

# Misdiagnosis of primary mucosa-associated lymphoid tissue lymphoma of the pleura: case report and literature review

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**Background:** Mucosa-associated lymphoid tissue (MALT) lymphoma is an indolent B cell lymphoma. Its occurrence in the pleura is rare, with atypical clinical manifestations. MALT of the pleura is easily misdiagnosed. This is the first case report of pleural MALT lymphoma in China.

**Case Description:** We report the case of a 54-year-old Chinese man with no notable medical history who complained of cough, sputum, and shortness of breath for 3 months. He had a positive purified protein derivative (PPD) test. An initial misdiagnosis of pleural tuberculosis was corrected, after 3 thoracoscopic biopsies and tests, to primary pleural MALT lymphoma. He received treatments of R-CHOP (rituximab, cyclophosphamide, epirubicin, vindesine and prednisolone) and traditional Chinese medicine. The patient was followed for 3 years until June 2022, with no obvious respiratory symptoms. Pleural MALT lymphoma is extremely rare, with only a few cases reported. This article describes our case, and includes an overview of 15 previously reported cases to summarize the characteristics, treatments, and prognosis of primary pleural MALT lymphoma.

**Conclusions:** Pleural MALT lymphoma is rare, and a correct diagnosis depends on tissue biopsy, immunohistochemical staining, and detection of gene rearrangement. Thoracoscopy is important to diagnose this disease. Multiple thoracoscopic biopsies may be necessary.

**Keywords:** Mucosa-associated lymphoid tissue (MALT); low-grade B-cell lymphoma; pleural dissemination; medical thoracoscopic biopsy; case report

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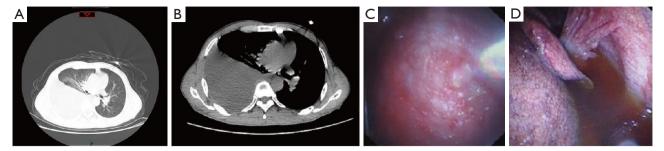
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## Introduction

Mucosa-associated lymphoid tissue (MALT) lymphoma accounts for about 7% of all B cell lymphomas (1). MALT lymphoma features the invasion of extranodal organs by heterogeneous small B cells, which may be marginal zone cells, cells resembling monocytoid B cells, small

lymphocytes, or scattered immunoblasts or centroblast-like cells (2). The pathogenesis of MALT lymphoma has been linked to the antigenic stimulation of marginal zone B cells. Clinical features of the malignancy vary, depending on the involved extranodal sites. Unlike aggressive lymphomas, their constitutional symptoms are not obvious. Although

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**Figure 1** Chest CT and thoracoscope of local hospital. (A,B) Chest CT scan: local thickened right pleura and bulk hydrothorax. (C,D) Thoracoscope: dark brown hydrothorax, congestive visceral pleura, and multiple intensive follicles of the diaphragm dome. CT, computed tomography.

most patients have stage I or II disease at presentation, bone marrow involvement seems more frequent in non-gastric MALT lymphoma relative to gastric diseases (3).

The stomach is the most frequently involved organ of MALT lymphoma, in as many as 35% of cases. Other sites include eyes, skin, lungs, salivary glands, and breasts. Primary pleural MALT lymphoma is extremely rare (4). Only 15 cases of primary MALT lymphoma in the pleura have been reported. Herein is described a case of pleural MALT lymphoma in a 54-year-old man, which was initially misdiagnosed as pleural tuberculosis. He presented with respiratory symptoms, and a right pleural lesion was observed on computed tomography (CT) scans. We present the following case in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-671/rc).

