A 55-year-old African-American man presented with a week-long history of cough with blood-streaked sputum. He denied fevers, night sweats, weight change, and sinus symptoms. He was physically active and had no dyspnea on exertion. He reported gastroesophageal reflux symptoms but denied any other complaints. His medical history included diverticulosis and depression. He took no medications. He was an active smoker with a 60-pack-year smoking history. In addition, he smoked crack cocaine with reported use 3 months prior. He denied alcohol or IV drug use. He had no significant travel, occupational, or exposure history.

His physical examination was unremarkable. A chest radiograph revealed an ill-defined infiltrate in the right lower lobe (Fig 1). Laboratory study findings, including cell counts and blood chemistry measurements, were normal. The results of HIV and hepatitis serology tests were negative. A presumed diagnosis of community-acquired pneumonia was made, and the patient was treated with an oral fluoroquinolone for 10 days.

At the 6-week follow-up, the patient reported complete resolution of symptoms. A repeat chest radiograph showed a persistence of the right lower lobe infiltrate. A CT scan of the chest demonstrated the presence of a focal airspace opacity in the right lower lobe with no evidence of hilar or mediastinal adenopathy (Fig 2). During bronchoscopy, the airways appeared normal with no endobronchial lesions. A BAL fluid culture grew *Stenotrophomonas maltophilia* but was negative for acid-fast organisms and fungi. Transbronchial biopsy specimens obtained from the right lower lobe posterior segment showed normal bronchial mucosa with adjacent lymphoid tissue but no evidence of malignancy. The patient was treated with trimethoprim-sulfamethoxazole for 3 weeks.

On serial follow-ups at intervals of 3 months and 6 months, he remained asymptomatic. However, radiographic persistence of the infiltrate with a slight interval increase in size was noted. Pulmonary function studies showed mild airflow limitation with normal diffusion capacity. A whole-body positron emission tomography study showed moderate meta-
bolic uptake in the area of the infiltrate. A subse-
quent CT-guided needle biopsy of the infiltrate was
nondiagnostic.

What is your diagnosis?
Diagnosis: Extranodal marginal zone lymphoma (previously known as MALToma).

Primary pulmonary lymphoma is defined as a clonal lymphoid proliferation affecting one or both lungs (parenchyma and/or bronchi) in a patient with no detectable extrapulmonary involvement at diagnosis or in the subsequent 3 months. Primary pulmonary lymphomas are rare tumors comprising about 3% of all extranodal lymphomas, and only 0.5% of all pulmonary malignancies.

Historical Data

Mucosa-associated lymphoma was first described by Issacson and Wright in 1983. The Revised European American Lymphoma classification and the World Health Organization in 1994 incorporated mucosa-associated lymphoma as a distinct subgroup of non-Hodgkin lymphoma under the term extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (ie, mucosa-associated lymphoid tissue [MALT]).

Cellular Origin

While the majority of the MALT lymphomas are GI in origin, about 30 to 40% arise in other sites, including the lungs, salivary glands, breast, and thyroid. MALT lymphomas are believed to arise from preexistent resident lymphoid tissue in the lungs. The presence of MALT/bronchus-associated lymphoid tissue (BALT) in the lung was first described in 1973 by Bienenstock and colleagues. Although, BALT is generally seen in the lungs of healthy children, it has also frequently been described in the lungs of smokers and in settings of chronic antigen stimulation, including infections and autoimmune diseases. It is speculated that the chronic antigenic stimulation triggered by persistent infections or autoimmune processes induces lymphoid aggregation, which then forms the background for the development of BALT lymphoma.

