

Extranodal Marginal Zone B-Cell Lymphoma of Mucosa Associated Lymphoid Tissue Presenting as Multiple Pulmonary Lesions: Case Report and Review of the Literature

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Abstract: We report a case of extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT) that presented as multiple pulmonary nodules and masses. Lung lesions were found incidentally on a chest radiograph in an asymptomatic patient. Abdominal CT scan was obtained that showed asymmetric gastric mucosal thickening. Biopsy of lung masses and gastric mucosa confirmed the diagnosis of MALT lymphoma. The subject of MALT lymphoma is reviewed.

Keywords: Pulmonary nodule, lymphoma, MALT lymphoma, BALT lymphoma.

INTRODUCTION

Mucosa associated lymphoid tissue (MALT) lymphoma of lung is a rare condition, accounting for less than one percent of all lymphomas [1]. This type of lymphoma should be considered in the differential diagnosis of multiple lung nodules. MALT lymphoma usually has an indolent course [1]; while the disease may involve multiple sites, even bone marrow involvement is not a predictor of poor survival [2]. The diagnosis is difficult to confirm as a result of the subtle changes on biopsy as well as the similarity of histologic findings to non-malignant MALT. Most patients require multiple biopsies [3]. In our case, immunoglobulin heavy chain gene rearrangement molecular studies confirmed the monoclonal nature of the lesions. Routine evaluation of the stomach is necessary due to the high incidence of gastric mucosal involvement in patients that present with MALT lymphoma of the lung. Treatment options include surgery, chemotherapy alone, rituximab alone, or a combination of all of these modalities.

CASE REPORT

A 58-year-old woman presented to the emergency department (ED) with a seafood allergy manifesting as skin erythema and facial swelling. On initial evaluation in the ED a chest radiograph was obtained that showed multiple pulmonary masses and nodules. She denied any pulmonary or systemic symptoms; including fevers, night sweats, weight loss, cough, dyspnea, hemoptysis, or chest pain.

The patient's medical history was significant for diet-controlled hypercholesterolemia. She denied ever smoking. She

had lived in Hawaii before moving to Pennsylvania. However, the patient traveled to Far East Asia and Italy 3 months prior to presentation.

On physical examination, the patient appeared well, in no distress with normal vital signs and no fever. Thyromegaly without discrete nodules was detected on palpation. There was no palpable cervical, supraclavicular, axillary, or inguinal lymphadenopathy. Thorough examination of the chest, heart, and abdomen did not reveal any abnormal findings. Her skin was free of lesions except the facial swelling and erythema noted on the initial evaluation. Neurologic examination also was normal.

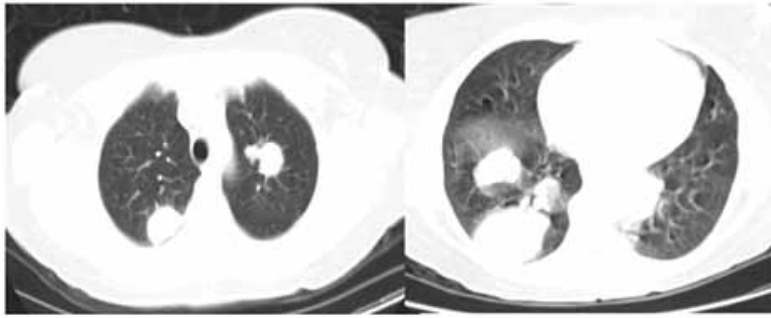
White blood cell count was $16.8 \times 10^3/L$; hemoglobin, platelet, blood chemistry, and serum lactic dehydrogenase were all normal. A computed tomography (CT) scan of the chest showed multiple bilateral pulmonary nodules; mediastinal lymphadenopathy and pleural effusion were not seen (Fig. 1a). A CT scan of the abdomen revealed asymmetric thickening of the gastric mucosa (Fig. 1b).

