Bilateral Pulmonary Nodules and Mediastinal Lymphadenopathy in a Patient with Sjogren's Syndrome

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ABSTRACT

Bronchus-associated lymphoid tissue is a normal component of the lung's immune system and may be analogous to gut-associated lymphoid tissue, a form of mucosa-associated lymphoid tissue. Bronchial-associated lymphoid tissue lymphoma is a distinct subgroup of low-grade B-cell extranodal non-Hodgkin lymphoma, classified as marginal-zone lymphoma. It is a rare disorder and appears with a distinct clinical and radiological presentation. We report a case of a patient with a history of Sjogren's syndrome who presented with bilateral pulmonary nodules and mediastinal lymphadenopathy, and who was diagnosed as having bronchus-associated lymphoid tissue lymphoma.

CASE PRESENTATION

A 69-year-old white woman with a history of Sjogren's syndrome and chronic dry mouth had a productive cough with whitish sputum for 1 week. She reported having very mild dyspnea on exertion but no orthopnea, no paroxysmal dyspnea, chest pain, or palpitation. She denied any hemoptysis, headache, ear pain, visual changes, or difficulty swallowing. Other than Sjogren's syndrome, she did not have any significant past medical or family history. The patient had a history of smoking (20 packs per year), but had quit about 30 years prior.

The patient looked comfortable without any acute distress. Her vital signs were within normal limits. Examination of the neck revealed diffuse bilateral enlargement of the parotid gland, with minimal tenderness on right parotid gland. Her thyroid was not enlarged. Chest examination revealed bilateral crepitations posteriorly on the base, without any wheeze. The remainder of her systemic examination, including cardiovascular, abdominal, and neurological, was normal.

Laboratory results including complete blood count, basic metabolic panel, and B-type natriuretic peptide were all within normal limits. A chest radiograph demonstrated bilateral interstitial infiltrates without any mediastinal lymphadenopathy. An echocardiogram was normal. A computed tomography (CT) scan of the chest was done to further define the infiltrate and showed bilateral subtle nodular densities, the largest in the right lower lobe measuring 2 cm x 1 cm. There were several smaller bilateral nodules measuring up to 1.1 cm in the left upper lobe (Figure 1). Subcarinal lymph node measuring 2.6 cm x 1.9 cm and bilateral hilar lymph nodes <1 cm in size were found. Bilateral patchy ground glass opacity also was seen.

Because of the history of Sjogren's syndrome, the following were considered in the differential diagnosis: underlying lymphoproliferative disorder, lymphocytic interstitial pneumonitis, vasculitis such as Wegener's granulomatosis, sarcoidosis, amyloidosis, nonspecific interstitial pneumonia, and multifocal bronchioloalveolar carcinoma. Infection was considered unlikely, since she did not have fever or purulent sputum and her white blood cell count was normal. The patient underwent video-assisted thoracic surgery with a wedge biopsy of the right lower lung, which was sent for histopathological examination.

The wedge biopsy of the lung showed extensive involvement of the parenchyma by a lymphoid proliferation of variable intensity, comprised predominantly of small lymphoid and plasma cells (Figure 2A). Apart from the presence of few Dutcher bodies, the plasma cells showed no significant cytologic atypia. The lymphoid infiltrate demonstrated bronchiolar lymphoepithelial lesions, involved walls of medium-sized blood vessels, and extended into the visceral pleura. There was no significant large lymphoid cell component. Few residual atretic non-neoplastic follicles with germinal centers were present. An immunostain for CD20 (Figure 2B) highlighted numerous ill-defined nodules of small B lym-

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phoid cells that aberrantly co-expressed CD43 but were negative for CD5, CD10, and cyclin-D1 (bcl-1). Immunostains for CD20 and cytokeratin cocktail highlighted the lymphoepithelial lesions. The CD23 immunostain, when interpreted in conjunction with the CD20 preparation, demonstrated colonization of residual follicle centers by the B cell proliferation. A CD3 immunostain decorated the background non-neoplastic small T lymphocytes. Chromogenic RNA in situ hybridization (CISH) for lambda and kappa light chains revealed a clear predominance of kappa light chain- over lambda light chain-associated RNA among the plasmacytic component, providing supportive evidence of kappa light chain restriction (Figure 2C). A Congo red stain revealed no amyloid deposition.

