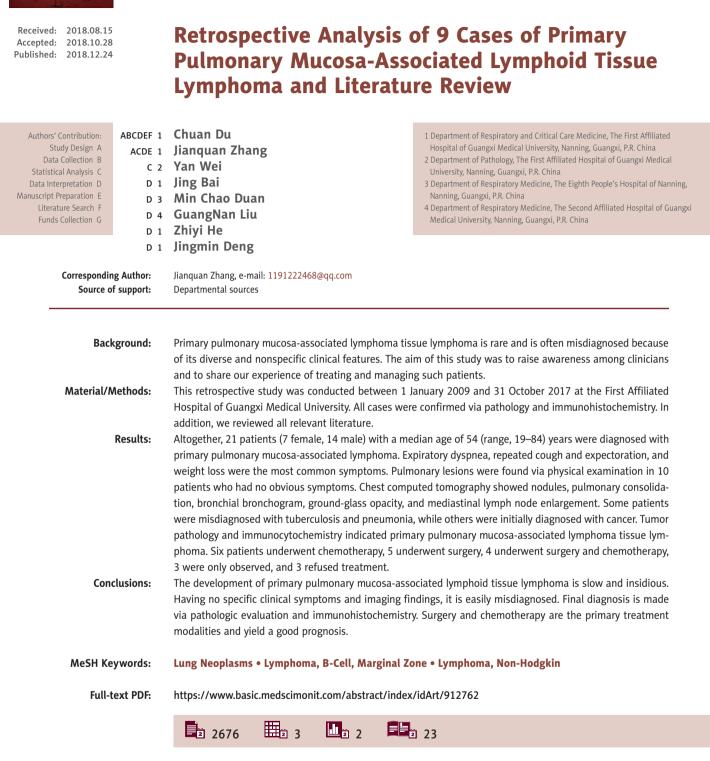
HUMAN STUDY

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MEDICAL

SCIENCE

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**BASIC RESEARCH** 

# Background

Mucosa-associated lymphoid tissue (MALT) lymphoma, an extranodal, marginal, low-grade B cell non-Hodgkin lymphoma, is often seen in the gastrointestinal tract, and is infrequently seen in the salivary glands, thyroid, prostate, skin, and lungs. Primary pulmonary MALT lymphoma is an extremely rare malignancy, accounting for only 0.5% to 1% of all cases of primary pulmonary malignant tumors [1,2]. The etiology and pathogenesis are controversial and uncertain [3]. Primary pulmonary MALT lymphoma occurs slowly and insidiously. Its clinical symptoms, laboratory findings, and imaging findings vary substantially, making diagnosis difficult, and there is no standard protocol for treatment. In the present study, we retrospectively analyzed the medical records and clinical characteristics of 9 patients diagnosed with primary pulmonary MALT between 1 January 2009 and 31 October 2017 at the First Affiliated Hospital of Guangxi Medical University. We also reviewed 12 cases previously reported. Herein, we share our experience to help correctly diagnose and provide appropriate and early treatment for this disease.

# **Material and Methods**

# **Study population**

The medical records of 105 patients diagnosed with pulmonary lymphoma between 1 January 2009 and 31 October 2017 at the First Affiliated Hospital of Guangxi Medical University were reviewed. Among them, 9 patients with primary pulmonary MALT lymphoma were retrospectively evaluated. Patients'

Table 1. Clinical characteristics of the present 9 patients.

information, including demographics (sex, age, and occupation), medical history (present history, comorbidities, and previous therapy), auxiliary examination results (hematological tests, imaging examinations, bone marrow biopsy, and pathological and immunohistochemical tests), treatment, and outcome, were collected from the medical records and summarized for analysis. The detailed data are presented in Table 1.

# Patient and public involvement

This study was a retrospective analysis and was approved by the First Affiliated Hospital of Guangxi Medical University Ethics Committee. All patients provided written informed consent.

