Bronchus-Associated Lymphoid Tissue Lymphoma and *Mycobacterium tuberculosis* Infection: An Unusual Case and a Review of the Literature

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Bronchus-associated lymphoid tissue lymphoma is a rare disease. It is the most common form of primary pulmonary lymphoma but accounts for less than 1% of all non-Hodgkin's lymphomas. We describe a 67-year-old man who, despite successful treatment of active miliary tuberculosis, developed progression of a concomitant bronchus-associated lymphoid tissue lymphoma. This case is in contrast to previous reports of gastrointestinal-mucosa-associated lymphoid tissue lymphomas and bronchus-associated lymphoid tissue lymphomas, in which treatment of the precipitating antigenic stimulus lead to remission of the lymphoma. *Key words: bronchus-associated lymphoid tissue lymphoma, non-Hodgkin's lymphoma, miliary tuberculosis.* [Respir Care 2007;52(6):755–758. © 2007 Daedalus Enterprises]

Introduction

Bronchus-associated lymphoid tissue (BALT) lymphoma is a rare disease. It is the most common form of primary pulmonary lymphoma but accounts for less than 1% of all non-Hodgkin's lymphomas.[1,2] It affects both sexes equally, and the majority of patients are 50–60 years old.[3,4] In the revised European American lymphomas classification it belongs to the group of extranodal marginal B-cell lymphomas, of which gastrointestinal-mucosa-associated lymphoid tissue (MALT) lymphoma is most common.[5,6] It appears that pathogenesis in this group is similar and may start with a chronic immunogenic stimulus that produces reactive lymphoid tissue (BALT in the case of the lung), which is normally not present in healthy human lungs.[7,8] When oligoclonal or monoclonal lymphoid proliferation occurs, BALT lymphoma develops.[9] Associated conditions include chronic hypersensitivity pneumonitis, panbronchiolitis, autoimmune diseases, and smoking.[10–14] Unlike MALT lymphoma, there is no common antigen responsible for the development of the majority of BALT lymphomas. Multiple case histories have been reported with different infections associated with BALT lymphoma, including *Mycobacterium avium* complex and *Mycobacterium tuberculosis*.[15,16] We report a patient with a history of remote pulmonary tuberculosis and BALT lymphoma. This case illustrates the difficulties of managing a patient with *Mycobacterium tuberculosis* and malignancy.

Case Summary

A 67-year-old man was admitted to the hospital because of an upper respiratory infection and a persistent right-sided lung mass. Eleven months prior, a chest radiograph revealed a diffuse miliary pattern, with consolidation in the right perihilar area. Sputum was positive on smear and culture for acid-fast bacilli. A polymerase-chain-reaction test for *Mycobacterium tuberculosis* was positive. His tuberculin skin test was negative. He underwent successful 4-drug treatment for 6 months, for active pulmonary tuberculosis. Sputum cultures during and after that treatment were negative.

His medical history included an ischemic stroke, diabetes mellitus type 2 that was diet-controlled, and iron-deficiency anemia. His only medication was iron sulfate, 325 mg/d. He had been immunized with Pneumovax. He

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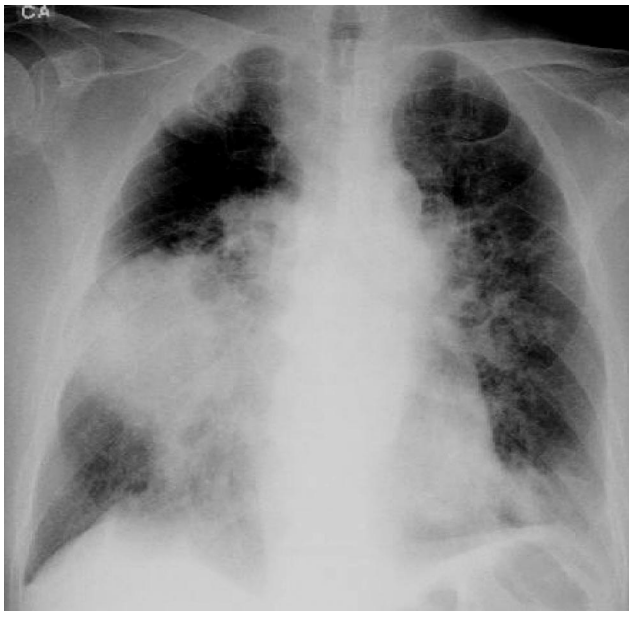

Fig. 1. Chest radiograph shows diffuse fibrotic changes in the left lung and a mass-like infiltrate extending from the right hilus to the lateral chest wall.

