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Case Report

From lymphocytic interstitial pneumonia to MALT lymphoma of lung: a case report with a 5-year diagnostic dilemma

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Abstract: Lymphocytic interstitial pneumonia (LIP) and mucosa- associated lymphoid tissue (MALT) lymphoma of lung are all uncommon disorders of respiratory system. MALT lymphoma of lung is a distinct and unique subtype of marginal zone B-cell non-Hodgkin's lymphoma (NHL) characterized by malignant cells arising from extranodal sites. They are characteristic of exuberant lymphoid infiltration in pathological tissue. Therefore, in some cases, they are too similar in clinical manifestation, chest imaging and pathology to make differential diagnosis. Here, we report a 43-year-old woman who underwent a tough process for the final diagnosis. From this case, we could get a well understanding of difference between LIP and MALT lymphoma of lung.

Keywords: Lymphocytic interstitial pneumonia, mucosa-associated lymphoid tissue lymphoma, lymphocytes, diagnosis

Introduction

Lymphocytic interstitial pneumonia (LIP) and mucosa-associated lymphoid tissue (MALT) lymphoma of the lungs are uncommon disorders of the respiratory system. Clinically, they are often asymptomatic and are usually identified incidentally based on radiographic abnormalities and biopsy. When present, symptoms are non-specific and can include cough, expectoration, dyspnea, chest pain, and occasionally hemoptysis. In the current study, we report a rare case of an individual who underwent a long and arduous process before a final diagnosis is reached. This case would perhaps provide a better understanding of the differences between LIP and MALT lymphoma of lung.

Case report

Case history

A 43-year-old woman was admitted into the Department of Respiration with complains of intermittent cough and yellow sputum for about five years.

In 2008, she began coughing with small amounts of blood-streaked sputum after catching a cold. The patient recalled that she had fever and did not have any night sweats, sthenalgia, or difficulty of breathing. Her clinical symptoms lessened after anti-infective therapy with cefazolin and levofloxacin, but did not disappear completely. Six months later, she felt fatigued with chest discomfort and complained of shortness of breath after moderate exercise. A computerized tomography (CT) of her thorax revealed blurred contours and dense opaque patches in the middle and lower lobes of her right lung. After a seven-day treatment with antibiotics, reexamination of her chest CT revealed no changes in the shadows in the right lung compared with the pre-therapy CT and no improvement in the symptoms. To confirm the diagnosis further, a bronchoscopic biopsy was performed. The results indicated fibroplasia around the bronchiole and small vessels, and same-sized lymphocytes disseminated diffusely in the lesions. There were no signs of vasculitis, angionecrosis, or granuloma. Based on these histopathologic features, the pathologist

