Severe Bullous Lung Disease Due to Marginal-Zone-Lymphoma-Associated Amyloidosis

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Introduction

Marginal-zone lymphoma is a rare primary lung malignancy that can be associated with pulmonary amyloidosis. Pulmonary amyloidosis can lead to cystic lung disease. We report a case of severe, progressive bullous lung disease believed to be caused by marginal-zone lymphoma-related pulmonary amyloidosis.

Case Summary

A 49-year-old male dentist presented to his primary care physician complaining of dyspnea. The patient had been an avid runner, but noted occasional wheezing and a decrease in his exercise tolerance. He was initially diagnosed with reactive airway disease, based on presenting symptoms, and empirically started on inhaled corticosteroids and a β agonist. His dyspnea progressed over the next year, and he was referred to a pulmonologist. Pulmonary function tests revealed moderate restriction and air-trapping: forced vital capacity (FVC) 2.08 L (49% of predicted), forced expiratory volume in the first second (FEV_1) 1.39 L (40% of predicted), FEV_1/FVC 0.67.

His medical history was notable for achalasia (which was treated with esophageal dilation), atopic dermatitis, and gastroesophageal reflux disease. He had undergone a tonsillectomy as a child. His only medications at the time of presentation were salmeterol/fluticasone twice daily and albuterol as needed. He had never smoked and did not drink alcohol or use illicit drugs. A recent esophagogastroduodenoscopy revealed no pathologic lesions and was negative for *Helicobacter pylori*. A recent screening colonoscopy was notable only for a tubular adenoma. His vital signs, physical examination, and basic laboratory evaluation were unremarkable. Antinuclear antibody; extractable nuclear antigen antibody; serum and urine protein electrophoresis; and serologies for hepatitis, human immunodeficiency virus, and *H. pylori* were all negative. His alpha-1 antitrypsin level was within normal limits.

No chest radiograph was available. A conventional chest computed tomogram revealed extensive bilateral bullous changes and multiple bilateral poorly circumscribed nodular densities in the lung parenchyma (Fig. 1). There were no pathologically enlarged mediastinal or hilar lymph nodes. Positron emission tomography revealed increased glucose uptake in both lungs, by the nodular densities seen on computed tomogram.

The differential diagnosis of severe bullous lung disease with associated bilateral nodules includes lymphoid interstitial lymphoma, desquamating interstitial pneumonia, pulmonary amyloidosis, sarcoidosis, pulmonary Langerhans-cell histiocytosis, and lymphangioleiomyomatosis. The absence of adenopathy argued against sarcoidosis. Lymphangioleiomyomatosis primarily affects women of childbearing age, whereas our patient was male. The remaining diagnoses generally require histopathology for diagnosis. The patient underwent an open lung biopsy.

Histology revealed extensive lymphocyte infiltration. Immunohistochemical studies confirmed a B-cell predominance, and the infiltrating lymphocytes stained strongly positive for CD20 (Fig. 2). Extensive amyloid deposition, with apple-green birefringence under polarized light, was seen with Congo red staining (Fig. 3). Kappa and lambda staining revealed a lambda light chain restriction. Based on the histopathology findings, we made a diagnosis of marginal-zone lymphoma with associated pulmonary amyloidosis.

Our patient underwent an extensive search for signs of systemic amyloidosis, including a transthoracic echocar-

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The authors report no conflicts of interest related to the content of this paper.

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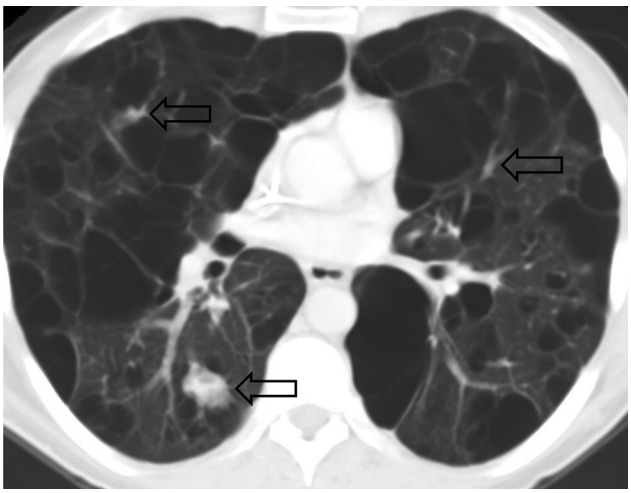

Fig. 1. Chest computed tomogram reveals extensive bilateral bullous changes and multiple parenchymal nodules (arrows).