## Diagnostic criteria for primary pulmonary MALT lymphoma

The diagnostic criteria for primary pulmonary MALT lymphoma [1] were: (1) specific histologic diagnosis indicating that primary pulmonary MALT lymphoma confirmed via pathology and immunocytochemistry; (2) the lesion was confined only to the lung with/without lung and mediastinal lymph node involvement; and (3) no lung lymphoid, bronchial tissue, or other organ involvement found within 3 months after diagnosis. Patients who satisfied these criteria were diagnosed with primary pulmonary MALT lymphoma.

#### **Statistical analysis**

Statistical analysis was performed using SPSS 22.0 for Windows 10 (SPSS, Inc., Chicago, IL, USA) and descriptive statistical methods included median (IQR), number, and percentile.

Number	Sex	Age (years)	Pathologic stage	Treatments	Prognosis	Follow-up time (months)
1	Male	54	IIIA	Surgery+CHOP*	CR*	45
2	Male	59	IA	R-FMD*+R-CVP*	CR	52
3	Male	54	IIA	RFC*	PR*	6
4	Male	50	IIIA	RFC+CHOP	CR	26
5	Male	48	IVB	FCD*	PR*	4
6	Male	74	IIIA	Observation	SD*	12
7	Male	77	IIA	None		
8	Female	50	IIA	None		
9	Male	67	Unsure	None		

CR\* - complete remission; PR\* - partial remission; SD\* - stable disease; CHOP\* - Cyclophosphamide + Adriacin + Leurocristine

+ Prednisone; R-FMD\* – Rituximab + Fludarabine + Mitoxantron + Dexamethasone; R-CVP\* – Rituximab + Cyclophosphamide

+ Vincristine + Prednisone; RFC\* - Rituximab + Fludarabine+ Cyclophosphamide; FCD\* - Fludarabine + Cyclophosphamide

+ Dexamethasone.

Table 2. Clinical characteristics of 21 patients.

Project	The present cases	Reported cases	Total	
M*: F*	8: 1	6: 6	14: 7	
Median age	55	51	54	
Symptomless	3	7	10	
Cough and expectoration	3	4	7	
Expiratory dyspnea	3	3	6	
Weight loss	5	1	6	
Short breath	2	2	4	
Pectoralgia	1	0	1	
Fever	1	1	2	
Lung CT (unilateral: bilateral)	2: 7	5: 7	7: 14	
Nodule	2	5	7	
round-like low-density shadows, shadow	2	0	2	
Ground-glass patchy shadow	1	3	4	
Interstitial changes	0	1	1	
Bilateral reticular changes prominent	0	1	1	
Multiple pulmonary consolidation patter	8	1	9	
Pleural effusion	2	1	3	
Bronchial bronchogram cavities	5	0	5	
Cavities	2	0	2	
Mediastinal lymph node enlargement	3	2	5	

M\* – Male; F\* – Female.

#### Literature review

We reviewed the literature on primary pulmonary mucosa-associated lymphoid tissue lymphoma published in PubMed and China National Knowledge infrastructure. We reviewed 12 reported cases. We combined and have presented the data on the 12 reported cases and the 9 present cases in Table 2 [3–14].

# **Results**

# Demographic data

Twenty-one patients (7 females and 14 males) with a median age of 54 (range, 19–84) years were diagnosed with primary pulmonary MALT lymphoma. The median time from the onset of symptoms to diagnosis for the 9 present cases was 24.00 (range, 0.17–144) months. Five of the 21 patients had a longterm history of smoking (up to 20 years) and all smoked about 20 cigarettes per day. None of the patients had a remarkable occupational history or were in contact with toxic substances that could have caused the cancer. Four patients were misdiagnosed with tuberculosis. Seven patients were initially diagnosed with pulmonary infection. Eight patients were initially suspected to have pulmonary tumors. They were all diagnosed with primary pulmonary MALT lymphoma via pathology and immunocytochemistry.

#### Clinical symptoms and signs

Among the 21 patients, 10 were asymptomatic during physical examinations. The remaining 11 patients mainly had respiratory symptoms, including expiratory dyspnea (n=6), repeated sputum and cough (n=7), shortness of breath (n=4), pectoralgia (n=1), fever (n=2), and weight loss (n=6). In addition, 5 patients had lymph node enlargement, 5 patients had dry or wet rales in the lungs, and 1 patient had pleural friction rub.