Based on the clinical presentation, radiologic appearance, and histologic examination, the patient was diagnosed with pulmonary extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue, with plasmacytic differentiation. The patient was treated with 6 cycles of R-CVP (rituximab, cyclophosphamide, vincristine, and prednisolone), and continues to do well 12 months after the diagnosis with no symptoms of lymphoma and no evidence of recurrence.

DISCUSSION

Mucosa-associated lymphoid tissue (MALT) is a group of lymphoid tissue scattered along mucosal linings. They protect the body from an enormous quantity and variety of antigens. The tonsils, Peyer patches within the small intestine, and the vermiform appendix are examples of MALT. The nomenclature incorporates location; therefore, MALT includes gut-associated lymphoid tissue (GALT) and bronchial mucosa-associated lymphoid tissue (BALT). Malignancies occurring in MALT are called MALT lymphomas, which are extranodal manifestations of marginal-zone lymphomas.

According to the most recent World Health Organization and Revised European-American Classification of lymphoid neoplasms classification[1,2] marginal zone lymphomas are B-cell non-Hodgkin lymphomas and encompass 3 distinctive subtypes of nodal, primary splenic, and extranodal lymphoma of MALT-type. MALT lymphomas are distinguished from nodal and splenic forms by their different clinical behaviour and cytogenetic characteristics. MALT lymphoma may arise from different anatomical sites including the stomach, skin, conjunctiva, orbit, salivary glands, thyroid, and lung,[3] with the stomach most commonly affected.[4] Lung involvement (BALT) is rare, accounting for less than 1% of all lymphomas.[5] BALT lymphoma includes two-thirds of all the primary non-Hodgkin lymphoma of the lungs.[5]

As the most frequent site of MALT lymphoma, the stomach serves as a model for pulmonary MALT lymphoma. MALT is absent from the lung in normal physiological circumstances. During chronic antigenic stimulation (eg, by *Helicobacter pylori*), MALT can increase in the stomach and undergo secondary lymphomatous transformation arising from marginal zone B-cells. In order to develop, the malignant B-cell clone requires the presence of T-cells specifically directed against *H pylori* antigens. Thus, *H pylori* eradication can lead to complete remission of gastric lymphoma.[6] So far no triggering antigens have been identified in the lung, but chronic antigenic stimulation in certain autoimmune disorders (eg, sarcoidosis, systemic lupus erythematous, rheumatoid arthritis, multiple sclerosis, Hashimoto's thyroiditis, and particularly Sjogren's syndrome) are considered to affect the onset of pulmonary MALT lymphoma.[6,7]

Most patients with BALT lymphoma are asymptomatic, and pulmonary lesions are incidentally discovered on a chest radio-

Figure 1. Computed Tomography Scan of the Chest Showing Bilateral Subtle Nodular Densities

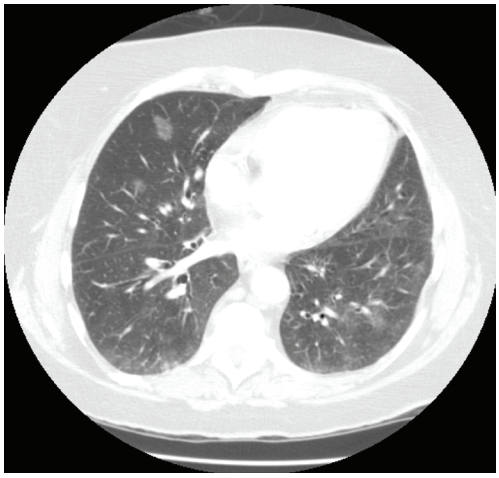
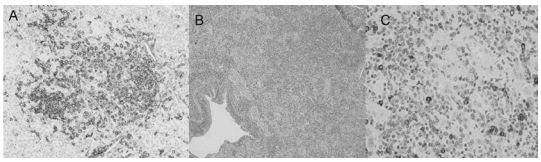