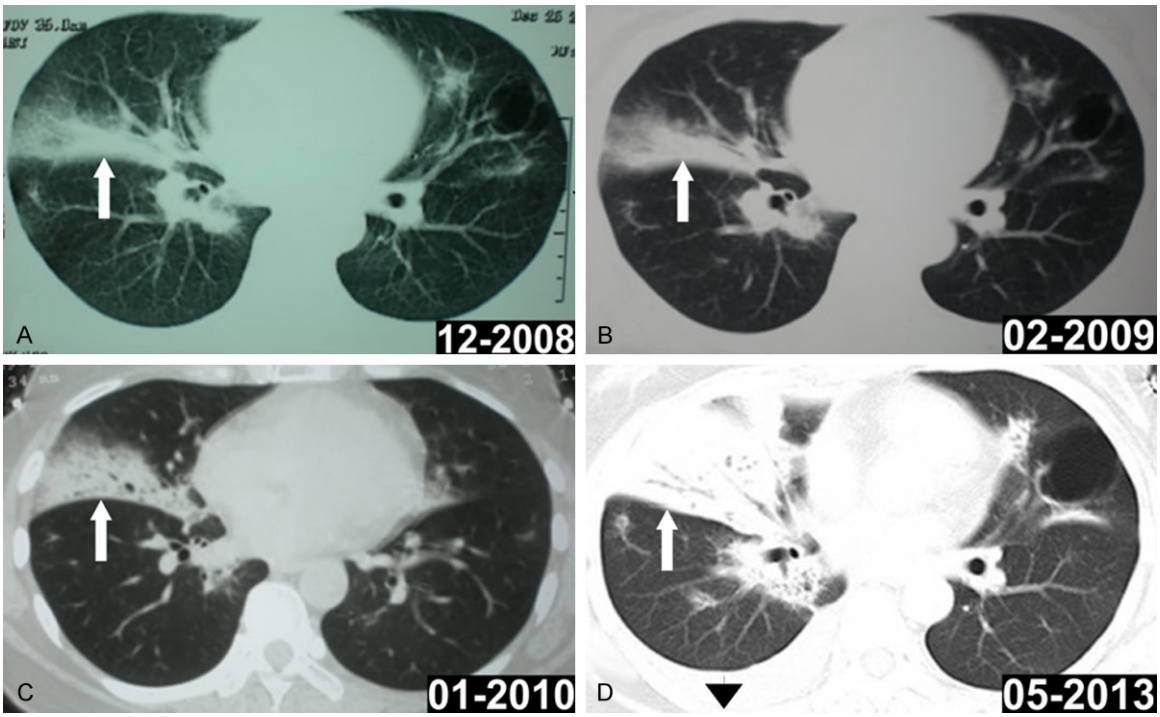

Figure 1. CT scans of nearly the same section of chest from 2008–2013 showed lesions and consolidation with signs of air bronchogram in the middle lobe of the right lung (A→D, white arrow). Right pleural effusion can be seen (D, black arrowhead).

reported a likely diagnosis of LIP. Consultation with local pulmonologists and pathologists resulted in LIP becoming the top consideration. Hence, a therapeutic regimen of oral prednisone was recommended to the patient. However, for fear of the adverse effects of long-term oral glucocorticoid treatment, the patient did not comply with the prescribed treatment and instead decided to observe the development of disease by herself.

Since then, she repeatedly experienced episodes of coughing with purulent sputum, as well as improvement in her symptoms after anti-infective treatment using ceftazidime and levofloxacin or sulbactam+cefoperazone (sulperazon). Her chest CT scans were reexamined twice, once in February 2009 and another in January 2010. The CT scan showed that the lesions in the middle lobe of right lung increased in size (**Figure 1A-D**). At the same time, new ill-defined infiltrates with non-homogeneous densities were also observed in both lungs. Biopsy of the samples obtained through bronchoscopy in February 2009 indicated large amounts of small lymphocytes infiltrated into the lesions, which was regarded as diagnostic evidence of LIP. The patient was once again prescribed oral glucocorticoid treatment but the patient refused treatment again. From onset until the current consultation, she only underwent symptomatic treatment.

Ten days before admission, she developed right chest pain. Chest ultrasonography showed right pleural effusion. Her symptoms improved slightly after taking sulperazon and azithromycin. However, the pleural effusion not only remained unresolved but instead increased significantly. She was admitted to our hospital in May 2013.

The patient is a pulmonologist with 20-year occupational history and denies any history of asbestos and silica exposure. She was a non-smoker and has no family history of disease.

Upon physical examination, her axillary temperature was 36.5°C, her blood pressure was 118/68 mm Hg, her pulse rate was 78 beats/min, and her respiratory rate of 20 breaths/min. There were no signs of butterfly erythema or swelling in her face and no palpable lymph nodes. Her sternum was non-tender and

Table 1. Laboratory values

Items	February-2009	May-2013	Units
WBCs	4.6	5.7	K/cumm
Neutrophil	65.9	71.7	percentage
Lymphocyte	21.8	19.1	percentage
Hemoglobin	12.5	12.3	g/dL
Platelets	241.0	288.0	K/cumm
ESR	14.0	90.0	mm/h
CRP (N<0.6)	1.2	9.9	mg/L
Urea nitrogen	6.1	5.87	mmol/L
Creatinine	45.0	52.8	umol/L
Plasma protein	6.0	7.3	g/dL
Albumin	3.6	4.3	g/dL
Bilirubin	8.9	9.2	umol/L
Alanine transaminase	15.0	13.0	IntUnits/L
Aspartate transaminas	16.0	15.0	IntUnits/L
IgG (N=7-16)	10.3	12.0	g/L
IgA (N=0.7-2.5)	1.7	2.2	g/L
IgM (N=0.6-2.1)	3.1	9.9	g/L
C3 (N=0.8-1.5)	1.1	1.0	g/L
C4 (N=0.1-0.4)	0.28	0.22	g/L
Autoantibody	Negative	Negative	No
AFB of sputum	Negative	Negative	No
HCV	Negative	Negative	No
HIV	Negative	Negative	No

WBC = white blood cell; C = Complement; ESR = erythrosedimentation; CRP = C reaction protein; AFB: acid-fast bacilli.

she had clear breath sounds with no rales. Right lower chest was dull to percussion. Heart sound was normal without murmurs. The remainder of her physical examination was unremarkable.