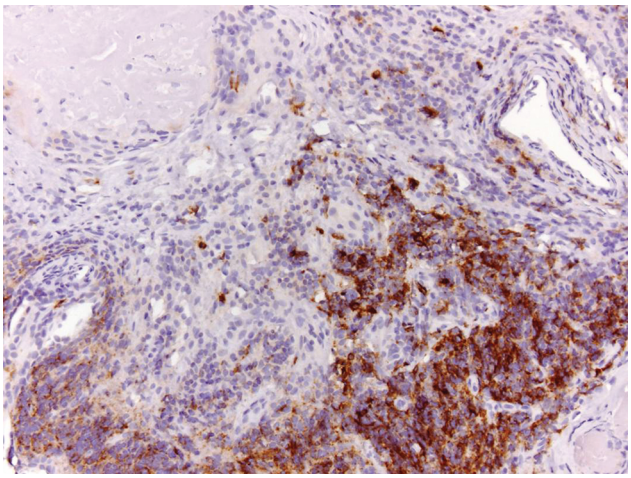

Fig. 2. Extensive B-lymphocyte infiltration of pulmonary parenchyma (magnification 20, CD20 stain).

diogram and bone-marrow biopsy, which was negative. He was treated with rituximab, an anti-CD20 monoclonal antibody, with good response. Despite treatment of the marginal-zone lymphoma, the bullous lung disease progressed, and he died while awaiting lung transplantation.

Discussion

Primary pulmonary lymphoma is described as a clonal lymphoid proliferation that affects one or both lungs, without detectable extrapulmonary involvement at diagnosis or within the subsequent 3 months.[1] Mucosa-associated lymphoid-tissue lymphoma, also known as marginal-zone lymphoma, is the most frequent form of primary pulmonary lymphoma.[2] Mucosa-associated lymphoid-tissue lymphomas are often described in association with autoimmune

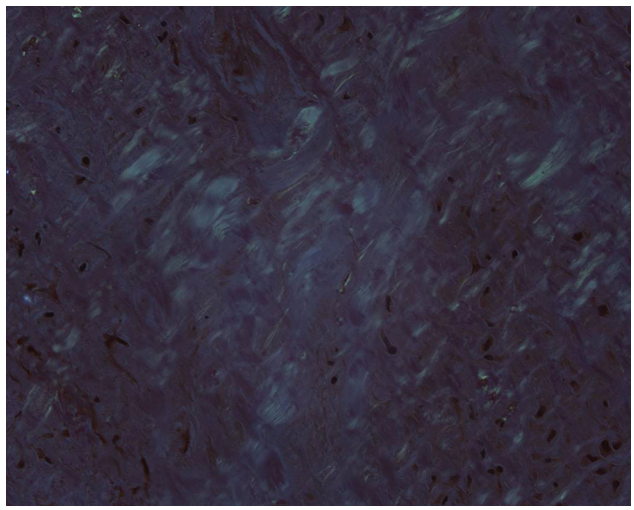

Fig. 3. Polarized light reveals apple-green birefringence consistent with amyloid deposition (magnification 20, Congo red stain).

disease, most commonly Sjögren syndrome. Cases have been reported in other chronic inflammatory conditions such as *H. pylori* infection, human immunodeficiency virus, chronic active hepatitis C, Lyme disease, and common variable immunodeficiency. Mucosa-associated lymphoid-tissue lymphoma may also develop in a patient with no preexisting condition.[3-11]

Mucosa-associated lymphoid-tissue lymphoma is rare, composing less than 1% of all primary lung malignancies.[2] The average age of onset is 50–60 years (range 12–79 y). Subjects less than 30 years of age are rarely affected. Males and females are equally affected.[12-18] Most patients are asymptomatic at the time of diagnosis, although cough, dyspnea, hemoptysis, and chest pain can occur. Extrapulmonary manifestations are, by definition, restricted to general signs, including fever and weight loss. These findings are present in approximately 25% of patients at the time of diagnosis.[12-18] Physical examination is usually unrevealing. Rales occur in $<$ 20% of cases.[18] The majority of patients are identified by incidental findings on imaging.

