The Expert Clinician

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A Man with a Decade of Persistent Pulmonary Opacities

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Case Vignette

A 59-year old man with a history of eosinophilic esophagitis and head trauma from a worksite injury presented to the hospital with intermittent right arm tingling. He was diagnosed with focal seizures related to past head trauma. A routine chest radiograph from the time of admission was notable for bilateral lower lung field opacifications (Figure 1); therefore, our pulmonary service was consulted for further evaluation.

He noted dyspnea with exertion during his work in construction over the previous 10 years. He initially attributed this to aging, and was ultimately evaluated by a physician after approximately 6 years of slowly progressive symptoms. He was diagnosed with pneumonia at that time; however, his dyspnea failed to resolve after several courses of levofloxacin. Repeat computed tomography (CT) of the chest was performed 1 year later with persistence of these findings. They were attributed to postinfectious changes, and no further workup was pursued at that time.

Physical examination was notable for normal oxygen saturation at rest and with exertion. Bronchial breath sounds with egophony were auscultated in the bilateral lower lung fields. Digital clubbing was present.

Outside imaging was reviewed. A chest radiograph from 10 years prior, performed during an evaluation of a worksite injury to his shoulder, demonstrated small, bilateral, lower lobe opacities. Chest CT

Figure 1. Chest radiograph at the time of admission to our hospital, demonstrating opacifications in the bilateral mid to lower lung fields.

Figure 2. (A) Chest computed tomography (CT) obtained from hospitalization for pneumonia 3 years before this presentation, demonstrating bilateral lower lobe consolidations, which have progressed on more recent CT. (B) Chest CT during admission to our institution, demonstrating bilateral lower lobe consolidation with air bronchograms and cavitation of left lower lobe lesion.

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from 3 years before admission, following up on the reported episode of pneumonia, demonstrated bilateral lower lobe consolidation with air bronchograms throughout (Figure 2A). A repeat Chest CT during admission to our institution (Figure 2B) demonstrated progression of the lesions with new cavitation of the left lower lobe consolidation.

Questions

1. *What is the differential diagnosis for a persistent pulmonary consolidation, present for years with slow progression?*
2. *What diagnostic approach should be pursued for this patient?*
3. *What are the treatment options and prognosis for this process?*

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Clinical Reasoning

Pulmonary consolidation demonstrating slow radiographic progression over the course of several years in the absence of concurrent systemic findings may be caused by malignancy, chronic infection, noninfectious inflammatory diseases, and congenital abnormalities.

Given the lack of other systemic symptoms or signs, combined with the slow rate of growth of the lesions, an indolent malignancy seemed most likely. However, the presence of these findings for such an extended period of time (at least 10 yr), with new cavitation, is atypical for most primary and metastatic malignancies affecting the lung. In one longitudinal study examining the doubling times of primary pulmonary malignancies, the median and maximum doubling times of adenocarcinomas, including adenocarcinoma *in situ*, were 387 days and 1,435 (3 yr, 11 mo) days, respectively. Squamous cell carcinoma of the lung had significantly shorter median and maximum doubling times of 160 days and 449 (1 yr, 3 mo) days, respectively. Other less common primary pulmonary malignancies, including pulmonary lymphoma, were observed to have median and maximum doubling times of 263 days and 4,263 days (11 yr, 8 mo), respectively (1). Based on the chronic, progressive imaging findings (Figure 2), in the absence of infectious symptoms or evidence of metastatic disease, we were concerned that these represented pulmonary lymphoma or adenocarcinoma *in situ*.

Infectious etiologies, particularly nontuberculous mycobacteria, may have a similar imaging appearance, including cavitation, and indolent course. However, the absence of cough, pre-existing structural lung disease, predisposing conditions, or other constitutional symptoms was atypical for infection.

Noninfectious inflammatory diseases, such as organizing pneumonia, lipoid pneumonia, sarcoidosis, and chronic eosinophilic pneumonia, were considered less likely based on the evolution of the radiographic findings with cavitation, presence of digital clubbing, and lack of other symptoms over this 10-year period. Finally, congenital abnormalities, such as pulmonary sequestration, can present with persistent abnormalities on imaging that evolve as a result of recurrent pneumonias.

Pulmonary sequestration has characteristic features, including an absence of communication with the normal tracheobronchial tree and pulmonary artery, and a separate systemic arterial blood supply. Our patient's imaging lacked these features.