Laboratory values are shown in **Table 1**. Biochemical examination of the pleural effusion was exudative. After admission, a reexamination of the chest CT scan in May 2013 showed that lungs had scattered ground-glass patches showing signs of air bronchogram and bullae. In contrast with prior chest imaging, lung lesions were aggravated and complicated, with right pleural effusion. There was no tumefaction of mediastinal lymph nodes and transbronchial lung biopsy revealed significant lymphadenosis.

Autopsy findings

At this point, the diagnosis was still unclear. Hence, bronchoscopic needle biopsies were performed. Hematoxylin and eosin (HE) staining of the lung specimens and observation under light microscopy indicated a huge number of small lymphocytic clusters (**Figure 2A**). Immunohistochemistry (IHC) of the lung tissues indicated that CD20 and CD43 were positively expressed, which revealed B cell lymphoma (**Figure 2B** and **2C**). Immunoglobulin heavy chain (IgH) gene rearrangement showed 100 bp band display in the first lane of the specimens from the lung tissues of the patient (**Figure 3** black arrow). Therefore, according to the results of the HE stain, IHC, and IgH gene rearrangement, the final diagnosis was low-grade B-cell MALT lymphoma of lung. After five cycles of chemotherapy (CVP), partial remission was achieved but a local recurrence was observed four months later.

Discussion

We described a patient suffering from lung MALT lymphoma that underwent a long and tedious process before a diagnosis was reached. However, diagnosis is only the beginning and several questions still need to be addressed. For instance, is the lung MALT lymphoma the primary cause or was it secondary to LIP and are there any links between the two diseases. We carefully studied her past medical history and clinical data for the past five years and reached a conclusion based on the clinical features, radiological characteristics, and histopathologic examination-the MALT lymphoma of the lungs was primary.

The clinical manifestation of the patient included chronic and progressive cough, fever, shortness of breath, and weight loss. However, the clinical manifestations were nonspecific and, thus, could not be used to definitively diagnose between LIP and lung MALT lymphoma. Recurrent respiratory tract infection (RRI) and progressive lesions in both lungs were the most predominant manifestations from 2008 to 2013. The RRI implied that the patient likely had immunodeficiency. Idiopathic LIP is very rare, whereas acquired LIP occurs most commonly in patients who have Sjogren's syndrome, acquired immunodeficiency syndrome, or Castleman's disease [1-3]. There were no autoimmune or immunodeficiency diseases found in this patient. On the other hand, monoclonal

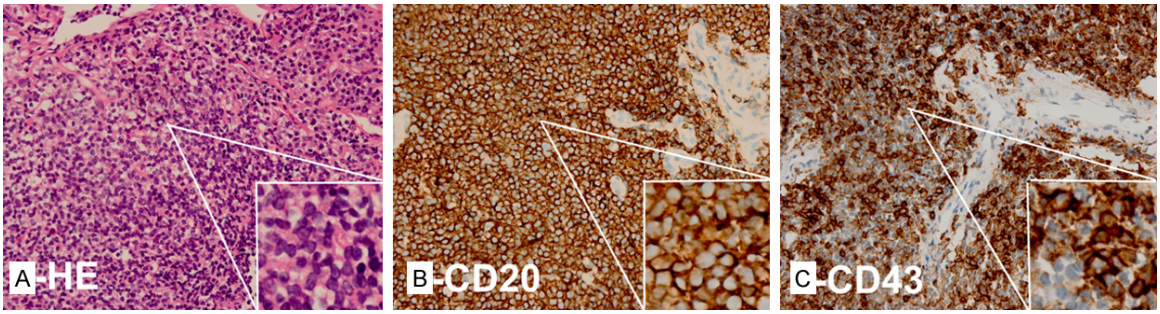

Figure 2. Pathological findings indicated numerous clusters of small lymphocytes through HE staining (A); IHC of lung tissues showing expression of CD20 and CD43 through positive staining (B, C).