Figure 2. Wedge Biopsy of Lung



(A) A dense interstitial lymphoplasmacytic infiltrate occupies the pulmonary parenchyma and involves a bronchiole (hematoxylin and eosin, low magnification). (B) An immunostain for CD20 highlights nodules of B lymphoid cells (intermediate magnification). (C) RNA chromogenic in-situ hybridization (CISH) for kappa (red chromogen) and lambda (brown chromogen) light chains reveals a clear predominance of kappa light chain over lambda light chain-associated RNA among the plasmacytic cells, providing supportive evidence of kappa light chain restriction (intermediate magnification).

graph done for an unrelated cause. Cough, dyspnea, and chest pain are the most common symptoms, with less than a quarter of patients having B symptoms (fever, night sweats, sweating).[5] Approximately two-thirds of patients are smokers. Crackles on chest auscultation are present in about one-third of patients.[5] The various patterns of pulmonary involvement are nodules, single or multiple localized areas of consolidation usually with an accompanying air bronchogram, peribronchial infiltrates, and reticulation, with one-third of patients presenting with bilateral ground glass opacities.[8]

Diagnosis is definitively made through histopathologic examination. Tissue from the lungs can be obtained by transbronchial biopsy, CT-guided biopsy, video-assisted or open thoracotomy. When histopathological examination with immunohistochemistry and CISH is not sufficient for diagnosis, immunoglobin heavy-chain gene rearrangement molecular studies are helpful in confirming the diagnosis of BALT lymphoma.[5] If the patient has involvement of mediastinal or hilar lymph nodes, biopsy can be done through mediastinoscopy, which can help with tissue diagnosis. Involvement of mediastinal/hilar lymph nodes are associated with poor overall prognosis.[9]

The treatment of BALT lymphoma includes the use of different chemotherapeutic agents for diffuse disease and surgery or radiation therapy for localized disease.[5] One-third of patients with non-gastrointestinal MALT lymphomas are found to have gastric involvement, and gastrointestinal surveillance is warranted in these patients.[10] BALT lymphomas usually have an indolent course, and the outcome has been generally favorable in most series, with a 5-year survival rate of >80% and a median survival time of >10 years.[11]

Surgery, chemotherapy, and radiation therapy, alone or in combination, are the options for the treatment of BALT lymphoma. The optimal management and use of these modalities have not been determined. The choice of therapy depends on the stage of the disease. Localized disease can be treated with surgery and radiation therapy, whereas disseminated disease requires chemotherapy. Oh et al[9] conducted a retrospective analysis of 61 biopsy-proven BALT lymphoma patients over a 17-year period (1991 – 2008) who were treated with different modalities. Those with localized disease were treated with surgery, radiation therapy, or chemotherapy, with some patients receiving adjuvant chemotherapy after surgery. Patients with disseminated disease were treated with chemotherapy. The overall survival and time to progression were noted. The chemotherapeutic agents used were R-CVP (rituximab, cyclophosphamide, vincristine, prednisolone), R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), or FND (fludarabine, mitoxantrone, dexamethasone). A total of 56 out of 61 patients were treated; 22 patients had surgery with or without chemotherapy and radiation therapy; 28 patients had chemotherapy alone; and 6 patients had radiotherapy. The total time of progression and overall survival did not differ between these groups. They concluded that no treatment was superior to another, and that chemotherapy should be considered as a first-line option to preserve lung function.

CONCLUSION

BALT lymphoma is a rare disease with a nonspecific presentation and diverse radiological appearance on chest radiography. It should be considered in the differential diagnosis in a patient with bilateral pulmonary nodules and ground glass opacity, particularly with underlying Sjogren's syndrome.

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