## Laboratory test results of the 9 present cases

Routine blood examinations revealed 1 case of increased white blood cell levels and 2 cases of increased hemoglobin (HGB). Meanwhile, the red blood cell, platelet, and HGB of the other 6 patients were in the normal range. The liver and kidney function of the 9 patients was within normal range. Serum ferritin was increased in 2 patients, CA-125 was increased in 5 cases,

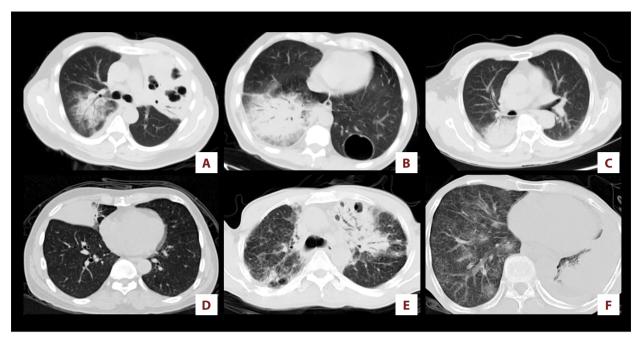


Figure 1. Representative CT images of the patient lungs are shown. (A) Two plaques and patchy high-density shadows are seen in every lobe of the lung, and air bronchograms are also evident. (B) The cavity was approximately 5.0×4.3 cm. Different-sized cavities in the left lung were noted in (A) and (B). (C) In the dorsal and posterior basal segments of the right lung, a piece of flaky soft tissue was seen, measuring approximately 5.2×4.6×5.7 cm. (D, E) A flaky shadow was seen in the dorsal segment of the left lower lobe, the right middle lobe, and the basal segment of the lower lobe. (F) The meniscus density shadow was seen in the left pleural cavity.

CA-153 was increased in 3 cases, non-small-cell lung cancer antigens was increased in 5 cases, and CA-199 was increased in 2 cases. Tumor markers were within normal range in 5 patients. Human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and syphilis helicoid test results were all negative. Bone marrow involvement was not noted on biopsy in 5 cases. As the respiratory symptoms of these patients were not severe. Only 1 patient underwent a pulmonary function test, and the lung function was as follows: forced expiratory volume in one second (FEV1) was 1.42 L; forced vital capacity (FVC) was 1.84 L; FEV1/FVC was 76.84%; maximal voluntary ventilation was 107.7 L/min; T<sub>LCO</sub> was 4.98 mmol/min/KPa; and residual volume-He was 0.93 L. The lung function indicated that the diffuse volume had decreased slightly, and the total lung function also decreased. It showed mild-to-moderate diffuse dysfunction, moderate mixed ventilation dysfunction, and mild peripheral airway obstruction. No obvious gene abnormality was found in 3 patients, and genetic analysis was not performed in 6 patients.

## **Imaging examinations**

Chest computed tomography (CT) showed pulmonary consolidation in 9 patients (Figure 1A), bronchial bronchogram cavities in 5 patients (Figure 1A), cavities in 2 patients (Figure 1A, 1B), ground-glass opacity in 4 patients (Figure 1C), nodules in 7 patients (Figure 1D), rounded low-density shadows in 2 patients (Figure 1E), pleural effusion in 3 patients (Figure 1F), and mediastinal lymph node enlargement in 5 patients. A total of 14 patients had bilateral lung lesions. Positron emission computed tomography (PET-CT) indicated high metabolism in lung lesions, with SUV values ranging from 1.6 to 5.87 in 5 patients. Of these 5 patients, 1 had a right neck lymph node with a diameter of 11 mm, and glucose metabolism increased in 1 patient who had a maximum SUV of 4.8. One patient had a massive mass with a diameter of 47 mm in the dorsal segment of the lower lobe of the right lung, and the glucose metabolism was increased in 1 patient who had a maximum SUV of 5.3. One patient had no lesions with malignant tumor structure and glucose metabolism in the scanning range. One was administered a PET-CT scan, which showed a slight increase in the metabolic activity of the nodule in the left upper lobe. The maximum standard uptake value (SUV) was 1.6. One PET scan revealed a high uptake (maximum standardized uptake value, 4.73–5.87) in the late phase.