## **Case presentation**

A 54-year-old Chinese man with no significant medical history complained of cough, sputum, and shortness of breath for 3 months. He was admitted to the local hospital. No evident abnormal outcome was shown by blood cell counts; liver and renal function, electrolytes, or procalcitonin tests; acid-fast smear, or sputum culture. However, the tuberculin purified protein derivative (PPD) test was positive. Enhanced CT scanning revealed lesions on the right pleural cavity, which was confirmed by thoracoscope (*Figure 1*). Pleural biopsy specimens showed inflammatory cell infiltration, fibrous proliferation, and compressed lymphocytes with leukocyte common antigen (LCA). Epithelioid cell proliferation and caseous necrosis were detected in the lesions. Immunohistochemical (IHC) staining revealed LCA(+), pan-cytokeratin (pan-CK) and

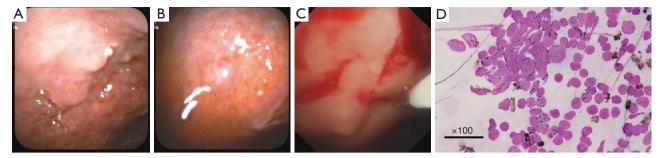
Cluster of Differentiation (CD)56(-), with Ki-67 (10%), which suggested a clinical diagnosis of tuberculous pleuritis. The patient was treated with a 4-drug anti-tuberculosis regimen at local municipal hospital. After 3 months, his symptoms had not improved significantly.

The patient was referred to our hospital. No significant abnormal results were found in blood routine test, and the PPD test was negative this time. Thoracocentesis was performed, and the pleura fluid proved to be exudative: total cell count 10,750×10<sup>6</sup>/L; white blood cell (WBC) count 5,200×10<sup>6</sup>/L; mononuclear cells 0.80%; total protein 38.5 g/L; globin 16.1 g/L; albumin 22.4 g/L; adenosine deaminase 18.7 U/L; and lactic dehydrogenase 332.3 U/L. Acid-fast staining and carcinoembryonic antigen tests were negative.

Thoracoscope examinations were performed twice in our hospital, and a pleural lump, tiny nodules, and effusion in his right thorax were found (*Figure 2*). Suspected dyskaryotic cells were detected via imprint cytology. Subsequent biopsy specimens showed diffuse infiltration of lymphocytes.

IHC staining was positive for the following (Figure 3): LCA, CD20, paired box domain gene 5 (PAX5), CD21, CD5, CD43, CD7, B-cell lymphoma-2 (BCL-2), CD24, kappa, multiple myeloma oncogene (MUM)1 (focally), and CD3 (scattered); and negative for: CK, B-cell lymphoma-6 (BCL-6), CD10, cyclin D1, and lambda. The Ki-67 index was about 10%. Immunoglobulin heavy chain (IgH) gene rearrangement was detectable. A diagnosis of MALT lymphoma was made, based on the pathological findings. Bone marrow aspiration was negative for lymphoma involvement.

On positron emission tomography/computed tomography (PET/CT), the following appeared hypermetabolic (*Figure 4*):



**Figure 2** Thoracoscope and exfoliative cytology in our hospital. (A-C) Thoracoscope showing: mass, nodular lesions on the tumor. (D) Dyskaryotic cell detected by imprint cytology (hematoxylin and eosin staining).

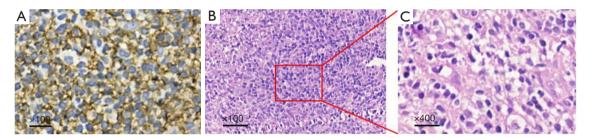


Figure 3 Histopathology and IHC. (A) IHC: malignant cells are strongly positive for CD20. (B) Hematoxylin and eosin staining: diffused small lymphocyte infiltrating (100x). (C) Findings under magnification: monocyte-like B cells (400x). IHC, immunohistochemistry.

