A 49-year-old woman, a nonsmoker, was admitted to hospital because of progressive shortness of breath, cough and hemoptysis. The patient’s history started 7 years earlier with slowly progressive dyspnea and an episode of hemoptysis for which she underwent an unremarkable bronchoscopy. Tuberculin testing was positive, but there were no signs of active tuberculosis neither on chest X-ray nor in the bronchial fluid obtained at bronchoscopy (negative stain and culture for *Mycobacterium tuberculosis*). During the following years the patient suffered from repeated bronchial and sinus infections and progressive dyspnea. Four years later there were again several episodes of hemoptysis but no abnormal findings on physical examination. Laboratory parameters including a differential leukocyte count, C-reacting protein, serum creatinine, liver enzymes, antinuclear antibodies, antineutrophil cytoplasmic antibodies, rheumatoid antibodies and urinalysis were within the normal range. Lung function tests revealed moderate to severe airflow obstruction, a decreased diffusion capacity for carbon monoxide and a severe hypoxemia (PaO\(_2\) 46 mm Hg). The chest X-ray showed fine interstitial opacities with a reticulonodular pattern (fig. 1). Bronchoscopy was again performed and showed a normal bronchial system. Bronchial brushing and bronchial washings revealed no bacteria, mycobacteria or malignant cells. The thoracic CT scan showed characteristic changes throughout the lungs (fig. 2).

What is your diagnosis?

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**Fig. 1.** Chest X-ray showing reticulonodular shadows with basal predominance.

**Fig. 2.** Thoracic CT scan showing diffuse, homogenous, small thin-walled cysts of varying sizes distributed throughout the lung fields.
Diagnosis: Lymphangioleiomyomatosis

Fig. 3. Histology of tissue obtained at thoracoscopy by wedge biopsy of the lingula. (APAAP technique and hemalum). This partially collapsed biopsy displays several parenchymal ‘holes’ (cystic spaces) and a subpleural slit. Nodular foci consisting of short irregularly arranged, round or plump fusiform cells, immunoreactive for smooth muscle actin, protrude into the cystic spaces (arrows).

Fig. 4. Middle magnification, APAAP technique and hemalum. The leiomyomatous cells are immunoreactive for HMB 45 in contrast to the unstained smooth muscle cells in a small pulmonary artery (arrow).

Diagnostic Procedures

As a next diagnostic step, thoracoscopy under local anesthesia was performed, and a wedge biopsy of lung tissue from the lingula was taken. Histology showed several parenchymal ‘holes’ (cystic spaces) and a subpleural slit. Nodular foci consisting of short irregularly arranged, round or plump fusiform cells, immunoreactive for smooth muscle actin, protruded into the cystic spaces (fig. 3). The leiomyomatous cells were immunoreactive for human melanin black (HMB) 45 (a monoclonal antibody derived from melanoma hybridomas), in contrast to the unstained smooth muscle cells in a small pulmonary artery (fig. 4). Seven years after the onset of the initial
Symptoms the patient now suffers from dyspnea grade III to IV. Lung function tests revealed severe airflow obstruction \( (FEV_1 \ 0.98 \text{ liters, } 36\% \text{ of predicted; } FVC \ 2.8 \text{ liters, } 86\% \text{ of predicted}) \). The diffusion capacity for carbon monoxide was reduced to 21% predicted. A 6-min walking test showed a maximal distance of 330 m with severe oxygen desaturation to 60%. The patient is scheduled for lung transplantation.

**Comment**

Lymphangioleiomyomatosis (LAM) is characterized by proliferation of atypical interstitial smooth muscle cells and cyst formation in the lung. LAM is a rare disease, the onset of symptoms occurs in females in their childbearing age (premenopausal period). The incidence of LAM is unknown. The patients usually present with slowly progressive shortness of breath and cough. The most common complications of LAM include hemoptysis, spontaneous pneumothorax (in up to 40% of patients, often recurrent; sometimes bilateral [1]) and chylous pleural effusions or chyloperitoneum (10%). The genetic disorders tuberous sclerosis and renal angiolipomas can be found in up to 50% of patients with LAM [2]. *The diagnosis of LAM should be suspected in a younger woman with dyspnea and recurrent pneumothoraces or chylous pleural effusions.*

The peribronchial proliferation of smooth muscle cells leads to the obstruction of small airways and to formations of cysts (diameter of cysts 0.1 cm up to several centimeters), but the pathogenesis of the cyst formation is still unknown. Obstruction of the lymphatic channels or of the thoracic duct can lead to a chylothorax, and the invasion of small venules may result in hemoptysis (rupture of venules). Lung function tests usually show an obstructive pattern, in contrast to most forms of interstitial lung diseases [3–5]. The diffusion capacity is typically decreased. The chest radiograph is often normal at the beginning of the disease, followed by interstitial shadows with a reticulonodular pattern and honeycombing. High-resolution CT can confirm the diagnosis. The characteristic findings of diffuse, homogeneous, small thin-walled cysts of varying sizes distributed throughout the lung fields are very specific. There is a strong correlation between the severity of the disease and the extent of cystic lesions [6]. The differential diagnosis includes histiocytosis X, tuberous sclerosis, extrinsic allergic alveolitis and sarcoidosis (cystic stage). Histology can be obtained by thoracoscopic or open lung biopsy or transbronchial lung biopsy [7].

Etiology of LAM is not known, but the proliferation of the smooth muscle cells is probably related to hormonal secretion, exacerbations related to the use of birth control pills, menstrual cycle or pregnancy have been documented [5]. Estrogen and progesterone receptors have been found in biopsy tissue [8]. There is a close relationship between LAM and the genetic disease tuberous sclerosis, with a clinical (renal angiolipomas), and immunophenotypic (HMB-45-positive smooth muscle cells) overlap [9–11].

The treatment of LAM is controversial. Reducing the estrogen level is the main aim, several therapies have been tried (oophorectomy, antiestrogens, androgens, progesterones, luteinizing hormone-releasing hormone analogues). Oophorectomy and treatment with progesterone seem to have a benefit in stabilization of the disease [3, 12], but there is no curative approach. However, no randomized studies are available. The median survival is 8–10 years after diagnosis [3, 13]. Lung transplantation has been successfully performed, and is a therapeutic option in patients with advanced disease [14].

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**Key Words**

Lymphangioleiomyomatosis

Lung cysts

Progressive dyspnea
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