The typical radiographic appearance of a mucosa-associated lymphoid-tissue lymphoma is alveolar opacities $<$ 5 cm in diameter. The margins may be well-defined or blurred, and approximately 50% have air bronchograms in the opacities. Lesions are bilateral in 60–70% of cases, and multiple in 70–77% of cases.[2,19,20] Chest radiograph will generally be abnormal; patchy bilateral infiltrates is the most common finding.

A recent study of positron emission tomograms from 6 patients with marginal-zone lymphoma found that five of the patients displayed heterogeneous uptake and one had homogeneous uptake. All 6 patients were metabolically active (modified standard uptake values were in the range 2.2–6.3).[21]

The diagnosis of primary pulmonary lymphoma relies mainly on the immunohistochemical features of the tissue sample. Transbronchial and endobronchial biopsies will occasionally provide adequate tissue to make a diagnosis, particularly when targeted at visible endobronchial lesions or radiographic abnormalities. In most cases, though, a surgical biopsy is required for definitive diagnosis.[2]

Mucosa-associated lymphoid-tissue lymphomas are indolent malignancies and have an excellent prognosis. The 5-year survival rate is > 80%, and the median survival time is > 10 y.[2] There is no consensus on treatment of primary pulmonary lymphoma, because there have not been enough studies of available treatments. Some authors have advocated simple observation, given the disease's indolence.[14] In general, surgical resection is reserved for localized tumors, and chemotherapy is given for bilateral or diffuse involvement. Multiple agents have shown efficacy, but combination regimens have not been proven superior to single drugs. Radiotherapy is rarely used.[2]

Pulmonary amyloidosis occurs when insoluble monoclonal light-chain fragments are deposited in lung tissue. This disorder most commonly occurs in systemic amyloidosis, either as a primary disease or secondary to chronic inflammatory conditions.[22] Localized amyloid deposition in lung tissue in the absence of systemic amyloid may also occur, but is much less frequent.[23] The association of mucosa-associated lymphoid tissue-lymphoma with localized pulmonary amyloidosis is well documented.[24-28] Amyloid production secondary to a primary pulmonary lymphoma has a similar histologic appearance to nodular amyloidoma, which can lead to morphologic confusion.[25]

The differential diagnosis for diffuse cystic lung disease includes lymphoid interstitial pneumonia, desquamating interstitial pneumonia, pulmonary Langerhans-cell histiocytosis, and lymphangioleiomyomatosis.[29] Cystic disease has been reported in patients with amyloidosis.[30,31] The proposed etiology is a valve-mechanism: amyloid deposition obstructs the small airways. Progressive cystic lung disease has also been reported in light-chain deposition disease.[32] In patients with amyloidosis from Sjögren syndrome, cystic lung disease may occur because of lymphoid interstitial pneumonia with associated bronchiolitis.[3]

In our patient we think the bullous lung disease occurred secondary to amyloidosis deposition rather than lymphocyte infiltration. This is difficult to prove definitively, but the fact that the bullous lung disease progressed despite resolution of the lymphoma after treatment with rituximab strengthens the argument. Though cystic lung disease has been reported with amyloid and other protein-deposition diseases, to our knowledge there is only one other reported case of cystic lung disease secondary to marginal-zone-lymphoma-associated amyloidosis.[33] The cystic disease in our patient was much more extensive than that described by Lantuejoul and colleagues.[33]

Teaching Points

Amyloidosis should be considered in the differential diagnosis of bullous lung disease. Bullous lung disease from amyloidosis may be progressive and severe. The presence of primary pulmonary amyloidosis should prompt a search for mucosa-associated lymphoid-tissue lymphoma, because those processes may be related. Diagnosis of primary pulmonary lymphoma relies on tissue diagnosis and immunohistochemical staining, which generally requires open lung biopsy. The prognosis of primary pulmonary lymphoma is favorable, with a 5-year survival rate > 80%.

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