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Case Report

Primary pulmonary extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type: a case report and literature review

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Abstract: Primary pulmonary mucosa-associated lymphoid tissue (MALT)-derived lymphoma is a low-grade B-cell non-Hodgkin's lymphoma. It is rare with unclear clinical and imaging findings, requiring biopsy or surgery for diagnosis. Here, we provide a new case to learn the symptoms, diagnosis and treatment of primary pulmonary MALT lymphoma. The patient was a 51-year-old male. During the annual physical examination in 2019, a shadow in the lower lobe of the right lung was accidentally found in his chest computed tomography image. In 2020, the size and density of the shadows increased, which was suspected to be lung adenocarcinoma. The patient underwent video-assisted thoracoscopic surgery and segmental resection. Pathological examination showed residual germinal centers around the tumor cells, and many inflammatory cells had diffusely infiltrated, mainly monocyte-like B cells. Immunohistochemical analysis showed that CD3, CD20, Bcl-2, CD43, CK-pan and CD23 were positive, while BCL-6, CD5, CD10, c-myc and cyclin D1 were negative. The patient was diagnosed with MALT extranodal marginal zone B-cell lymphoma. The patient did not receive chemotherapy or radiotherapy after the operation but was still under close observation. Primary pulmonary MALT develops slowly and tends to be inert and spontaneous. Due to the lack of specific clinical symptoms and imaging findings, it can easily be misdiagnosed as tuberculosis, lung cancer, or infection. Thoracoscopic resection may be a good choice for the diagnosis and treatment.

Keywords: Extranodal marginal zone lymphoma, mucosa-associated lymphoid tissue, thoracoscopic resection

Introduction

Isaacson and Wright first proposed mucosa-associated lymphoid tissue (MALT) lymphoma in 1983 [1]. It is a low-grade malignant non-Hodgkin lymphoma characterized by a homogenous B-cell population in MALT [2]. MALT lymphoma is a relatively rare disease, and the most common site is gastrointestinal, but it can also develop in many different organs, including the salivary gland, orbit, thyroid gland and lung, etc. [3].

Primary pulmonary MALT lymphoma is a sporadic disease, representing 0.5% of all primary lung cancer [4], and patients often have nonspecific symptoms. Its clinical cause is unclear, and there is no consensus on the best approach for its management. Herein, we describe a case of surgically resected primary pulmonary MALT lymphoma and discuss our experience of treatment [5]. Pulmonary MALT lymphoma is a low-grade B-cell lymphoma originating from mucous tissue with a median age of 60 [6]. Its incidence has been increasing recently, possibly related to chronic infection and autoimmune disorders [7]. It has been reported that 30% of patients with lung MALT lymphoma are complicated with connective tissue diseases, such as systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, hepatitis C and acquired immune deficiency syndrome [8]. Nearly 50% of patients are asymptomatic at the time of visit. Usually, physical examination finds chest abnormalities and suggests further diagnosis [9]. Some patients may have cough, dyspnea, chest pain and hemoptysis, etc. The primary symptoms are fever and decreased body mass, and the

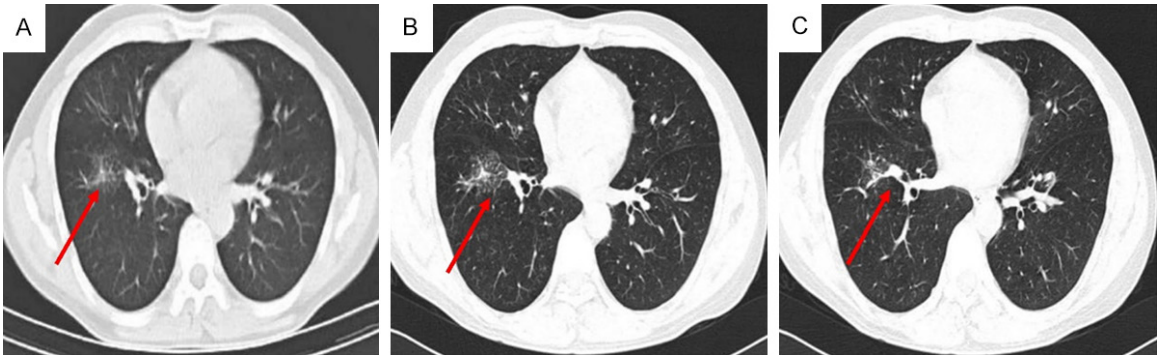

Figure 1. Chest computed tomography. A: The patchy low-density shadow in the right inferior lobe was found in 2019. B: The patchy shadow was increase in size and density in 2020. C: Air bronchogram was found in the shadow in 2020.

clinical manifestations are related to the lesion site and the scope of invasion [10].

