CASE REPORT
HEMATOLOGY

Pulmonary Mucosa-Associated Lymphoid Tissue Lymphoma: A Report of 2 Cases and Literature Review

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Abstract: Pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma is indolent and progresses more slowly than other malignant lymphomas. The clinical features are not specific and the diagnosis can often be difficult. Here, we present two rare cases of pulmonary MALT lymphoma. Both patients were incidentally found lesions in the lungs with chest computed tomography during physical examination. They were finally diagnosed by pathological biopsy. One received complete resection, the other was treated with chemotherapy. There were no recurrence in the two patients during follow-up. We also review relevant literature to provide a better recognition of this disease.

Keywords: Pulmonary mucosa-associated lymphoid tissue lymphoma; Clinical features; Case report.

Introduction

Primary pulmonary lymphomas (PPLs) are rare lymphoproliferative malignancies that constitute 3–4% of extranodal non-Hodgkin lymphoma (NHL) and 0.5–1% of primary pulmonary neoplasms. MALT lymphoma is the most common subtype of primary B-cell lymphoma of the lung, which is very rare, accounting for less than 1% of primary malignant tumors in the lung. It is indolent, progresses slowly and has a good prognosis. Most patients do not have any symptoms at the time of diagnosis, and only a small number of patients may present as coughing, dyspnea, hemoptysis, and chest pain. Diagnosis is often difficult due to its low incidence and atypical symptoms. The confirmation mainly relies on pathological biopsy, and there is no uniform standard for treatment. Here we reported two rare cases of pulmonary MALT lymphoma that were successfully treated with surgical resection or chemotherapy and achieved complete remission.

Case presentation

Case 1
A 75-year-old man with a history of hypertension had a physical examination in other hospital a month ago, and chest computed tomography (CT) showed an occupied lesion in the posterior segment of the upper lobe of the right lung, with a cystic cavity containing air. But the patient was asymptomatic. Then the patient received a surgery and the lesion was resected. Immunohistochemistry of the specimens showed expression of CD79a and CD20 but negative for CD23, CD10, Kappa, Lambda, IgM, and CD43. While immunostaining for CD3 and CD5 were scattered positive. Gene analysis revealed IgH and IgK gene clonal rearrangement of B cells. There was no clonal rearrangement of TCRγ gene in T cells. The pathological diagnosis of pulmonary MALT lymphoma was made. After confirmation of the diagnosis, the patient was referred to our hospital for further treatment in January, 2021. Upon examination, there were no obvious abnormalities. His laboratory tests revealed renal insufficiency, with an endogenous creatinine clearance rate of 45.7 ml/min, glomerular filtration rate of 43.6 ml/min, and β2-microglobulin of 3.54 mg/L. D-dimer was 1478.0 ng/ml. IL-6 was 5.95 pg/ml. Lymphocytes and NK cells test showed that the percentages of CD4(+)CD8(-) T cells, CD4(+)/CD8(+)T cells, NK cells were 68.67%, 2.60%, and 3.04%, respectively. Other laboratory examinations including, cancer serum markers, immunoglobulin complements, thyroid function, coagulation test, and EB virus test were within normal limits or negative. His chest and abdominal CT revealed no abnormality except for the changes after partial resection of the upper lobe of the right lung (Fig. 1). Bone marrow cell has no found lymphoma cells, the ultrasonography of superficial lymph nodes, and morphology of blood cells are normal. We made a diagnosis of pulmonary MALT lymphoma (classified as stage I group A). Because the patient was asymptomatic and the lesion resection had been performed at other hospital, he did not received further chemotherapy. The patient has been regularly followed up one year, and his chest CT showed no signs of recurrence (Fig. 2).