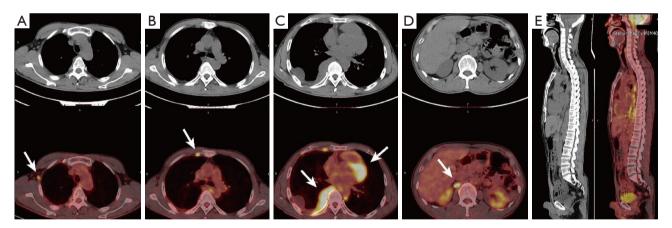


Figure 4 PET/CT. Increased tracer uptake in the thickened pleura (A), internal mammary area (B), mediastinal (C), and adrenal gland (D); corresponding CT fused images are shown. (E) is the site of involvement shown in sagittal view of the patient. The white arrows indicate the involved site of the lesion in PET/CT. PET/CT, positron emission tomography/computed tomography.

the lesion of the right pleura (with a local thickness of 46 mm); lymph nodes of the right axilla, internal mammary area, cardiophrenic angle, and adrenal gland; and bilateral hilar and mediastinal lymph nodes. The patient was discharged after one course of chemotherapy with R-CHOP (rituximab 600 mg day 0, cyclophosphamide 600 mg days

1–2, epirubicin 30 mg days 1–3, vindesine 2 mg day 1, and prednisolone 55 mg days 1–5), with respiratory symptoms improved. The timeline and duration of each treatment of this patient is shown in *Figure 5*. For personal reasons, the patient discontinued chemotherapy and switched to traditional Chinese medicine. During a June 2022 follow-up,

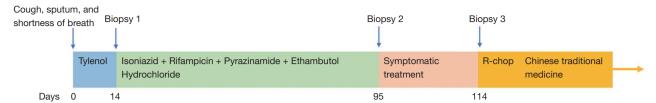


Figure 5 The timeline and duration of each treatment of our patient.

the patient had no obvious respiratory symptoms but felt weakened. The patient has not stopped smoking. We are still contacting the patient although he has been relocated for work reasons and that some data has been lost.

### **Ethics approval**

This study was approved by the Ethics Committee of Second Xiangya Hospital of Central South University (No. 2021099). All procedures in this study were performed in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

#### **Discussion**

Primary pleural MALT lymphoma is a rare malignant tumor, and its etiology remains controversial. Few cases have been reported. The development of the tumor is generally linked with prolonged antigen stimulation of the pleura, mainly through chronic infection and autoimmune diseases. Typical chronic infections include tuberculous pyothorax and tuberculous pleurisy. Autoimmune diseases may be Sjogren's syndrome, rheumatoid arthritis, and autoimmune disorders triggered by human immunodeficiency virus or Epstein-Barr virus infection (1,5). Inflammation is a possible etiological factor, and may explain the infiltration of inflammatory cells in the tumor tissue of MALT lymphoma. This makes distinguishing lymphoma from inflammatory benign conditions challenging.

The case we report was initially misdiagnosed as tuberculous pleurisy, and the corrected diagnosis was made after a repeated thoracoscope and pathological investigation. Therefore, for patients with an occupying lesion who have responded poorly to anti-TB diagnostic therapy, repeated biopsy and histopathological exams are necessary.

Pleural MALT lymphoma occurs among all age groups, although most reported cases have been in the elderly. The diagnosis depends on the results of specimen biopsy and immunohistochemistry, as clinical symptoms, physical examination, laboratory parameters, and even imaging contribute little. In addition, the accuracy of the pathological diagnosis is influenced by the stage of the disease, quality of the biopsy samples, and experience of the pathologist. The methods for obtaining a tissue specimen include thoracoscope, bronchoscopy, CT-guided percutaneous lung puncture, and surgery. Compared to the other methods, surgery may result in more samples and an improved rate of correct diagnosis, but is more invasive and expensive.

The present case is the first of its kind reported in China. Our data is relatively complete, which will aid in clinical diagnosis and treatment in the future. However, some follow-up data were lost due to the patient's relocation for work. For the literature review, the following online databases were searched for relevant English and Chinese language articles: Medline PubMed; Web of Science; Science Direct; Elton B. Stephens. Company (EBSCO); Offshore Vessel Inspection Database (OVID); China National Knowledge Internet (CNKI); Wanfang Database; Vip Paper Check System (VPCS); Chinese Science Citation Database (SCSD); and SinoMed (CMB). The terms used in the search were: "lymphoma", "pleura", "pleural", "primary", and "MALT",

