A 40-year-old, obese, African American woman presented with progressively worsening shortness of breath and exertional dyspnea that had been present for the past 6 months. Her symptoms were associated with a dry cough, right pleuritic chest pain, and occasional wheezing. She denied recent episodes of fever, night sweats, or hemoptysis or any changes in weight or appetite, and there was no prior history of asthma, angina, or pneumothorax. She had never smoked, and alcohol consumption was rare. Her medical history was significant for myasthenia gravis, rheumatoid arthritis, and the periodic use of oral contraceptive pills during the past 20 years. On physical examination, the woman was afebrile and in no acute distress. The lungs had equal air entry bilaterally with no wheezing and minimal crackles over the bases. Pulmonary function tests showed a forced vital capacity of 2.22 L (71% of predicted), a forced expiration volume in 1 second of 1.9 L (78% of predicted), and a total lung capacity of 3.71 L (84% of predicted). Her electrocardiogram was normal, and the blood cultures were negative. The chest radiograph had a reticular pattern that appeared more prominent at the bases. A high-resolution computed tomographic scan showed innumerable, small, well-defined, thin-walled cysts evenly distributed throughout both lung fields (Figure 1); the intervening lung parenchyma was normal, and no pulmonary nodules were identified. To secure a definitive diagnosis, an open lung wedge biopsy was performed. Cross sections of lung tissue showed spongy red-brown parenchyma with multiple scattered 0.1- to 0.2-cm cystic spaces. Histologic examination showed multiple cysts (Figure 2, hematoxylin-eosin, original magnification ×100) and a lacy whorled pattern of modified smooth muscle proliferation around bronchi, bronchioles, and blood vessels (Figure 3, hematoxylin-eosin, original magnification ×300). This modified smooth muscle proliferation appeared to extend into the walls of adjacent alveolar ducts and alveoli with the formation of septal nodules. The pathologic process was diffuse; intervening lung tissue between involved foci had patchy chronic inflammation and numerous hemosiderin-filled macrophages. HMB-45 immunohistochemical stain was positive in the modified smooth muscle cells (Figure 4, HMB-45, original magnification ×300). These cells also immunostained positive for proliferating cell nuclear antigen, whereas stains for estrogen and progesterone receptors and melan A were negative. Fungal and bacterial cultures performed on the biopsy tissue were negative.

What is your diagnosis?
Pathologic Diagnosis: Pulmonary Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM), also known as lymphangioleiomyomatosis, is a rare disorder of unknown etiology limited almost exclusively to women of reproductive age. The lungs are mainly involved, with a disordered proliferation of smooth muscles around airways, lymphatics, and blood vessels. Progressive dyspnea, repeated pneumothoraces, cough, hemoptysis, and chylous pleural effusions are the usual presenting findings. The disease is progressive, and the prognosis is poor, as increasing airflow obstruction leads to respiratory failure or cor pulmonale. The rate of progression is highly variable, with some patients improving over years, whereas others worsen with rapid decline and death. Pregnancy and menopause have been noted to worsen the disease process, whereas improvement is seen after menopause. Mediastinal or peri-aortic lymph nodes and thoracic duct may be involved with or without lung changes. In some instances, LAM is associated with renal angiomyolipomas and is considered part of the tuberous sclerosis complex. Although pulmonary LAM mainly occurs in women of child-bearing age, cases have been reported in men and in postmenopausal women on hormonal replacement therapy.

The diagnosis of LAM should be suspected in women when dyspnea is associated with pneumothorax or when emphysema is seen without a history of smoking. Lung function tests in patients usually show airflow obstruction and impaired gas transfer as predominant features. Initially, the chest radiograph may be normal. As the disease progresses, a pattern of interstitial fibrosis or reticular shadowing develops, with associated cysts and blebs. Unlike other interstitial processes in which lungs are usually shrunken, lungs in LAM appear expanded or normal in size. The appearance on high-resolution computed tomographic scans is characteristic, with thin-walled cysts distributed throughout the lung fields. The size of cysts varies from small lesions to bullous emphysema, and the intervening parenchyma usually appears radiographically normal. Low attenuation hilar and mediastinal lymphadenopathy and alveolar shadowing representing hemorrhage are also seen in some cases. Langerhans cell histiocytosis is the main radiologic differential diagnosis. Features such as a nodular pattern in the early disease process and a sparing of the costophrenic angle help differentiate this entity from LAM.