The gold standard for diagnosing MALT lymphoma is histopathology of biopsy specimens, usually obtained by computed tomography (CT)-guided percutaneous lung puncture or tracheoscopy. Bronchoalveolar lavage (BAL) usually shows average cell count, and lymphocytic alveolitis occurs in about 60% of cases [11]. Therefore, clonal type and phenotype analysis of alveolar lymphocytes are helpful for MALT diagnosis, but BAL test is not commonly used in clinical practice.

Case presentation

Informed consent was provided by the patient. A 51-year-old male non-smoker was found to have a patchy low-density shadow in the right inferior lobe of the lung, which was identified incidentally by chest CT during an annual physical examination in 2019 (**Figure 1A**). In 2020, the shadow was found to increase in size and density, which was suspected to be lung adenocarcinoma. The patient was referred to our hospital for further evaluation. On admission, the patient reported no symptoms and nor any discomforts. He underwent regularly physical examination and had no significant medical history or family history.

He had a neutrophil to lymphocyte ratio of 2.65, AFP of 5.0±0.5 ng/ml, CA199 of 11.23±2.2 U/ml and CA125 of 11.2±2.5 U/ml. No hepatitis B virus, hepatitis C virus, syphilis helicoid or human immunodeficiency virus infection was found. The patient underwent a thoracic CT, which identified a patchy mid-density shadow near the oblique fissure of the right inferior lobe (2.8×3 cm), and an air bronchogram was also evident (**Figure 1B** and **1C**).

According to the results of the imaging examinations and clinical features, we suspected the mass was a lung adenocarcinoma. A biopsy was not performed due to potential needle metastasis and blooding risk. The patient consented to undergo a video-assisted thoracoscopic surgery with segment resection (S7+8) of the right inferior lobe, including the mass. The gross feature of the surgical specimen was a pale-gray, 2.8 cm nodular mass (**Figure 2**). Microscopic examination of the resected tissue revealed residual germinal centers around the tumor cells and a large number of inflammatory cells diffusely infiltrated, mainly monocyte-like B cells. Immunohistochemistry analysis showed that the lymphocytes were positive for CD3, CD20, BCL-2, CD43, CK-pan and CD23 but negative for Bcl-6, CD5, CD10, C-myc and cyclin D1 (**Figure 3** and **Table 1**). Based on the above-mentioned pathological findings, the patient was diagnosed as extranodal marginal zone B-cell lymphoma of MALT. The patient did not receive chemotherapy or radiotherapy after surgery, but he was kept under close observation because of the potential progression of the MALT. As of when writing this report, the patient has remained well during the three months of follow-up after surgery.

Discussion

MALT lymphoma is generally associated with chronic antigen stimulation, including microbial

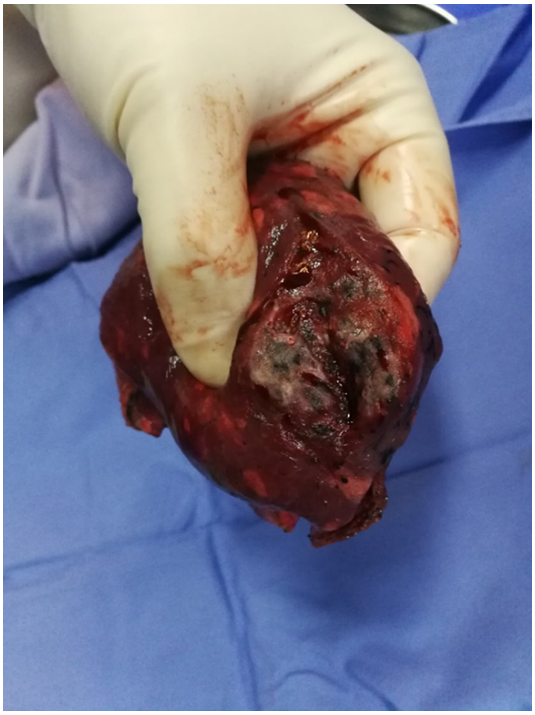

Figure 2. Gross appearance showed the cut surface of the tumor with a pale-gray pattern.

antigens and auto-antigens [12]. There are certain relationships between antigens and MALT lymphomas, such as gastric MALT lymphoma with H pylori-associated chronic gastritis [13], thyroid MALT lymphoma with Hashimoto disease [14], small intestine MALT lymphoma with Campylobacter jejuna infection, and thymic MALT lymphoma with Sjögren's syndrome. Thus, a plausible hypothesis is that causative antigens can stimulate the development of pulmonary MALT lymphoma [15]. To date, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis and Sjögren's syndrome are considered risk factors for developing pulmonary MALT lymphoma [16]. These suggest that antigens might also contribute to developing pulmonary MALT lymphoma. However, the etiology of pulmonary MALT lymphomas has not yet been clearly identified, and more evidence is required.