CT guided transthoracic core biopsy of a right lower lobe lesion was performed. In order to evaluate the gastric mucosal abnormalities seen on the abdominal CT scan, gastroscopy was performed and mucosal biopsies were obtained. Histopathologic examination of the gastric biopsy revealed a sheet-like proliferation of small lymphocytes that extended in to the lamina propria (Fig. 2a). There was focal plasma cell differentiation within the infiltrate but no recognizable nodal architecture. Multiple lymphoepithelial lesions were identified, with distortion and eosinophilic transformation of the glandular epithelium (Fig. 2b). Gastric biopsy was negative for *Helicobacter pylori* infection. The lung biopsy showed a similar infiltration of lymphocytes with abundant pale cytoplasm and inconspicuous nucleoli (Figs. 2c,d).

The morphologic appearance of the cells in the gastric and lung biopsies was consistent with extranodal marginal

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A.



B.



Fig. (1). A) CAT scan of chest demonstrates bilateral pulmonary lesions. B) Note greater curvature mucosal thickening (arrow).

zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT). The diagnosis of MALT lymphoma was confirmed by immunohistochemical staining and molecular studies for immunoglobulin heavy chain rearrangement established clonality. The MALT lymphoma that involves bronchial associated lymphoid tissue (BALT) is called BALT lymphoma. For staging purposes, a bone marrow biopsy was performed that showed small aggregates of CD20 positive lymphocytes involving her bone marrow. These lymphocytes had an immunophenotype similar to those seen in the gastric and lung biopsies. The immunohistologic findings and molecular study results are summarized in Table 1.

DISCUSSION

Marginal zone lymphoma (MZL) is defined in the Revised European-American Classification of lymphoid neoplasms [4] and World Health Organization classification [5] as B-cell non-Hodgkin's lymphoma (NHL) and encompasses the three distinctive subtypes of nodal, primary splenic, and extranodal lymphomas of MALT type.

Extranodal lymphoma of MALT type was first described in 1983 and represents 5 to 8 percent of non-Hodgkin's lymphomas [6, 7]. These lymphomas arise from different anatomical sites including stomach, skin, conjunctiva, orbit, salivary glands, thyroid, lung, breast, liver, bowel, urinary tract, lung [6, 8], adrenal [9], trachea [10], gallbladder [11], and esophagus [12]. Stomach involvement is seen in 50% of MALT lymphomas [7] and multiple mucosal involvements have been reported in 13% of cases [8]. MALT lymphoma of lung or extranodal MLZ of bronchial associated lymphoid tissue (BALT) is rare and accounts for less than 1% of all lymphomas [3]. Although BALT lymphoma is rare, it includes two-thirds of primary NHLs of lung [3].

MALT lymphomas are composed of tumor cells that may resemble small lymphocytes, germinal center centrocytes, or monocytoid cells [6]. The percentage of blasts is usually less than 10% [8]. Lymphoepithelial lesions, formed by invasion of individual glands by lymphoma cells, are characteristic of MALT lymphoma. MALT lymphoma cells express B-cell-associated antigens (CD19, CD20, CD22) and are usually negative for CD5 and CD10. MALT lymphoma B-cells are closely related to post-germinal center stage of B-cell development and their IgH variable region gene sequence shows a high degree of somatic mutation as well as and intraclo-

variation [6]. Studies of gastric and salivary gland MALT lymphomas have shown immunoglobulin heavy chain variable regions that are often found in autoantibodies [13]. These findings are consistent with observations that MALT lymphomas are commonly seen in autoimmune disorders [6]. The most common numerical cytogenetic abnormality in MALT lymphoma is trisomy 3 (60%), and the most commonly reported structural abnormality is [11,18] (q21; q21) [6].