Given the concern for malignancy, our patient underwent a bronchoscopy with bronchoalveolar lavage (BAL) and endobronchial ultrasound-guided transbronchial biopsies of the areas of consolidation. Lavage fluid revealed 30% lymphocytes, with the remainder being macrophages. Microbiologic studies from tissue and lavage were negative. Biopsy results revealed an extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma (Figure 3). Serum protein electrophoresis and whole-body positron emission tomography (PET)/CT scan did not reveal any evidence of extrapulmonary disease. Serum flow cytometry did not reveal evidence of a monoclonal B lymphocyte population. Our patient was therefore diagnosed with primary pulmonary MALT lymphoma.

Discussion

Epidemiology and Clinical Course of MALT Lymphoma

Primary pulmonary lymphomas (PPL) constitute up to 1% of primary lung cancers, with the vast majority being MALT lymphomas. Once referred to as "pseudolymphoma" in the literature, because its indolent nature resulted in skepticism about malignant potential, extranodal marginal zone lymphoma is now known to be a malignancy that arises from MALT (2). The marginal zone is a pale area surrounding the mantle zone of a lymphoid follicle, composed of a mixture of naive and memory B cells. MALT lymphoma most commonly occurs in the stomach (35%) in association with *Helicobacter pylori* infection. Other common sites include the ocular adnexa (13%), skin (9%), lungs (9%), and salivary glands (8%) (3). Pulmonary MALT lymphoma, sometimes referred to as "BALT lymphoma" for bronchus-associated lymphoid tissue, is believed to progress slowly, over the course of years, though the rare nature of the disease limits understanding of its natural history. In contrast to gastrointestinal MALT lymphoma, pulmonary MALT lymphomas

are more likely to be multifocal within the lungs, but uncommonly spread to involve other organs. Involvement of the lymph nodes or bone marrow at the time of diagnosis portends a worse prognosis (4). Other low-grade B cell lymphomas, such as follicular and mantle cell lymphoma, account for less than 10% of PPLs. High-grade B cell lymphomas may occur in the lungs in isolation or be seen concurrently with or transforming from MALT lymphoma (4). In addition, lymphomatoid granulomatosis is a rare lymphoproliferative disorder sometimes characterized as a PPL (5–7).

It is postulated that the malignant transformation of lymphoid tissues results from chronic inflammatory stimulation due to an autoimmune process, infection, or recurrent injury (5). *Chlamydophila* and *Achromobacter* have been implicated in small studies (8). As with other non-Hodgkin lymphomas, an association has been observed between Sjogren's syndrome and pulmonary MALT lymphoma (9, 10).

Treatment of MALT lymphoma may include active surveillance, chemotherapy, or surgical resection. Chemotherapy regimens are instituted in cases of progression, compromise of lung function, or patient and provider preference. Chemotherapy most typically consists of chlorambucil-based regimens, and may include rituximab (11). In addition, in cases of limited disease, surgical resection may be curative (4). Pulmonary MALT lymphoma has a good overall prognosis, with a 5-year survival of approximately 90% (4).

Diagnostic Considerations

On chest imaging, pulmonary MALT lymphoma most frequently appears as a mass-like consolidation with distinct air bronchograms throughout. It may also appear as a solitary nodule or multiple nodules. Although airway dilatation is commonly observed, cavitation, as seen in this case, is rarely reported. The majority of cases do not have associated lymphadenopathy (12). Approximately 50% of patients are asymptomatic at the time of diagnosis, with findings often incidentally noted on chest radiography or CT imaging (3).

When MALT lymphoma is suspected on imaging, testing, including lactate dehydrogenase, peripheral blood flow cytometry, and serum and urine protein

Figure 3. Biopsy of the lesion showed fragments of airway with dense, crushed lymphoid infiltrate (A; 10× magnification) and separate fragments of atypical lymphoid tissue (B; 10× magnification). The cells were small and monomorphic with relatively abundant, pale cytoplasm and condensed chromatin, conferring the classic monocytoid morphology seen in mucosa-associated lymphoid tissue (MALT) lymphoma (C; 100× magnification). By immunohistochemistry, the majority of the cells were CD20-positive B cells (D; 50× magnification), which were negative for CD5 and CD10 (not pictured). CD3 highlighted a subset of admixed T cells (E; 50× magnification). CD43 showed appropriate bright expression in T cells, as well as dim aberrant expression within the B cells (F; 50× magnification). A proliferation index by MIB1 (Ki67) was approximately 10% (not pictured). Concurrent flow cytometry confirmed the presence of a λ -restricted B cell population that had coexpression of CD19 and CD20, but was negative for CD5 and CD10. Cytogenetic evaluation revealed a baculoviral inhibitor of apoptosis repeat containing 3 (BIRC3)/MALT1 translocation (46,XY,t[11;18](q21;q21)). Taken together, these findings are consistent with MALT lymphoma.