MALT lymphoma cells originate from the marginal zone B cells surrounding the mantle zone and germinal center. These cells function as the noncirculatory memory B cells and antigen-presenting cells. The growth of MALT lymphomas and their propensity to stay localized may be related to antigen stimulation and the associated local immune reaction. Ig gene rearrangement and the high degree of somatic mutation in the heavy-chain variable gene regions that have been demonstrated in lymphoma cells suggests an antigen-driven clonal expansion of the lymphoma cells. Unlike the well-recognized association of Helicobacter pylori and gastric MALT lymphoma, the putative antigen associated with BALT lymphoma remains unknown.

Clinical Characteristics

Risk Groups: A total of 30 to 40% of MALT lymphomas has been reported in patients with pre-existing autoimmune diseases, including Sjögren syndrome, rheumatoid arthritis, systemic lupus erythematosus, pernicious anemia, and Hashimoto thyroiditis, and in settings of immunodeficiency (ie, AIDS and common variable immune deficiency). Although smoking is associated with the occurrence of BALT in the lungs, it has not been clearly identified as a risk factor in development of pulmonary MALT lymphomas.

MALT lymphoma of the lung often occurs in the fifth to seventh decade of life. Although a female predominance has been suggested, it has not been observed in all series.

Clinical Presentation

Nonspecific pulmonary complaints and constitutional features have been reported in a minority of patients at presentation. The majority of patients are asymptomatic with incidental abnormalities observed on chest radiographs leading to an evaluation. CBC findings are usually normal. In about a third of the patients, a monoclonal gammopathy, typically of IgM class, is seen on serum electrophoresis results. An elevated β2-microglobulin level has been reported as an independent predictor of poor outcome.

Imaging

The common radiographic appearances are pulmonary masses or mass-like areas of consolidation or nodules, unilateral or bilateral, and in peribronchial or bronchovascular distribution. Frequently, air bronchograms are seen within the nodules and masses. The patent airways within the consolidated lung appear dilated and, occasionally, can be mistaken for cavitation. Lymphadenopathy also may be observed on CT imaging. High-resolution CT scans may show areas of ground-glass opacity and peribronchovascular thickening at the tumor margins.

Diagnosis

Bronchoscopy may demonstrate mucosal changes in a few patients. Although transbronchial or percutaneous needle biopsies may yield the diagnosis in a minority of cases, the small biopsy specimens may lack the lymphoepithelial lesions, and fail to reveal cytologic atypia or the pattern of architectural destruction that is crucial for making the diagnosis. BAL fluid may demonstrate an increased cellularity with a predominant lymphocytosis, and flow cytometry analysis can aid in establishing the diagnosis.
However, in a large proportion of the cases reported, a surgical biopsy is essential for establishing the diagnosis.

Staging

The Ann Arbor classification of Hodgkin lymphoma with some modifications has been used for staging in non-Hodgkin lymphomas. CT imaging is performed to rule out nodal disease. In light of the propensity for mucosal generalization, an extensive staging workup, including upper and lower GI endoscopies, ear, nose, and throat evaluation, and bone marrow biopsies, is recommended. Given the indolent clinical course, in the majority of patients the lymphoma is localized to the lung at the time of diagnosis.

Histopathology

Low-grade MALT lymphomas demonstrate a characteristic pattern of spread along the bronchovascular bundles and interlobular septa, with subsequent expansion and destruction of the alveolar walls and filling of the alveolar spaces. Eventually, the lymphangitic infiltrates coalesce to form a mass with sparing of the airways and vessels creating the air bronchogram and angiogram sign that is typically observed on imaging studies.

The characteristic histologic features of MALT lymphoma include the following:

1. Proliferation of neoplastic centrocyte-like cells (ie, lymphocytes with large irregular nuclei and abundant pale cytoplasm), small lymphocytes, and plasma cells (Fig 3);
2. Lymphoepithelial lesions showing lymphoid cell migration from marginal zone through ciliated bronchial and bronchiolar epithelium;
3. Scattered reactive follicular hyperplasia;
4. Immunophenotyping studies showing a B-cell lineage (ie, CD19+, CD20+, CD23+), while lacking CD5, CD10, and BCL1 (markers for mantle lymphoma and chronic lymphocytic lymphoma or small lymphocytic lymphoma); and
5. Occasionally, deposits of amyloid may be seen. When present, this portends a poor prognosis.