Pulmonary MALT lymphoma usually occurs at 50-60 years of age, but there are also a few patients younger than 30 years old. Most studies have shown no difference in the incidence between men and women, and few studies have shown that it attacks more men are than women [17]. As the development of pulmonary MALT lymphoma was slow and insidious, symptoms and signs were unspecific. Approximately 30-50% of patients were asymptomatic at diagnosis [4]. Patients with symptoms usually show nonspecific respiratory symptoms, such as cough, dyspnea, expectoration and chest pain [18]. Hemoptysis, fever and weight loss were observed in those with aggressive disease forms [19], which were difficult to distinguish from pulmonary inflammation, lung cancer and tuberculosis.

On radiological examination, pulmonary MALT lymphomas typically manifest as multiple or solitary distributions of lesions, including consolidation with air bronchograms, nodules, mass, GGO and diffuse interstitial lung disease patterns [20]. Hilar and mediastinal lymphadenopathy is present in 30% of the patients [21]. The above imaging findings were unspecific. Due to nonspecific clinical features, biomarkers and imaging findings, this lesion is easily misdiagnosed with tuberculosis, lung cancer and infection. Pathology is the only method to diagnose primary pulmonary MALT lymphoma. Therefore, obtaining a specimen for diagnosis is essential during a bronchoscopy, a needle biopsy or a thoracotomy. Our patient's CT imaging showed a patchy low-density shadow with an air bronchogram. After monitoring by repeated CT imaging, we interpreted the results as suspected lung adenocarcinoma. However, pathological findings in our case revealed pulmonary extranodal marginal zone B-cell lymphoma of MALT.

Currently, no standard therapeutic strategies or guidelines for pulmonary MALT lymphoma have been estimated because of the small number of patients worldwide. Based on the clinical stage, histology and performance status [22], surgery, chemotherapy, immunotherapy, radiotherapy or a combination had been commonly used. Since it is challenging to diagnose accurately without pathology, thoracoscopic resection is probably the best choice for both diagnosis and therapy. Radiotherapy is considered in patients with limited lesions and contraindications [23]. Because the disease has indolent characteristics, develops slowly and tends to be invasive and spontaneous, clinical observation has been emphasized for asymptomatic patients [24]. Some studies have reported that asymptomatic patients

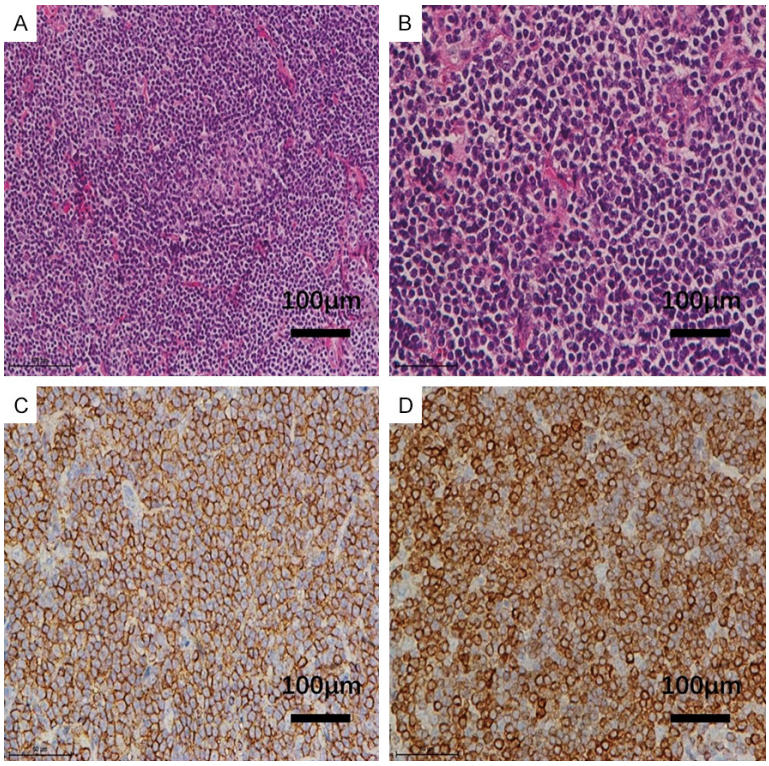

Figure 3. Characteristics of histological examination. A: Pathological findings revealed that there were residual germinal centers around the tumor cells. B: The lesion was infiltration with small lymphocytes infiltration, mainly monocyte-like B cells. C: Tumor cells were positive for CD20 expression. D: Tumor cells were positive for BCL-2 expression (×100).