## **Diagnostic procedures**

Four patients were misdiagnosed with tuberculosis and 1 patient was misdiagnosed for 2 years. Seven patients were initially diagnosed with pulmonary infection, and after multiple antibiotic treatments, the patient's condition did not improve. Eight patients were initially suspected to have a pulmonary tumor, and they were diagnosed with primary pulmonary MALT

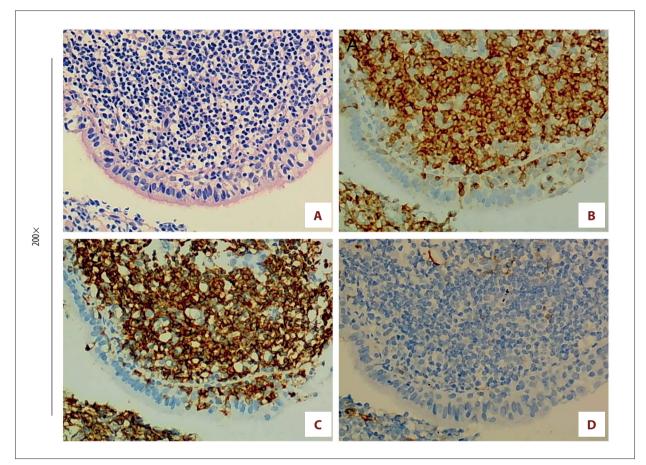


Figure 2. Histology images of a lung section. (A) There are many diffuse lymphocytic cells gathered at the center of the samples in HE staining. (B–D) Tumor cells showed strong positive expression for Bcl-2 (B) and CD20 (C), and negative expression for CD10 (D).

lymphoma via pathology and immunocytochemistry. Ten of 21 patients showed no clinical symptoms. Lung biopsy was performed via brightness-modulation (or CT) ultrasound-guided percutaneous lung biopsy (n=2), flexible fiberoptic bronchoscopy (n=2), and surgery (n=6). The other 11 patients who showed respiratory symptoms were diagnosed via brightness-modulation (or CT) ultrasound-guided percutaneous lung biopsy (n=4), flexible fiberoptic bronchoscopy (n=3), surgery (n=1), or videoassisted thoracoscopic lung biopsy (n=3). In fiberoptic bronchoscopy, alveolar lavage was given, and the lavage fluid was subjected to fungal and bacterial culture to rule out infection with particular pathogens and to detect tumor cells. If lesions were seen on bronchoscopy, specimen samples were obtained for pathological and immunohistochemical studies. If no obvious lesion was seen, lung tissue samples were obtained from nonspecific sites for pathology and immunohistochemistry.

#### Pathology and immunohistochemistry

Histologically, the tumors consisted of diffuse proliferative small lymphocytic lymphoma (Figure 2A). The B cells were smaller, the

nuclei were slightly irregular, and the nucleoli were not obvious. Some cancer cells infiltrated bronchial and glandular tubes to form lymphoepithelial lesions. Immunohistochemically, Bcl-2 (Figure 2B), CD20 (Figure 2C), and CD79a were diffusely expressed in lymphoid cells, whereas staining for CD10 (Figure 2D), cyclin D, CD3, CD5, and CD30 yielded negative results. The Ki-67 was less than 10%. The Ki-67 labeling index of 14 patients indicated a low proliferative index and their values ranged from 2% to 15%.

## **Treatments and outcomes**

Among the 21 patients, 6 received chemotherapy, 5 underwent surgery, 4 underwent surgery and chemotherapy, 3 continued on observation, and 3 refused treatment. According to the evaluation of pulmonary imaging and clinical symptoms following the treatment of 18 accepted treatments, 14 patients achieved complete remission (CR), 2 patients achieved partial remission (PR), 2 patients achieved stable disease, and 3 patients were lost to follow-up. The median follow-up time was 14 months (range, 3–52). The details of treatment and prognosis of the patients are presented in Table 3.