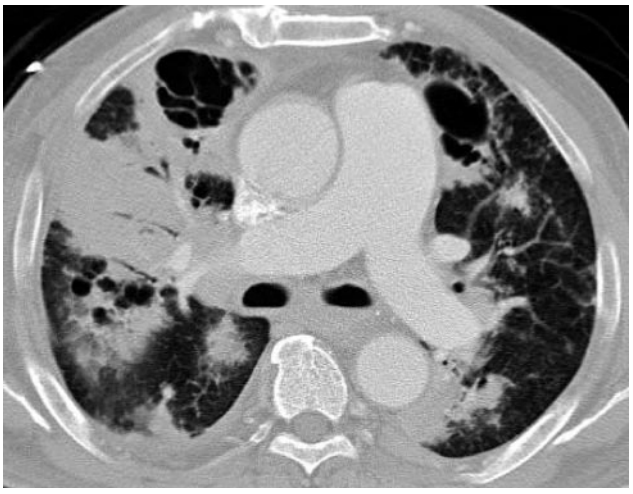

Fig. 2. Chest computed tomogram shows multiple masses, some with air bronchograms and small cavities.

was a nonsmoker and drank occasionally. On physical examination he appeared well and in no distress. His temperature was 36.1°C, his pulse was 63 beats/min, and his respiratory rate was 20 breaths/min. The initial blood pressure was 84/52 mm Hg, but improved to 100/60 mm Hg after a 500 mL normal saline fluid bolus. His teeth were in good repair. No lymphadenopathy was noted. His chest examination revealed bronchial breath sounds over the anterior and posterior lower lung zones. His liver and spleen were not enlarged. Noteworthy diagnostic data included a hemoglobin of 10.5 g/dL with normal indices, a white blood cell count of 18.3×10^3 cells/μL with 62% neutrophils and 20% bands. His platelet count was 737×10^3 cells/μL. Cardiac enzymes, liver function tests, blood, sputum, and urine cultures were unremarkable. Serum immunelectrophoresis showed a protein of 7.5 g/dL, with an elevated gamma fraction of 2.7 g/dL. No human immunodeficiency virus test was performed. His chest radiograph showed diffuse fibrotic changes in the left lung and a mass-like infiltrate extending from the right hilus to the lateral chest wall (Fig. 1). No miliary pattern was seen. There was an increase in the size and density of the right perihilar mass, compared to the post-treatment chest radiograph 11 months prior.

A subsequent computed tomogram of the chest (Fig. 2) during this admission revealed multiple masses: a 6-cm $\times$ 2.5-cm mass in the right upper lobe, a 1.7-cm round mass in the right upper lobe, a 4-cm round mass in the right lower lobe, a 8.5-cm $\times$ 7.5-cm mass in the right middle lobe, and 4.5-cm round mass in the left lower lobe. Air bronchograms were seen in the right-sided masses and a possible cavity was noted in one of the upper-lobe lesions. There was subcarinal lymphadenopathy.

The patient was placed in respiratory isolation and started on empirical antibiotic treatment with moxifloxacin and clindamycin, and his symptoms improved. A computed-tomography-guided transthoracic core needle biopsy of the right middle-lobe mass was performed. Acid-fast fungal and bacterial smears and subsequent cultures were negative. Hematoxylin-and-eosin-stained sections of the core needle biopsy revealed a lymphoid infiltrate composed of small lymphocytes with round to slightly irregular nuclei and scant cytoplasm. Flow cytometric analysis showed that the lymphocytes expressed B-cell antigens (CD19, CD20, CD22) with kappa light chain restriction. These cells were also negative for CD5, CD10, and CD23. The overall cellular morphology and immunophenotype were consistent with a low-grade B-cell lymphoma. Further workup revealed no lesions elsewhere, and the overall findings were believed to be compatible with a marginal zone lymphoma, in this case a BALT lymphoma.

A positron emission tomogram showed increased metabolic activity in all of the lesions, with the highest activity in the right lower and right middle lobes. Bronchoscopy was unremarkable. Bronchoalveolar lavage fluid was negative for acid-fast bacilli and fungal cultures. Cytology was negative. After the culture results, he was treated with 8 cycles of rituximab. The patient left for Chuuk, Micronesia, before his response could be assessed, and he was lost to follow-up.