Case 2
A 41-year-old woman with a history of hepatitis B had a physical examination at the local hospital 20 days ago and a consolidation of the lungs was found by chest CT. However, she was asymptomatic and did not undergo further treatment. The patient was referred to the department of respiratory medicine of our hospital in April, 2020, with a complaint of shortness of breath and discomfort after exercise for 3 days. Physical examination showed no obvious abnormalities. A laboratory examination revealed...
the following: elevated lactate dehydrogenase, 323 U/L; ferritin, 524.00 ng/ml; tissue polypeptide antigen, 379.90 U/L. Peripheral blood cells, urine examination, electrolytes, and troponin were normal. A CT scan for chest revealed a consolidation in the upper lobe of the left lung lingual segment. Both lungs were scattered with pleomorphic lesions, considering the possibility of secondary tuberculosis. Pure ground glass nodules were also found in the posterior segment of the right upper lobe and the tip of the left upper lobe (Fig. 3). Further evaluation by bronchoscopy indicated that the carina was sharp and the mobility was good. The bronchial mucosa of the right lung and the lower lobe of the left lung was smooth, the lumen was unobstructed, and there were no definite new organisms or stenosis in the lumen. There were no obvious new organisms, stenosis and bleeding in the lingual and proper bronchial openings of the left upper lobe of the lung. GM examination of the bronchoscopy lavage fluid, concentrated bacteria examination, sputum culture, etc. were all negative. Bronchoscopy collected a few epithelial cells of bronchial mucosa. Lavage fluid also showed a few epithelial cells and inflammatory cells. However, the diagnosis remained unclear. Considering it may be pulmonary lymphoma, inflammatory pseudotumor or lymphoid granulomatosis. So the patient was treated for pneumonia, and
anti-infective treatment was started with twice a day intravenous infusion of 1.5g cefotizime sodium. Half a month later, another chest CT scan were performed, with no changes. In order to confirm the diagnosis, a CT-guided percutaneous lung biopsy was performed in May, 2020. The biopsy of the left lung revealed a population of small lymphocytes. Immunohistochemistry showed B-cell clonal hyperplasia, and mucosal-associated lymphoma could not be excluded. Then gene rearrangement analysis demonstrated that there was a clonal rearrangement of the IgH gene. On May 22, 2020, the patient was transferred to the department of hematology. Superficial lymph nodes examination was normal. Enhanced CT of the whole abdomen showed a cyst in the right kidney and the right adrenal gland was slightly thickened. A small amount of fluid was found in the pelvic cavity. The pathological morphology of blood cells, flow cytometry of bone marrow, and chromosome analysis were performed, with no lymphoma evidence. Based on examinations above, the diagnosis of pulmonary MALT lymphoma was clear. Because the patient had symptoms of fever and night sweats during the course of the disease, and her lungs had diffused lesions, the disease was divided into stage II group B. She received 6 courses of BR regimen (rituximab 375 mg/m², d1; bendamustine 90 mg/m², d1-d2) chemotherapy. Follow-up six months, her chest CT showed that the upper lung lesions were smaller (Fig. 4) and further evaluation by PET/CT revealed complete remission.

Discussion

MALT lymphoma is a subtype of marginal zone lymphoma (MZL), which belongs to non-Hodgkin’s lymphoma. The stomach is the most common site, followed by eye appendages, lungs and salivary glands. MALT lymphoma is the most common type of indolent B-cell primary pulmonary lymphoma. In terms of etiology, MALT lymphoma is related to chronic inflammation caused by infection and autoimmunity. Previous studies have found association of different infectious agents with MALT lymphomas at various anatomical sites, such as H pylori infection in gastric MALT lymphoma, Chlamyphila psittaci infection in the ocular adnexal MALT lymphoma. Although a study suggested that achromobacter xylosoxidans may involve with pulmonary MALT lymphoma, there was no data showing a causal relationship, and further studies are needed to investigate the related microorganisms. Autoimmune diseases, such as systemic lupus erythematosus, multiple sclerosis, and Hashimoto’s thyroiditis, especially Sjogren’s syndrome, are all risk factors for pulmonary MALT lymphoma. Besides, cytogenetic and molecular changes may be associated with the occurrence of pulmonary MALT lymphoma. The most common cytogenetic abnormality is t (11; 18) (q21; q21), and the other rare ones are t (14; 18) (q32; q21) and t (1; 14) (p22; q32). The translocation of the above chromosomes leads to the constitutive activation of the nuclear factor KB signaling pathway, which promotes the development of pulmonary MALT lymphoma. In our two cases, the patients had neither autoimmune diseases nor pathogenic infection. And cytogenetic changes above are not found. At present, the cause of the disease is still unclear.

Pulmonary MALT lymphoma tends to occur in the elderly, with a median age of 59 years, and more women than men. Most patients are asymptomatic at the time of diagnosis, and only imaging abnormalities are found during physical examination. Some patients may present as coughing, dyspnea, hemoptysis, and chest pain. These symptoms are rare and atypical, so it is difficult to differentiate from other diseases in the lung. In our two cases, one was an elderly male without any clinical symptoms, and only imaging abnormalities were found during physical examination. The other was a middle-aged female with symptoms of shortness of breath, fever, and night sweats. It was insufficient to establish a diagnosis of pulmonary MALT lymphoma according to these symptoms.