The gross appearance of lung tissue in LAM is quite characteristic, with multiple air-filled cysts essentially replacing the lung parenchyma. The surgeon might describe an extrusion of chylous fluid from pleural surfaces. Microscopically, the lungs are characterized by cystic air spaces and a patchy nodular proliferation of abnormal smooth muscle cells (LAM cells). The proliferating LAM cells appear to spin off the muscle coats of bronchi, bronchioles, veins, or lymphatics and extend into the walls of adjacent alveolar ducts and alveoli; this imparts a unique, whorled, histologic appearance. The intervening parenchyma often looks remarkably normal. The proliferating cells lead to an obstruction of bronchiolar, venous, and lymphatic channels, causing the formation of cystic blebs, localized pulmonary hemorrhages, and lymphatic cysts. Cystic blebs and lymphatic cysts may rupture into the pleural spaces, causing pneumothoraces and chylous pleural effusion, respectively. The cystic air spaces in LAM are usually lined by flattened or ciliated bronchiolar epithelial cells and are probably formed by uncontrolled proteolytic activity, causing the destruction and eventual amalgamation of alveoli. In early lesions, smooth muscle cells accumulate in the alveolar walls with the presence of a surrounding hemorrhage, hemosiderin-laden macrophages, and edema. The nodules are larger and more compact in advanced stages of the disease, whereas hemorrhage and edema become less prominent. The LAM histologic score (LHS) can be used to grade the severity of the disease. The LHS is determined by quantitatively estimating the percentage of tissue involved by proliferating LAM cells and cystic lesions (LHS-1, <25%; LHS-2, 25%–50%; and LHS-3, >50%). Higher scores are thought to be associated with a lower 5-year survival rate.

Because of the patchy nature of LAM, an open lung biopsy has been the gold standard for the diagnosis of this disease. The sensitivity and specificity of histologic analysis have improved with the use of HMB-45 monoclonal antibody, which helps exclude conditions that may mimic this entity, such as metastatic endometrial sarcoma, benign metastasizing leiomyoma, and idiopathic pulmonary hemosiderosis. LAM shares HMB-45 immunostaining with other unusual neoplasms such as clear cell tumor of the lung and renal angiomyolipoma. Immunohistochemical and electron microscopic techniques have identified different forms of LAM cells. LAM cells can microscopically appear as large peripheral spindle or epithelioid cells or as smaller cells with little cytoplasm. HMB-45 staining is usually distributed along the periphery of the nodules in the large epithelioid cells; these cells are also shown to immunostain for estrogen and progesterone receptors. Small spindle-shaped cells that are centrally located in the LAM nodules can lack HMB-45 reactivity but show immunostaining with proliferating cell nuclear antigen. Although the diagnosis of LAM requires an open lung biopsy, in the appropriate clinical setting, a transbronchial biopsy in conjunction with HMB-45 immunostaining and high-resolution computed tomographic findings may be sufficient to make the diagnosis.

Because LAM is thought to be hormonally dependent, hormonal manipulation in the form of progesterone or antiestrogen supplementation has been used for the treatment of this disorder. For treatment purposes, it usually does not seem to matter whether the lesion is estrogen and progesterone receptor positive or negative. Surgical or chemical oophorectomy in conjunction with other treatments has shown some response in a few cases. Lung transplantation is reserved for severe disease and has been carried out successfully in patients with end-stage LAM. Focused research on the clinical and biological aspects of this disorder would provide increased insight into the disease mechanism and possibly lead to further advances in management issues.

References