Most of the patients with BALT lymphoma present between the ages of 20 and 80 years with a median age of 61 years. Almost one-third of the patients, like our patient, are asymptomatic and pulmonary lesions are discovered incidentally on chest radiograph obtained for unrelated reasons [3]. Pulmonary symptoms include cough that could be productive (36%), dyspnea (18%), and chest pain (9%). B symptoms (weight loss and night sweats) are not common in BALT lymphoma and have been reported in only 14% of cases [3]. In one case series 68% of the patients with BALT lymphoma were smokers. Crackles on lung auscultation can be found in less than one-third of the patients [3]. Lymph node involvement has been reported in 21% of the patients with non-gastric MZL of MALT type. Anemia and elevated lactate dehydrogenase are also an uncommon laboratory finding. About 12 to 18% of the patients with MALT lymphoma have a history of immune disorders or chronic inflammatory processes [3, 8]. Associated diseases include common variable immune deficiency [3], rheumatoid arthritis [9, 14], polymyositis [9], Sjögren's syndrome [9], mixed connective tissue disorder [9], and sarcoidosis [9, 15].

Pulmonary lesions on chest CT may be unilateral or bilateral. Although BALT lymphoma can present as a solitary lesion, it more often appears as multiple pulmonary lesions. Lesions can appear as nodules, consolidations, or linear opacities [1]. Attenuation of lesions varies from 40 to 60 Hounsfield units (HU) on non-enhanced CT of chest but they enhance homogeneously by contrast material [16]. BALT lymphoma lesions are usually centered on airways (bronchocentric) and are mostly peripheral [1]. Peribronchovascular interstitial thickening and ground-glass opacities are also described in 30% of the patients with BALT lymphoma [1].

Diagnosis of BALT lymphoma can be challenging. In one study 42% of the patients with BALT lymphoma had a