The radiographic presentation of pulmonary MALT lymphomas is nonspecific. Multiple bilateral lesions were common. Consolidation was the most frequent radiographic finding, followed by nodules and masses. Ground glass opacities were rare. The air bronchogram sign was present frequently in consolidation patterns, while bronchiectasis (especially cystic bronchiectasis) and CT angiogram signs were characteristic manifestations

18F-FDG PET/CT is widely used in the diagnosis and efficacy evaluation of Hodgkin’s lymphoma and non-Hodgkin’s lymphoma. 18F-FDG PET/CT had a sensitivity of 83.1% in non-conjunctival ocular adnexal MALT lymphoma, which could be used for staging of the disease to guide treatment. In recent years, studies have found that the detection rate of 18F-FDG PET or PET-CT in MALT lymphoma was 71%, especially in the lungs (94%) and the other apex of the left upper lobe were also been found. The imaging patterns and distribution of the two patients were atypical, which were similar to that of other lung diseases (such as pneumonia, tuberculosis, lung cancer), making it difficult to diagnose. But features such as air bronchial signs, bronchiectasis, and CT angiography signs may provide clues for pulmonary MALT lymphoma.

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In addition, for patients with MALT lymphoma after immunotherapy, both 18F-FDG PET and MRI may help predict complete remission after treatment. Therefore, 18F-FDG PET/CT can be used for the staging of pulmonary MALT lymphoma and the evaluation of the therapeutic effect after treatment. In our two cases, the patients both received PET/CT examinations during follow-up periods, which showed complete remission.

Tissue biopsy is the gold standard for diagnosis of pulmonary MALT lymphoma. Clinically, bronchoscopy, CT-guided needle biopsy, and open thoracic biopsy are often used to obtain tissue specimens, and combined with comprehensive analysis of immunohistochemistry and cytogenetics to accurately classify lymphoma subtypes to exclude other diseases. The pathological features of pulmonary MALT lymphoma showed that lymphoid infiltration destroys the lung structure. The cells in the lymphoid infiltration are heterogeneous, composed of small centro cyte-like lymphocytes, monocyte-like lymphocytes and varying numbers of plasma cells. Plasma cells may contain immunoglobulin, forming intracytoplasmic Russell bodies and nuclear Dutcher bodies. Monoclonal plasma cells also exist, but there are often mixed...
with reactive polytypes of plasma cells. Usually, scattered large immunoblasts and fibroblasts can be found at the infiltration site, and tumor cells infiltrate the bronchioles or alveolar epithelium to cause lymphoepithelial lesions [2,12]. Pulmonary MALT lymphoma belongs to B-cell lymphoma, and immunohistochemical stains are positive for CD19, CD20, CD22, CD79a, and Bcl-2, but negative for CD5, CD10, CD23 and cyclin D1. In pulmonary MALT lymphoma, the most common chromosomal abnormality is t (11:18) (q21; q21) (30-50%), and the other rare ones are trisomy 3 (20%), t (14:18) (q21; q21) (6-10%), trisomy 18 and t (1:14) (p22; q32) (2%) [4,13]. Genetic testing can find rearrangements of the heavy and light chains of immunoglobulins. In our first case, the man obtained a sample by surgical resection. In our second case, the woman had no positive findings through bronchoscopy. After that, a CT-guided percutaneous lung biopsy was performed to obtain the sample. Both patients were diagnosed by pathological biopsy, combined with pathological morphology and immunohistochemistry. They were diagnosed as pulmonary mucosa-associated lymphoid tissue lymphoma. Their genetic tests revealed the IgH and IgK gene clonal rearrangement of B cells. But the chromosome examinations of two patients showed no abnormalities.

At present, there is no consensus on the treatment of MALT lymphoma in the world. The main treatment methods for pulmonary MALT lymphoma include watching and waiting, surgical resection, radiotherapy, chemotherapy and immunotherapy. Watching and waiting is suitable for asymptomatic patients with negative pathological biopsy and limited lesions, or patients who are not suitable for radiotherapy or systemic chemotherapy due to their health status and comorbidities [13]. For patients with localized lesions (stage I, II), surgical treatment is still controversial. Some scholars believed that surgical resection could improve the treatment effect and prolong disease-free survival. A retrospective study by Lee et al. showed for pulmonary MALT lymphoma, patients with low-stage (IE / IIE) mainly were treated via surgical resection (76.7%, n=33), while patients with high-stage (IIE / IVE) mainly received systemic chemotherapy (87.5%, n=7). The proportion of patients achieving complete response was significantly higher in the low-stage disease group (81.4% vs 25.0%), but the proportion of patients developing progressive disease was higher than in the high-stage disease group (50% vs 7.0%). It demonstrated for patients with pulmonary MALT lymphoma, surgical resection was main treatment for patients with localized pulmonary MALT lymphoma, and had a good therapeutic effect [14,15]. On the contrary, some experts believe that surgical resection should not be the first-line treatment option for patients with localized pulmonary MALT lymphoma, but should aim at protecting lung function [16]. The study by Zhao et al. concluded that there was no difference in progression-free survival between the chemotherapy group and the surgery combined with chemotherapy group. In order to maintain lung function and reduce the risks associated with surgery, chemotherapy may be the best choice for the treatment of pulmonary MALT lymphoma [17]. Radiotherapy is also suitable for patients with localized lesions, but we must pay attention to the toxicity of radiotherapy, especially radioactive pneumonitis [18].