	Treatment	Total	CR*	PR*	SD*
Asymptomatic	Chemotherapy	2	2	0	0
	Surgery	4	3	0	1
	Chemotherapy + surgery	2	2	0	0
	Observation	1	1	0	0
	Stopped treatments	1	_	_	_
	Chemotherapy	4	1	2	1
	Surgery	1	1	0	0
Symptom	Chemotherapy + surgery	2	2	0	0
	Observation	2	2	0	0
	Stopped treatments	2	-	-	-

#### Table 3. Treatment and prognosis of 21 patients.

CR\* - Complete remission; PR\* - partial remission; SD\* - stable disease.

# Discussion

Mucosa-associated lymphoid tissue (MALT) lymphoma was first described by Isaacson and Wright in 1983 [1]. Primary pulmonary MALT lymphoma, an extranodal marginal low-grade B cell non-Hodgkin lymphoma, is a rare disease [2,15]. However, it is the most common primary pulmonary lymphoma, comprising 70–90% of all cases [2,4,5]. It occurs most commonly in males an average of 60 years old [6,16]. MALT lymphoma most commonly arises from the gastrointestinal tract, although it has been reported in other organs, including the salivary glands, lungs, the head and neck region, ocular adnexa, skin, thyroid, and breast [8]. Helicobacter pylori infection is considered to be a cause of gastric MALT lymphoma [17]. The etiology of the disease remains unclear [3], but the NSCLC antigen, smoking, immunodeficiency, autoimmune disease, Sjogren syndrome, infection, pulmonary reactive lymphoid tissue lesions, and pulmonary sarcoidosis are known to be important factors leading to the development and progression of primary pulmonary MALT lymphoma [10,14,18–21]. These factors stimulate the B cells of the bronchial mucosa-associated lymphoid tissue, causing monoclonal hyperplasia, and can eventually lead to primary pulmonary MALT lymphoma. In the present study, 1 patient had a history of rheumatoid arthritis and 5 patients had a longterm history of smoking, and these factors may be associated with the development of primary pulmonary MALT lymphoma.

Approximately 30–50% of patients who are asymptomatic at the time of initial diagnosis upon physical examination are diagnosed with malignancy [2,6,13].

Approximately 47.6% of patients in our study were asymptomatic during physical examinations and their lung imaging was abnormal. However, it is uncertain why other patients underwent testing if they were asymptomatic. As primary pulmonary MALT lymphoma develops slowly and insidiously, some patients have no early clinical symptoms. The exact nature of the lung abnormalities associated with this disease is unclear, and it is uncertain whether they are inflammatory, infectious, or malignant. If they are malignant tumors, the best opportunity for making a diagnosis and providing treatment may be missed. A lung biopsy should be performed via brightness-modulation (or CT) ultrasound-guided percutaneous lung biopsy and flexible fiberoptic bronchoscopy because it is safer and less traumatic than surgery.

The symptomatic nature of these lesions may become evident with a prolonged course of the disease [18]. The patients tend to show nonspecific respiratory symptoms, including repeated cough and expectoration and expiratory dyspnea. Immunocompromised patients can have local or systemic infections characterized by fever and yellow sputum, among other symptoms [3,6]. Primary pulmonary MALT lymphoma invades the airway mucosa-associated tissue. The main clinical symptoms are cough, expectoration, and respiratory distress. Care must be taken to distinguish primary pulmonary MALT lymphoma from pulmonary inflammation, tuberculosis, and alveolar carcinoma. Pulmonary lesions in both lungs are common. Their associated imaging findings are typical and consist of nodules, pulmonary consolidation, and bronchial bronchogram cavities.