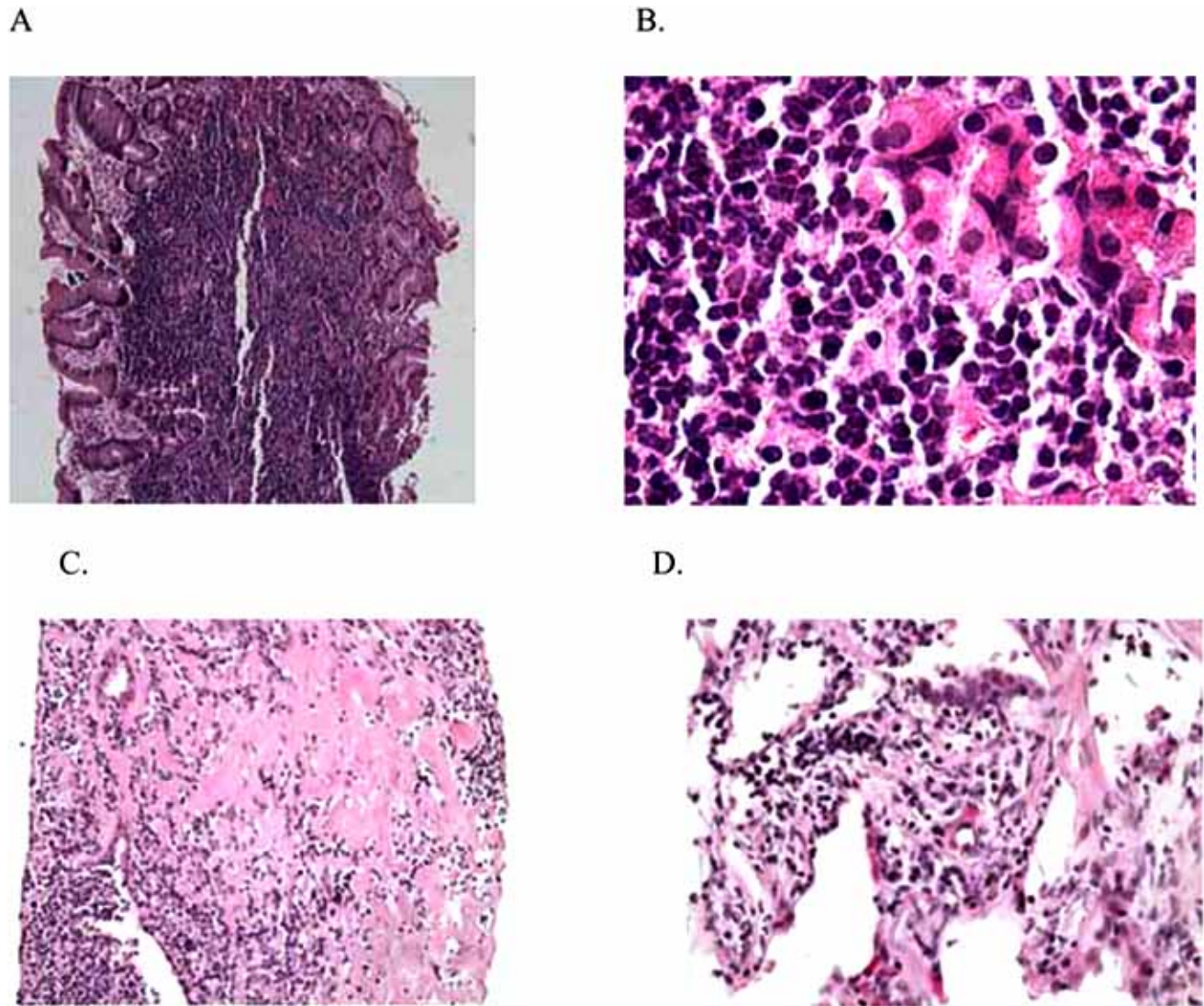


Fig. (2). **A)** The gastric biopsy showed a sheet-like proliferation of lymphoid cells with extension in to the lamina propria (H&E, 100X). **B)** A lymphoepithelial lesion within the gastric biopsy. There is distortion and eosinophilic transformation of the glandular epithelium (H&E, 400X). **C)** The core biopsy of a lung lesion showed a lymphocytic infiltrate (H&E, 40X). **D)** The cells have pale cytoplasm and inconspicuous nucleoli (H&E, 100X).

history of previous biopsies before confirming the definitive diagnosis. In the same study the diagnosis of BALT lymphoma was obtained after a delay of 5 to 36 months [3]. Although histopathologic findings alone could be suggestive of BALT lymphoma, they are usually insufficient to differentiate benign BALT tissue from BALT lymphoma. Immunoglobulin heavy chain gene rearrangement molecular studies are particularly helpful in confirming the diagnosis of BALT lymphoma by establishing clonality. Transbronchial biopsy, CT guided biopsy, video assisted thoracic surgery (VATS) procedure, or thoracotomy has been used to obtain lung tissue for diagnosis [3]. Gastric involvement has been found in 33% of the patients presenting with non-gastrointestinal (GI) MALT lymphoma at the time of initial evaluation [17]. In our case, the patient had abnormal gastric findings on an abdominal CT scan and gastric biopsy showed involvement of the gastric mucosa. These findings suggest that evaluation

of the stomach should be a part of the initial workup of non-GI MALT lymphomas including BALT lymphomas.

The optimum management of BALT lymphoma has not been clearly established. Different chemotherapeutic regimens, with or without rituximab, have been described to achieve complete remission in BALT lymphoma. These regimens are as follows: CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) [3], MCP (mitoxantrone, chlorambucil, prednisone) [18], CVP (cyclophosphamide, vincristine, prednisone) [3], Rituximab [3], RCD (rituximab, cyclophosphamide, dexamethasone) [3], and RF (rituximab and fludarabine) [3]. Surgery and radiation therapy can be considered for treatment of localized disease. Patients with bone marrow or lymph node involvement have the worse prognosis. Nevertheless these patients 5 to 10 year survival is as high as 75% [8]. Because BALT lymphoma is not an aggressive lymphoma and the majority of patients are

asymptomatic, the “wait and see” policy is a reasonable approach in patients that are not good candidates for surgery, radiotherapy, or chemotherapy.

