registries suggest that, worldwide, the sporadic form affects about 30 000–50 000 women and the form associated with the tuberous sclerosis complex about 180 000–240 000 women. There are no specific epidemiologic risk factors for lymphangioleiomyomatosis, including family history.

Lymphangioleiomyomatosis has been termed a great "mimic"; affected women frequently receive a misdiagnosis of asthma, emphysema or pulmonary fibrosis. A high index of suspicion and a high-resolution CT scan leads to the correct diagnosis in about 80% of cases. With a CT scan and supporting clinical evidence, a lung biopsy may not be necessary for a definitive diagnosis.

After onset of the disease, the patient's lung function is lost at an average monthly rate of 7–9 mL of FEV_1 and 5 mL of FVC. This loss is caused by diffuse infiltration of the pulmonary interstitium by atypical smooth muscle cells (lymphangioleiomyomatosis cells), which leads to cystic destruction of lung parenchyma.[2] The origin of the smooth muscle cells is unknown; recurrence of the condition in transplanted lungs suggests that the cells metastasize from a remote site. Benign kidney tumours (angiomyolipoma) occur in about 60% of cases.[1,2] The classic presentation of lymphangioleiomyomatosis is pneumothorax or chylothorax. Patients who have had one pneumothorax are at high risk of additional collapses; chemical or surgical pleurodesis is often warranted. However, as in our patient, lymphangioleiomyomatosis often occurs in patients who have not had a pneumothorax.[1]

Treatment of lymphangioleiomyomatosis is supportive and generally includes avoiding medications that contain estrogen (although not supported by evidence, it is presumed that estrogen plays a role in the predilection of the condition among women). Additional supportive measures may include bronchodilator therapy, treatment of anxiety and depression, pulmonary rehabilitation and assessment for hypoxemia and pulmonary hypertension, supplemental oxygen therapy and lung transplantation. In general, a lung transplant should be considered when FEV_1 approaches 30%. Embolization or cauterization of renal tumours may also be required.

Much remains unknown about this disease. Women with lymphangioleiomyomatosis are advised not to become pregnant because it is thought that the condition may become exacerbated during pregnancy. Avoiding exposure to tobacco smoke is also advised. Case reports describing the risk of pnemothoraces during air travel may overestimate the danger of air travel; however, oxygen supplementation during flight may be required by patients with relatively advanced disease.[3]

Recent studies suggest that the median survival from the onset of symptoms is about 15 years. The complications associated with lymphangioleiomyomatosis are extensive and greatly affect women's daily lives.

As international lymphangioleiomyomatosis registries mature, more information is becoming available about the symptoms, prevalence and natural history of this disabling condition. Basic scientific research into lymphangioleiomyomatosis has led to an international randomized trial of rapamycin that will begin shortly.

Erica Weir
Community Health and Epidemiology
Queen's University
Kingston, Ont.
Marsha Cohen
Women's Health Research Institute
Women's College Hospital
Toronto, Ont.

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