electrophoresis, may be supportive of the diagnosis, although, ultimately, pursuit of a tissue diagnosis is required. Tissue is often best obtained through bronchoscopic approach, as transbronchial biopsies have a reported sensitivity of nearly 90% (13).

Less commonly, a surgical lung biopsy is performed, particularly in cases of solitary lesions where biopsy can be curative. An elevated BAL lymphocyte percentage (greater than 15%) may be observed in cases of MALT lymphoma, but lacks

sensitivity and specificity for the diagnosis. BAL flow cytometry demonstrating a clonal B cell population with the translocation specific to MALT lymphoma, t(11;18)(q21;q21), is a complimentary diagnostic to biopsy (13).

Immunohistochemistry studies on biopsy specimens are necessary to make an accurate diagnosis of pulmonary MALT lymphoma, allowing for exclusion of alternative processes, including reactive follicular hyperplasia, or lung localization of mantle cell, follicular, lymphoplasmacytic, or lymphocytic lymphomas (13). At the time of tissue diagnosis, CT of the chest, abdomen, and pelvis with intravenous contrast may be performed to assess for additional sites of disease. PET/CT has a reported sensitivity of 80–100% for the evaluation of metastatic disease in pulmonary MALT lymphoma, in contrast to its low sensitivity in gastric MALT lymphoma (14). The diagnosis of PPL has been said to require the absence of extrapulmonary disease before, at the time of, or within 3 months after, the diagnosis. Cytogenetics may also be helpful in situations of extrapulmonary disease, as the BIRC3/MALT1 translocation, t(11;18)(q21;q21), would be supportive of pulmonary and gastrointestinal origin, as opposed to nodal marginal zone lymphoma or MALT lymphomas of other primary sites (5). If patients exhibit symptoms localized to other mucosal sites, these should be assessed through imaging or direct inspection and biopsy, such as with endoscopy in the case of the gastrointestinal tract. Serologic testing for Sjögren's syndrome should be pursued in all patients given the frequency of association (9, 10).

Answers

1. *What is the differential diagnosis for a persistent pulmonary consolidation, present for years with slow progression?*

The differential diagnosis includes malignancy, particularly pulmonary lymphoma and adenocarcinoma, chronic infectious processes, such as mycobacteria, and inflammatory processes, such as organizing pneumonia, lipoid pneumonia, and sarcoidosis

2. *What diagnostic approach should be pursued for this patient?*

Diagnostic options include bronchoscopy with BAL for microbiologic studies, white blood cell differential, flow cytometry, and transbronchial biopsy. Surgical lung biopsy is an alternative option for limited disease. Given the accessibility of our patient's lesions by bronchoscopy, transbronchial biopsies offered a minimally invasive approach with low risk of complications and high sensitivity. Whole-body CT or PET/CT should be performed to evaluate for additional sites of disease.

3. *What are the treatment options and prognosis for this process?*

Treatment of pulmonary MALT lymphoma may include active surveillance, or chemotherapy including a chlorambucil-based regimen, often given in combination with rituximab. Overall

prognosis is good, with 90% 5-year survival.

Follow-Up

Given the extent of disease and progression of imaging, our patient is currently undergoing treatment with rituximab and bendamustine chemotherapy. His tumor biopsy was cultured for associated infectious triggers, though none were found, and a thorough evaluation for autoimmune disease was unrevealing.

Insights

- PPL, most frequently MALT lymphoma, is a rare cause of chronic progressive pulmonary infiltrates.
- The evaluation of persistent pulmonary infiltrates must include investigation of malignant and chronic infectious etiologies, and should include biopsy of suspect lesions when progression occurs on serial imaging.
- MALT lymphoma has a good overall prognosis, and treatment may include active surveillance, chemotherapy, or surgical resection. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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