Table 1. Immunologic and Histochemical Findings

Biopsy Site	Results	
Gastric mucosa	CD20	Positive
	CD3	Negative
	CD10	Negative
	CD23	Negative
	CD5	Negative
	IgH gene rearrangement	Positive
Right lower lobe	CD20	Positive
	CD3	Positive
	IgH gene rearrangement	Positive
Bone marrow	CD20	Positive
	CD10	Negative
	CD23	Negative
	IgH gene rearrangement	Positive

CONCLUSION

Extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue can present as multiple pulmonary lesions and should be considered in the differential diagnosis of these findings. Pulmonary and B symptoms are not common. Immunoglobulin heavy chain gene rearrangement molecular studies are particularly helpful to establish the diagnosis. We recommend routine evaluation of the stomach due to the high incidence of gastric mucosal involvement in non-GI MALT lymphoma. Poor prognostic factors include bone marrow and lymph node involvement. Treatment options should be tailored to the patient characteristics, side effect profile, and extent of the disease.

REFERENCES

[1] Wislez M, Cadranel J, Antoine M, *et al.* Lymphoma of pulmonary mucosa-associated lymphoid tissue: CT scan findings and pathological correlations. *Eur Respir J* 1999; 14: 423-429.

[2] Thieblemont C, Berger F, Dumontet C, *et al.* Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. *Blood* 2000; 95: 802-806.

[3] Ahmed S, Kussick SJ, Siddiqui AK, *et al.* Bronchial-associated lymphoid tissue lymphoma: a clinical study of a rare disease. *Eur J Cancer* 2004; 40: 1320-1326.

[4] Harris NL, Jaffe ES, Stein H, *et al.* A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994; 84: 1361-1392.

[5] Harris NL, Jaffe ES, Diebold J, *et al.* World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia 1997. *J Clin Oncol* 1999; 17: 3835-3849.

[6] Cavalli F, Isaacson PG, Gascoyne RD, Zucca E. MALT Lymphomas. *Hematology* 2001; 241-258.

[7] Armitage J, Weisenburger D. New approach to classifying non-Hodgkin's lymphomas: Clinical features of the major histologic subtypes. *J Clin Oncol* 1998; 16: 2780-2795.

[8] Zucca E, Conconi A, Pedrinis E, *et al.* Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. *Blood* 2003; 101: 2489-2495.

[9] Nicholson AG, Wotherspoon AC, Jones AL, *et al.* Pulmonary B-cell non-Hodgkin's lymphoma associated with autoimmune disorders: a clinicopathological review of six cases. *Eur Respir J* 1996; 9: 2022-2025.

[10] Okubo K, Miyamoto N, Komaki C. Primary mucosa-associated lymphoid tissue (MALT) lymphoma of the trachea: a case of surgical resection and long-term survival. *Thorax* 2005; 60: 82-83.

[11] Shim CS, Raymond L, *et al.* Primary mucosa-associated lymphoid tissue lymphoma of the gallbladder. *Am J Med* 2002; 112: 505-506.

[12] Shim CS, Lee JS, Kim JO, *et al.* A case of primary esophageal B-cell lymphoma of MALT type, presenting as a submucosal tumor. *J Korean Med Sci* 2003; 18: 120-124.

[13] Yumoto KK, Furukawa M, Kuriyama T, Mikata A. Low-Grade Pulmonary Mucosa-associated Lymphoid Tissue Lymphoma with or without Intraclonal Variation. *Am J Respir Crit Care Med* 1998; 158: 1613-1619.

[14] Douglas KM, Raza K, Stevens R, *et al.* Bronchial MALT lymphoma in longstanding rheumatoid arthritis. *Rheumatology (Oxford)* 2005; 44: 687-689.

[15] Sharma OP. Sarcoidosis and B-cell MALT lymphoma. *Sarcoidosis Vasc Diffuse Lung Dis* 2002; 19: 235.

[16] Takamori M, Noma S, Kobashi Y, *et al.* CT findings of BALT OMA. *Radiat Med* 1999; 17: 349-354.

[17] Dabaja BS, Ha CS, Wilder RB, *et al.* Importance of esophagogastroduodenoscopy in the evaluation of non-gastrointestinal mucosa-associated lymphoid tissue lymphoma. *Cancer J* 2003; 9: 321-324.

[18] Wöhrer J, Drach M, Hejna W, *et al.* Treatment of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) with mitoxantrone, chlorambucil and prednisone (MCP). *Ann Oncol* 2003; 14: 1758-1761.