The literature search uncovered 15 cases of pleural MALT lymphoma (*Table 1*). The male-to-female ratio of the reported cases is 3:1, and the ages ranged from 39 to 86 years (median age 67.5 years). The nations included 10 and 2 cases in Japan and the United States, and one case each in Canada, Spain, and Tunisia (n=1). At the time of diagnosis of pleural MALT lymphoma, most patients were also experiencing complications due to other diseases:

Table 1 Reported cases of pleural MALT lymphoma

No.	Ref.	Sex	Age, y	Initial symptoms	Radiological findings	IHC/FCM	BM infiltration	Treatment	Outcome	Nation
1	(6)	М	79	Pulmonary mass	Mass of L upper lobe & pleural nodules	IHC: CD20 <sup>+</sup> , CD79a <sup>+</sup>	No	NA	NA	Japan
2	(7)	М	47	Fever, chest pain	Consolidation of R lower lobe basal segment with a small hydrothorax	IHC: CD20 <sup>+</sup> , IgM <sup>+</sup>	No	Rejected	Stable disease	Canada
3	(8)	F	67	Dyspnea	Hydrothorax R-sided	FCM: CD20 <sup>+</sup> , CD19 <sup>+</sup> , CD79a <sup>+</sup> , IgM <sup>+</sup>	Yes	Cladribine + RIX: 3 courses	Complete response	Japan
1	(9)	М	79	Back pain	Thickened mediastinum & pleura with hydrothorax R-sided	IHC: CD20 <sup>+</sup> , CD79a <sup>+</sup> , CD45RO <sup>+</sup> , Bcl-2 <sup>+</sup>	NA	Surgery	NA	Japan
5	(10)	F	65	Pleural thickening	Thickened R pleura with hydrothorax	IHC: CD20 <sup>+</sup> , CD79a <sup>+</sup> , CD3 <sup>+</sup>	No	RIX-CHOP: 6 courses	Complete response	Japan
3	(11)	F	74	Cough, fatigue	Thickened pleura with bulk hydrothorax R-sided	IHC: CD20 <sup>+</sup> , kappa <sup>+</sup>	No	RIX alone	Relapsed 2 y later	Japan
7	(12)	М	52	Pleura mass	Bulky mass in superior lobe of the R lung	IHC: CD20 <sup>+</sup> , CD3 <sup>+</sup>	NA	NA	NA	Spain
3	(13)	М	86	No	Diffused thickness of parietal pleura	IHC: CD20 <sup>+</sup> , CD79a <sup>+</sup>	NA	NA	NA	Japan
9	(14)	F	68	Dyspnea	Nodular lesions of pleura with hydrothorax R-sided		Yes	RIX-CHOP	Hydrothorax disappeared	Japan
10	(15)	М	76	Hydrothorax	Diffused thickness of parietal pleura with hydrothorax R-sided	IHC: CD20 <sup>+</sup> , CD79a <sup>+</sup> , CD5 <sup>+</sup>	NA	Surgery + IMCT (RIX-CHOP)	Hydrothorax significantly reduced	Japan
1	(16)	М	64	Cough, chest pain, dyspnea, fatigue, weight loss	Thickened pleura with bulk hydrothorax R-sided	IHC: CD20 <sup>+</sup>	No	IMCT (RIX-CHOP) + radiotherapy	Complete response	Tunisia
12	(17)	М	39	Abnormal signs on X-ray	Mass of R pleura, no hydrothorax	IHC: CD20 <sup>+</sup> , CD79a <sup>+</sup> , Bcl-2 <sup>+</sup>	No	NA	NA	Japan
13	(18)	М	71	Dyspnea, cough, weight loss	Bulk hydrothorax R-sided	FCM: CD20 <sup>+</sup> , CD19 <sup>+</sup> , CD22 <sup>+</sup> , CD3 <sup>+</sup> , kappa <sup>+</sup>	NA	Rejected	NA	U.S.
14	(19)	М	71	Hydrothorax	Hydrothorax L-sided	IHC: CD20 <sup>+</sup> , CD19 <sup>+</sup> , kappa <sup>+</sup> , Bcl-2 <sup>+</sup> , MIB <sup>+</sup>	NA	RIX alone	Alive after 5 y follow-up	Japan
15	(20)	М	62	Dyspnea & weight loss	Bulk bilateral hydrothorax with compressive pulmonary atelectasis	FCM: CD19 <sup>+</sup>	Yes	BR	Hydrothorax reduced	U.S.
16	This study	M	54	Cough & shortness of breath	Significant local thickened R pleura with hydrothorax R-sided	IHC: CD20 <sup>+</sup> , CD3 <sup>+</sup> , CD5 <sup>+</sup> , CD23, CD21 <sup>+</sup> , CD43 <sup>+</sup> , CD7 <sup>+</sup> , kappa <sup>+</sup> , BcI-2 <sup>+</sup> , PAX5 <sup>+</sup> , MUM1 <sup>+</sup> , ki67 10%	No	RIX-CHOP	Hydrothorax reduced	China