Some patients also have pleural effusion, tuberous, hollow atelectasis, and mediastinal lymph node enlargement [5,17]. Chest imaging shows bilateral lung lesions that can be divided into 4 categories: solid, consolidation of masses, nodular type, and mixed type [17]. No specific findings are found on imaging, with various characteristics commonly overlapping [3]. These indicate the need for increased vigilance to differentiate primary pulmonary MALT from primary bronchial lung cancer,

tuberculosis, sarcoidosis, interstitial disease, and other uncommon infections.

The disease is usually misdiagnosed because of its occult nature, and nonspecific clinical features and imaging findings. In this study, some of the patients were misdiagnosed with TB, lung cancer, and infection. Primary pulmonary MALT should be considered in similar cases in the future.

Pathology is the only method to diagnose lung primary pulmonary MALT lymphoma. Pathological tissue is obtained via lung surgery, flexible fiberoptic bronchoscopy, or brightness-modulation ultrasound-guided percutaneous lung biopsy. Tumor cells of primary pulmonary MALT consist of lymphoid cells, lymphocytes, plasma cells, centroid cells, and mononuclear B cells. The proportion of cells differ. Tumor cells are small, with slightly irregular nucleus and little cytoplasm. Small lymphocytes are distributed diffusely in bronchial mucosa and lymphoepithelial lesions [17]. B cell antigens, including CD20, CD79a, and Bcl-2, are expressed [10], while CD5, CD10, and Cyclin D1 (T cell markers) are not expressed [6]. The Ki-67 is usually very low [17] and since Ki-67 is an important measure of tumor proliferation, it is questionable whether it can be used for standard treatment. This has not yet been reported. The Ki-67 was seen in less than 15% of cases in our study. According to the expression and distribution of the Ki-67 antigen in the cells, the cell phase in the proliferative cycle can be determined. The high labeling rate of the Ki-67 indicates poor prognosis, while the low labeling rate indicates that the tumor is inert and the prognosis is good [22]. It is questionable whether we can provide chemotherapy or surgical treatment based on the Ki-67 rate. There are no specific standards yet and more research is needed.

The standard treatment modality for primary pulmonary MALT lymphoma is still debated [3]. The treatments are associated with the clinical stage, histology, and performance status [15] and include surgery, radiotherapy, and chemotherapy alone or in combination. Lung surgery is a better choice for patients with localized tumors [3], and it is both a diagnostic and treatment modality for these patients [23]. The need for further treatment, such as chemotherapy and radiotherapy, is decided according to whether there are residual lesions after lung resection. Recently, clinical observations have been highlighted in the management of these patients [19,20] given that the disease is insidious, develops slowly, has low malignant potential, and tends to be inert and spontaneous [8]. Asymptomatic patients may not need treatment because they tend to self-healing by themselves when immune function is enhanced [20]. Studies have reported cases of complete remission [5,8,19]. If the corresponding symptoms or lesions of patients on clinical observation progress, further clinical treatment should be given [5]. Chemotherapy is recommended for bilateral lung disease and metastasized tumors [20], and it is primarily recommended for patients at an advanced stage, those in whom surgery failed to completely remove the tumor, and those with recurrence. CHOP is the most commonly used regimen because of its good tolerance [3]. Rituximab for primary pulmonary MALT lymphoma can prolong survival and reduce symptoms in CD20positive patients [6,10,23].

Primary pulmonary MALT lymphoma has a good prognosis due to its slow development. The median survival time is more than 10 years [15]. The 1-, 5-, and 10-year survival rates are 91–95%, 68–81%, and 53–75%, respectively [2,3,6,15,17]. However, the factors affecting prognosis are unclear [15].

# Conclusions

Primary pulmonary MALT lymphomas are extremely rare but tend to have a good prognosis. They have no specific clinical manifestations and imaging findings; thus, they are easily misdiagnosed as TB, lung cancer, and infection. Diagnosis depends on pathology and immunohistochemistry. Primary pulmonary MALT lymphomas should be considered in patients who do not improve after anti-infection treatments for lung disease. In the present study, we described clinical findings and discussed diagnostic measures and treatment options based on our clinical experience with primary pulmonary MALT and a review of literature, to help avoid misdiagnosis and mistreatment of such patients.

### Acknowledgements

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# **Conflict of interest**

None.

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