Discussion

There is an established causal relationship between chronic antigenic stimulation and the development of

MALT lymphomas. Best described is the *Helicobacter pylori* infection in the pathogenesis of MALT lymphoma. Treatment of the underlying infection leads to resolution of the lymphoma.[17,18] The development of human BALT lymphoma is likewise thought to be at least partially driven by chronic inflammatory stimuli.[14] There are 2 reported cases of a chronic lung infection associated with a BALT lymphoma. In one case, infection with *Mycobacterium avium* led to bronchiectasis; BALT lymphoma was found after a diagnostic wedge resection.[15] In the second case, *Mycobacterium tuberculosis* was associated with the development of BALT lymphoma.[16] Continuous antibiotic treatment controlled the infection and resulted in a long-term suppression of the lymphoma.[15] Since *Helicobacter pylori* and *mycobacteriae* are both intracellular pathogens, they might be able to induce individual translocation more readily than other infectious agents. BALT does not occur in every patient with tuberculosis infection. The microenvironmental effects between genetic factors of the microorganism and the genetic background of the host probably play an important role.[19]

Unlike most cases of MALT lymphoma, the antibiotic treatment in our patient did not suppress the underlying lymphoma. The right middle lobe consolidation apparent on his chest radiograph at the time that tuberculosis was diagnosed worsened to a mass-like consolidation after appropriate treatment with a 4-drug regimen for tuberculosis.

Except for the recent upper respiratory infection, there was no documented coexisting pulmonary disease, and the tuberculosis infection might have been the antigenic stimulus that led to BALT lymphoma. Usually in patients with tuberculosis infection there are just clusters of unorganized B cells, but in some patients after tuberculosis infection, homeostatic chemokines participate in the formation of tertiary structures at sites of chronic inflammation.[20] Also, the T-effector lymphocyte priming to fight tuberculosis infection happens in the lung. In a susceptible host, maybe with or because of underlying diabetes or certain recent viral infections, the likelihood of developing BALT lymphoma is higher.[21,22]

An ultrasound-guided transthoracic core needle biopsy was used to make the diagnosis and to rule out tuberculosis in our patient. The biopsy showed a lymphoplasmocytic infiltrate, and flow cytometry was done, which is helpful when working with small samples or unexpected results.[23] In the pathology of the case report[16] that linked tuberculosis and BALT lymphoma, the atypical lymphoid infiltrations were found only in close proximity to the tuberculoid granulomas, and not elsewhere. The biopsy in our patient had no granulomas, and the culture for tuberculosis was negative. Subsequent bronchoscopy with bronchoalveolar lavage and transbronchial biopsies showed no evidence of BALT lymphoma, tuberculosis, or other pathology.

A positron emission tomogram was obtained. There are several limitations to imaging lymphoma with positron emission tomography. Normally, malignancies have a higher uptake of the tracer than do other conditions. However, low-grade non-Hodgkin's lymphomas usually have low uptake. And some benign etiologies, such as tuberculosis, can have a high uptake.[24] Lymphoma was known to be in the right middle lobe, and there was no evidence of active tuberculosis at that time. We thought the high uptake in the bilateral pulmonary lesions was due to the lymphoma, and therefore believed our patient had multilobar disease.

Treatment of BALT lymphoma depends on the extent of disease. Localized disease can be resected for cure. In patients with large unresectable or bilateral lesions, surgery is of no value.[25] Combination chemotherapy, radiotherapy, or immunotherapy with antibodies has been used in these patients. Two effective pharmaceutical combinations are cyclophosphamide plus doxorubicin plus vincristine plus prednisone, and cyclophosphamide plus vincristine plus prednisone.[26,27] Ahmed et al reported on the use of rituximab, a monoclonal chimeric anti-CD20 antibody, as a single-agent treatment in 2 patients with BALT lymphoma. Both patients had a partial response.[28]

In our patient, all the treatment options carried the risk of reactivating his tuberculosis. Although BALT lymphoma is generally indolent, we thought that he warranted treatment because of the multilobar disease and rapid progression over 11 months. After active tuberculosis was ruled out, rituximab was started. The patient remained clinically stable, without evidence of recurrent tuberculosis. After finishing 8 cycles of rituximab, he was lost to follow-up.

In this interesting case of BALT lymphoma associated with pulmonary tuberculosis, the tuberculosis may have precipitated the lymphoma, and the lymphoma may have facilitated miliary spread. Despite treatment of the tuberculosis, the lymphoma progressed, which is in contrast to previous reports of MALT and BALT lymphomas, in which treatment of the precipitating antigenic stimulus led to remission of the lymphoma.

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