Immunohistochemistry and studies for clonal rearrangement of Ig heavy-chain genes can be helpful in distinguishing MALT lymphomas from nonneoplastic lymphoproliferative disorders such as lymphocytic interstitial pneumonitis and nodular hyperplasia when the morphologic characteristics are equivocal.

Figure 3. High-power view of the infiltrate demonstrates the proliferating centrocyte (ie, large lymphocytes with pale abundant cytoplasm and irregular nuclei), plasma cells, and small lymphocytes. Also seen is the lymphoid cell migration through the ciliated bronchiolar epithelium, which is referred to as the lymphoepithelial lesion (on the lower left side of the image) [hematoxylin-eosin, original ×40].

Treatment and Prognosis

In the absence of any prospective studies, the optimal therapy remains unclear. In most series, surgical resection, either alone or in combination with chemotherapy, has been the mainstay of therapy. Chemotherapy also has been used in patients with residual disease after resection or in those with extrapulmonary involvement. No difference in response rates was seen with single-agent chemotherapy or in multiple chemotherapeutic drug regimes. The role of monoclonal antibodies and antibiotics is uncertain.

The prognosis is excellent for patients with localized MALT lymphomas. In a series of 51 cases of MALT lymphomas treated with surgery alone or in combination with chemotherapy and radiation, a 100% 2-year survival rate and a 94% 5-year survival rate were reported. Most series have reported a 5-year survival rate of > 80% and a median survival time of 10 years. However, survival and progression-free survival are shorter than those for the age-matched general population.

The prognostic factors have not been well defined for pulmonary MALT lymphomas. The presence of intratumoral amyloid is associated with adverse outcome, while the presence of lymphoepithelial lesions is linked with a favorable outcome.

t(11;18)(q21;q21) is associated with MALT-type lymphoma and results in API2-MALT1 fusion. Preliminary data from a series of 51 cases suggest that the API2-MALT1 fusion alteration may define
a homogeneous MALT lymphoma subtype that is clinically more indolent and histologically more “typical.”

Local and extrathoracic relapse have been noted, making long-term surveillance necessary. Although transformation to high-grade lymphoma has been reported, these cases may represent large B-cell lymphomas that have been initially mistaken for MALT lymphomas.

Our patient underwent a video-assisted thoracoscopic resection of the right lower lobe with hilar lymph node dissection. The resected lung demonstrated infiltrating sheets of lymphocytes in a peribronchial distribution with lymphoepithelial lesions and a characteristic immunophenotype, establishing a diagnosis of MALToma. The hilar lymph nodes were not involved. Further workup confirmed the presence of stage IE disease. No further treatment was initiated given the performance of curative resection. At the annual follow-up, the patient was well with no evidence of local or systemic recurrence.

**CLINICAL PEARLS**

1. Pulmonary MALTomas, although rare, present as an airspace opacity and should be considered in the differential diagnosis of a persistent infiltrate.

2. Pulmonary MALTomas occur predominantly in the fifth to seventh decade of life and may be associated with autoimmune diseases and immunodeficiency states.

3. The radiographic differential diagnosis of pulmonary nodules or masses with air bronchograms in a peribronchial distribution should include MALT lymphomas.

4. The diagnosis can be established with bronchoscopy and flow cytometry, but frequently requires surgical biopsy.

5. Optimal therapy is unclear, with surgical resection, chemotherapy, or the combination being used.

6. The overall prognosis is favorable, with the majority of patients having limited-stage disease and an indolent clinical course.

**SUGGESTED READINGS**


Tschernig T, Pabst R. Bronchus-associated lymphoid tissue (BAL T) is not present in the normal adult lung but in different diseases. Pathobiology 2000; 68:1–8