MALT, mucosa-associated lymphoid tissue; IHC, immunohistochemistry; FCM, flow cytometry; BM, bone marrow; F, female; M, male; BR, bendamustine and rituximab; RIX, rituximab; CHOP, cyclophosphamide, epirubicin, vindesine, and prednisolone; IMCT, immunochemotherapy; NA, not available.

2 cases of hypertension, and one case each of rheumatoid arthritis, hypertension, ovarian abscess, chylothorax, pyothorax, post-total gastrectomy, meningitis, and chronic obstructive pulmonary disease. In order of reported frequency of symptoms, there were 6, 4, and 3 patients, with dyspnea, cough, and weight loss. Two patients each had chest pain and fatigue, and one patient each had fever, back pain, and sputum.

Abnormal physical signs of the respiratory system were found in 5 patients. Imaging methods for 15 patients consisted of CT scan, and X-ray was used for one patient. All 16 patients showed abnormal imaging results: pleural thickening and hydrothorax were shown by 15 and 12 patients, respectively. Pulmonary nodules and atelectasis occurred in 2 patients each, and one patient experienced mediastinal superficial lymph node enlargement.

Biopsy was performed in all reported cases, CD20 positivity was detected in 13 samples through IHC staining. Two pleural effusion samples were detected by flow cytometry, which showed positive results for CD20 (8,18). Another patients received thoracoscopic surgery with pleural biopsy, which revealed CD19 positivity (20).

There is no standard therapy recommended for pleural MALT lymphoma. Various therapeutic regimens have been applied among the known cases, including radiotherapy, surgery, and chemotherapy. Nine patients accepted chemotherapy-based regimens: R-CHOP alone or combined with surgery, radiotherapy, or both; bendamustine and rituximab; cladribine and rituximab; or rituximab only. One patient received surgery only. Another 2 patients refused any further treatment. Treatment has not been described for the remaining 4 cases.

In most cases, patients achieved varying degrees of remission and a favorable prognosis. One 76-year-old man responded well to surgery plus R-CHOP regimen, with hydrothorax significantly reduced 2 months later (15). Another 3 patients underwent a R-CHOP regimen, one of which achieved complete response after 6 cycles. No mortality was reported (10). The patients who accepted only rituximab still survive, 2 and 5 years, respectively, after treatments. Gomyo *et al.* (8) reported a patient who was given 3 cycles of a cladribine plus rituximab regimen, and sustained a complete response during the 19 months of follow-up.

In conclusion, fewer than 1% of MALT lymphoma lesions are found in the pleura. Patients commonly present at the hospital with respiratory symptoms and hydrothorax. Diagnosis of the malignancy depends on pathology and IHC methods. Compared to other indolent B cell lymphomas, most cases of primary pleural MALT lymphoma have similarly good outcomes.

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#### **Footnote**

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-671/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-671/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of Second Xiangya Hospital of Central South University (No. 2021099). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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