Lymphangioleiomyomatosis

Definition and Epidemiology

Lymphangioleiomyomatosis is a rare, slowly progressive, neoplastic disorder resulting in cystic lung disease and kidney angiomyolipomas that occurs in association with the tuberous sclerosis complex or sporadically in women of childbearing age.

Pathology

The disease is characterized by extensive infiltration of the lungs and lymphatics with growths of smooth muscle–like lymphangioleiomyomatosis cells. Mutations in the *TSC1* or *TSC2* gene, which encodes tumor suppressor proteins that normally act as inhibitors of protein synthesis and cell growth, may result in tuberous sclerosis or lymphangioleiomyomatosis. Mutations in *TSC2* are associated with greater disease severity.

Clinical Presentation

Dyspnea and spontaneous pneumothorax are the most common presentations, with chylous pleural effusions and hemoptysis also occurring. These clinical presentations result from lung parenchymal destruction, airway narrowing, and lymphatic obstruction caused by the abnormal proliferation of the smooth muscle–like cells.

Imaging studies show an interstitial pattern with middle and upper lung predominance; multiple, thin-walled cystic lesions; and characteristically preserved lung volumes. Pleural effusion or pneumothorax may be seen on imaging. CT of the abdomen may reveal fat-containing kidney lesions consistent with angiomyolipomas. Pulmonary function tests typically show a progressive obstructive pattern, although mixed obstruction and restriction may also be seen.

Diagnosis

Although the clinical features coupled with characteristic imaging are often diagnostic, lung biopsy may be necessary in some cases. It demonstrates interstitial nodules composed centrally of spindle-shaped cells that stain for smooth muscle cell actin and for HMB-45, an antibody to the melanocytic glycoprotein 100, with staining involving the alveolar walls, lobular septa, venules, small airways, and pleura.

Treatment

Treatment involves management of pleural complications, including the use of pleurodesis to prevent recurrent pneumothorax or effusion, bronchodilator and oxygen therapy, and avoidance of pharmacologic estrogens, which may exacerbate the disease. Progesterones have been used in an attempt to modulate disease progression, but efficacy data are limited.

Because the products of the *TSC1* and *TSC2* genes normally act as inhibitors of the mammalian target of rapamycin (mTOR), pharmacologic mTOR inhibitors such as sirolimus and everolimus have been studied in lymphangioleiomyomatosis. Sirolimus stabilized lung function in lymphangioleiomyomatosis (level 1 evidence), and sirolimus and everolimus treatment resulted in angiomyolipoma shrinkage (level 1). Lung transplantation can be performed in patients with severe pulmonary dysfunction.

Prognosis

Lymphangioleiomyomatosis is a slowly progressive disease that can result in potentially fatal complications, especially respiratory failure.

Eosinophilic Lung Disease

Eosinophilic lung diseases are characterized by pulmonary infiltrates and eosinophilia of the peripheral blood or lung. Because eosinophilia is a feature of many diseases, distinguishing primary pulmonary eosinophilic lung disorders from lung disorders in which eosinophilia has a specific cause is important.

Eosinophilic lung diseases can be categorized as follows: primary pulmonary eosinophilic disorders (e.g., acute and chronic eosinophilic pneumonia, hypereosinophilic syndrome), pulmonary disorders of known cause associated with eosinophilia (e.g., asthma, allergic bronchopulmonary aspergillosis, drug reactions, parasitic infections), lung diseases associated with eosinophilia (e.g., HP, COP, IPF), malignancies associated with eosinophilia (e.g., lung cancer, leukemia, lymphoma), and systemic disease associated with eosinophilia (e.g., rheumatoid arthritis, sarcoidosis, Sjögren syndrome).

Acute eosinophilic pneumonia is characterized by fever, a nonproductive cough, and dyspnea of less than 7 days' duration, often leading to acute respiratory failure. This disease typically affects male smokers between the ages of 20 and 40 years who are otherwise healthy. Chest imaging reveals diffuse bilateral pulmonary infiltrates. Eosinophilia is not found in the peripheral blood initially but may occur 7 to 30 days after onset. Abundant eosinophils can be found in BAL fluid, and a level of greater than 25% of all nucleated cells is helpful in making the correct diagnosis. Although lung biopsy is typically not required to make the diagnosis, it can show eosinophilic infiltration with acute and organizing diffuse alveolar damage. Treatment with corticosteroids typically offers rapid and complete clinical and radiographic resolution without recurrence or residual sequelae (level 3 evidence).

Chronic eosinophilic pneumonia is an idiopathic disease predominantly of middle-aged women with a history of asthma. Also called *prolonged pulmonary eosinophilia*, this illness is characterized by a productive cough, dyspnea, malaise, weight loss, night sweats, and fever associated with progressive peripheral lung infiltrates that have been described as resembling the photographic negative of pulmonary edema on chest radiographs (E-Fig 17-9). On presentation, most patients with chronic eosinophilic pneumonia have a peripheral eosinophilia of greater than 30% and BAL fluid eosinophilia.

Histologic examination shows eosinophils and histiocytes in the lung parenchyma and interstitium, areas of COP, but minimal fibrosis. Spontaneous remissions have been reported, but respiratory failure can develop. Typically, treatment with corticosteroids is rapidly effective. Prolonged therapy is recommended because relapses are common (level 3 evidence), unlike treatment for acute eosinophilic pneumonia.

Simple pulmonary eosinophilia (i.e., Löffler syndrome) is characterized by transient migratory infiltrates that last less than 1 month. Some cases are asymptomatic, but dyspnea and dry cough may occur. Pathologic examination of tissues reveals