Table 1. Antigen expression in patients with different subtypes (%)

Antigen	T lymphocyte type	B lymphocyte type
CD20	9	57.85
BCL-2	13	60.88

obtain complete remission by enhancing self-immunity [25]. If the related symptoms or lesions of the patients developed during the clinical observation, intervention should be implemented immediately. For bilateral or extra-pulmonary lesions, recurrence or progression, chemotherapy has been recommended [26]. CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone) is widely used as a first-line protocol in clinical practice [5]. Anti-CD20 monoclonal antibody (rituximab) effectively treats MALT lymphoma and can produce a 50 to 70% remission rate regardless of the disease location [27]. In our patient, we performed thoracoscopic segment resection for both diagnosis and therapy. Instead of chemotherapy or immunotherapy after surgery, we are following up continuously. The prognosis of patients with primary pulmonary MALT lymphoma is good, with a median survival time of over 10 years.

Conclusions

We reported a case of pulmonary extranodal marginal zone B-cell lymphoma of MALT, which is a rare and indolent disease. Clinical manifestations and imaging findings were unspecific. Diagnosis depends are pathology and immunohistochemistry. Therapeutic strategies include surgery, chemotherapy, immunotherapy, radiotherapy and clinical observation. Thoracoscopic resection is probably the best choice for both diagnosis and therapy.

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Disclosure of conflict of interest

None.

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References

[1] Cohen D, Perry C, Hazut-Krauthammer S, Kesler M, Herishanu Y, Luttwak E, Even-Sapir E and Avivi I. Is there a role for [(18)F]FDG PET-CT in staging MALT lymphoma? Cancers (Basel) 2022; 14: 750.

[2] Hu M, Gu W, Chen S, Mei J and Wang W. Clinical analysis of 50 cases of primary pulmonary lymphoma: a retrospective study and literature review. Technol Cancer Res Treat 2022; 21: 15330338221075529.