Chemotherapy is suitable for patients with lesions involving both lungs or external locations, recurrence and progression [17]. Due to the lack of large-scale randomized controlled trials, there is currently no recommendation for the best chemotherapy regimen. Some drugs with anti-tumor activity, such as fludarabine, cladribine, chlorambucil, bendamustine, etc. can be used for the treatment of MALT lymphoma, and have significant effects. In addition, rituximab single-agent therapy was well tolerated, with an overall response rate of 73% [19]. Moreover, some small-sample single-center studies have found that rituximab combined with chemotherapy was more effective and may be the most suitable treatment option [1]. A retrospective phase III trial showed that compared with rituximab monotherapy, rituximab combined with chlorambucil had a significantly higher 5-year event-free survival rate for patients with extranodal marginal zone lymphoma (68% vs 50%, p=0.02), and the complete response rate also increased (78% vs 65%), but grade 3-4 neutropenia was more common. In a phase II trial, 60 patients with extranodal marginal zone lymphoma were treated with rituximab combined with bendamustine. The results showed that: 32 cases of non-gastric MALT lymphoma (56%) and 6 cases of multifocal MALT lymphoma (11%) had an objective response rate (ORR) of 100%, a 2-year event-free survival (EFS) of 93%, and a 4-year EFS of 88% [13]. A single-center retrospective study showed that: rituximab combined with cladribine in the treatment of 8 patients with stage IV pulmonary MALT lymphoma, the overall response rate reached 100%, two-year progression-free survival (PFS) and two-year overall survival (OS) was 80.0% (95% CI, 20.3-96.7%) and 100%, respectively. Although the sample size was limited, rituximab combined with cladribine may be the first-line treatment for advanced pulmonary MALT lymphoma [13]. Immunotherapy can also be applied to the treatment of MALT lymphoma. Lenalidomide, bortezomib, and drugs that target B cell receptor signal transduction, such as ibrutinib and idelalisib, had certain effects in MALT lymphoma [19]. In our first case, the man had a localized lesion and was treated with surgical resection. In our second case, the woman who had diffused lesions in both lungs, was treated with BR regimen for 6 courses of chemotherapy. Both of them have been regularly followed up in the outpatient department, and no recurrence had been found.

The prognosis of pulmonary MALT lymphoma is good, the overall 5-year survival rate is more than 80%, and the median survival time is more than 10 years [19]. The prognostic factors of MALT lymphoma have not been studied clearly. However, the prognostic factors proposed by some researchers were age > 70 years old, Ann Arbor staging 2, elevated lactate dehydrogenase. Another multivariate analysis found that the location of the disease, elevated β2-microglobulin levels, and the Ann Arbor staging of stage IV affect the prognosis [2,20].

Pulmonary MALT lymphoma is a group of low-grade B-cell lymphoma that develop slowly and insidiously, and usually has a good prognosis. The disease has atypical clinical symptoms and lack of specific imaging findings, making it difficult to differentiate from other diseases. The diagnosis is mainly based on pathological biopsy. There is no uniform standard for treatment. The current treatment depends on the location and stage of the disease. The main treatment methods include watching and waiting, surgery, chemotherapy, radiotherapy and immunotherapy. In the future, a large sample of randomized controlled studies will be needed to find the best treatment.

**Abbreviations**

CT, computed tomography; EFS, event-free survival; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; ORR, objective response rate;
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OS, overall survival; PFS, progression-free survival; PPLs, Primary pulmonary lymphomas.

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Conflict of interest

The authors report no conflicts of interest in this work.

Authors’ contributions

Conceptualization and supervision: YZ, XYT, YL; Methodology, investigation, visualization and project administration: XTX, YZ, XYT, YL; Funding acquisition: YZ; Writing – original draft, review and editing: XTX, YL.

References