[3] Horino T, Inotani S, Takamatsu K, Ohnishi H, Komori M and Terada Y. Bronchus-associated lymphoid tissue (BALT) lymphoma and autoimmune disease. QJM 2022; 115: 405-407.
[4] Shen H and Zhou Y. Clinical features and surgical treatment of primary pulmonary lymphoma: a retrospective study. Front Oncol 2022; 12: 779395.
[5] Lin H, Zhou K, Peng Z, Liang L, Cao J and Mei J. Surgery and chemotherapy cannot improve the survival of patients with early-stage mucosa-associated lymphoid tissue derived primary pulmonary lymphoma. Front Oncol 2022; 12: 965727.
[6] Owari M, Harada-Shirado K, Togawa R, Fukatsu M, Sato Y, Fukuchi K, Endo M, Takahashi H, Kimura S, Osaki T, Souri M, Ichinose A, Shibata Y, Hashimoto Y and Ikezoe T. Acquired von willebrand syndrome in a patient with multiple comorbidities, including MALT lymphoma with IgA monoclonal gammopathy and hyperviscosity syndrome. Intern Med 2022; [Epub ahead of print].
[7] Peng Y, Qi W, Luo Z, Zeng Q, Huang Y, Wang Y, Sharma A, Schmidt-Wolf IGH and Liao F. Role of 18F-FDG PET/CT in patients affected by pulmonary primary lymphoma. Front Oncol 2022; 12: 973109.
[8] Sheng A, Zhou P, Ye Y, Sun K and Yang Z. Diagnostic efficacy of CT radiomic features in pulmonary invasive mucinous adenocarcinoma. Scanning 2022; 2022: 5314225.
[9] Souza LVS, Souza AS Jr and Marchiori E. Bronchial and tracheal mucosa-associated lymphoid tissue lymphoma. Arch Bronconeumol 2021; 57: 767.
[10] Xie X, Dong M, Zhang L, Ding D, Huang X, Shen W and Zhou Z. With the increasing health awareness: clinical and computed tomography findings in primary pulmonary mucosa-associated lymphoid tissue lymphoma lymphoma. J Comput Assist Tomogr 2022; 46: 894-899.
[11] He H, Tan F, Xue Q, Liu L, Peng Y, Bai G, Zhang M and Gao S. Clinicopathological characteristics and prognostic factors of primary pulmonary lymphoma. J Thorac Dis 2021; 13: 1106-1117.
[12] Karki NR, McElhone P, Savage N and Abdel Karim N. Diagnosis and management of cold agglutinin disease associated with low-grade B-cell lymphoma in a patient receiving pembrolizumab for lung cancer. BMJ Case Rep 2021; 14: e243751.
[13] Kido T, Ishimoto H, Ishii H, Hara K, Ozasa M, Kawabata H, Kawanami T, Suzuki Y, Yoshikawa H, Hara A, Sakamoto N, Matsumoto N, Yoshii C, Fukuoka J, Fujita M, Nakazato M, Kadota J, Mukae H and Yatera K. Combined detection of lymphocyte clonality and MALT1 translocations in bronchoalveolar lavage fluid for diagnosing pulmonary lymphomas. Sci Rep 2021; 11: 23430.
[14] Nasrullah A, Gordon A, Javed A, Tariq U, Raja A and Alhajhusain A. Maltoma veiled in the lung-a rare case of pulmonary and gastric maltoma. Respir Med Case Rep 2021; 33: 101403.
[15] Perlepe G, Kotsiou OS, Karetsi E, Papadopoulos D, Ioannou M and Gourgoulianis KI. Persistent consolidation: a MALT-easer. Thorax 2021; 76: 1057-1059.
[16] Singh M, Nain G, Jain S, Singh S and Malhotra V. Fine needle aspiration cytology of primary thyroid non-Hodgkins lymphoma: experience from a tertiary care center of North India. J Cancer Res Ther 2022; 18: 185-189.
[17] Roy AM, Venkata AN and Yadala S. A 44-year-old woman with a 10-year history of dyspnea and pulmonary nodules. Chest 2021; 159: e247-e250.
[18] Shiraishi K, Akiyama S, Tohyama M and Sayama K. Lichen myxedematosus associated with pulmonary mucosa-associated lymphoid tissue lymphoma. J Dermatol 2022; 49: e46-e47.
[19] Kelemen K, Rimsza LM and Craig FE. Primary pulmonary B-cell lymphoma. Semin Diagn Pathol 2020; 37: 259-267.
[20] Zhou H, Yang Z and Wu S. Primary pulmonary mucosa-associated lymphoid tissue lymphoma with radiological presentation of middle lobe syndrome diagnosed by bronchoscopy: a case report. Hong Kong Med J 2022; 28: 263-266.
[21] Tanahashi H, Yamaguchi K, Koura T, Kambara T, Yamada K, Sakamoto S, Horimasu Y, Masuda T, Miyamoto S, Nakashima T, Iwamoto H, Fukushima N, Fujitaka K, Hamada H, Ichinohe T, Ohshima K and Hattori N. Primary pulmonary mucosa-associated lymphoid tissue lymphoma with the high expression of IgG4. Intern Med 2022; 61: 1043-1048.
[22] Timilsina S, Damato A, Budhathoki N, Grossbard ML and Braunstein M. Characterization of second primary malignancies in mucosa-associated lymphoid tissue lymphomas: a SEER database interrogation. Clin Lymphoma Myeloma Leuk 2022; 22: 76-81.
[23] Torrente-Nieto A, Bonnin Vilaplana M and Rojas Calvera E. Isolated lobar consolidation as a form of presentation of pulmonary MALT lymphoma. Med Clin (Barc) 2022; 158: 298.
[24] Wu T, Huang Y, Wang Z, Cao H, Ding Q and Deng Z. Pulmonary MALT lymphoma: imaging findings in 18 cases and the associated pathological correlations. Am J Med Sci 2022; 364: 192-197.

[25] Uhl B, Prochazka KT, Fechter K, Pansy K, Greinix HT, Neumeister P and Deutsch AJ. Impact of the microenvironment on the pathogenesis of mucosa-associated lymphoid tissue lymphomas. World J Gastrointest Oncol 2022; 14: 153-162.

[26] Vela V, Juskevicius D, Dirnhofer S, Menter T and Tzankov A. Mutational landscape of marginal zone B-cell lymphomas of various origin: organotypic alterations and diagnostic potential for assignment of organ origin. Virchows Arch 2022; 480: 403-413.

[27] Yang Y, Mei J and Lin F. Primary solid pulmonary mucosa-associated lymphoid tissue lymphoma mimicking lung cancer. Asian J Surg 2022; 45: 506-507.