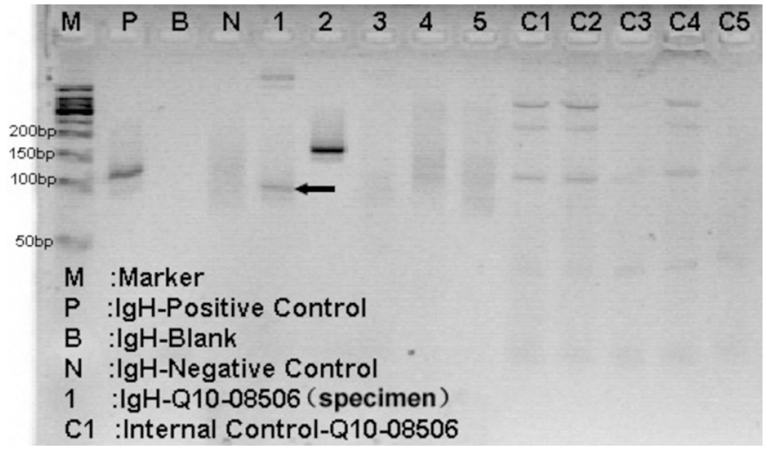

Figure 3. Immunoglobulin heavy chain (IgH) gene rearrangement showed 100 bp band display in the first lane of the specimens of the lung tissues of the patient (black arrow).

hyperimmunoglobulinemia, which is caused by plasma cells and was detected in early 2009, is one of the most important immunological characteristics in MALT lymphoma of lungs [4]. However, LIP usually presents with hypoimmunoglobulinemia, especially IgG [5].

The results of chest imaging of the patient supported a diagnosis of MALT lymphoma. The dominant CT features of LIP are ground glass attenuation, centrilobular and subpleural lung nodules, and thickening of the interlobular septa [6]. The prominent CT feature of lung MALT is pulmonary consolidation with air bronchogram [7]. Chest CT scan of the nearly same section showed persistent consolidation with an air bronchogram in the middle lobe and lack of LIP characteristics (**Figure 1**, white arrow). Right pleural effusion further supported evidence of malignant lymphoma. However, radiographic features merely presented the possibility of diagnosis and supplied clinical clues that could not be used as basis for diagnosis. These features could sometimes appear deceptive, particularly for patients with atypical features upon chest imaging.

Histopathologic examination is recognized as the gold standard for the final diagnosis of MALT lymphoma of lung and has three levels: HE staining, immunohistochemistry, and gene rearrangement. Large numbers of small lymphocytes that were identical size and morphology were seen in the HE stained sections (**Figure 2A**). According to patient's medical records, HE staining and IHC were also conducted in 2009, which indicated a number of small B lymphocytes in the lung tissue sections. However, an examination of the IgH gene rearrangement was performed at that time, which played a decisive role in the subsequent diagnosis. Most of the cases of pulmonary MALT lymphoma can be diagnosed based on morphology and immunohistochemistry staining if the lesions are typica1. However, PCR detection of IgH gene rearrangement would be helpful in differential diagnosis. Hence, when HE staining and IHC are not definitive, IgH gene rearrangement should be used for exclusion. In addition, t (11;18) (q21;q21) is a specific chromosomal translocation associated with MALT lymphoma, thus, gene detection would be even more helpful for the diagnosis [8].

Nonetheless, lung MALT lymphomas are a subgroup of low-grade B-cell lymphomas that arise from extranodal sites that have accumulated MALT because of a chronic inflammatory disorder. On the other hand, LIP is a chronic and inflammatory disorder of the lung, and very few MALT lymphomas of the lung are secondary to LIP [9]. Therefore, we could not absolutely exclude that it was secondary to LIP. As far as this case is concerned, we provided a detailed description of evidence that supported findings that the MALT was the primary diagnosis. However, there were some clinical features that were not completely accounted for by the MALT lymphoma. For instance, Treasure *et al.* found all their eight low-grade MALT lymphomas to be negative for CD43 , whereas some reports have stated that mantle cell lymphomas are positive for CD43 [10, 11]. Positive CD43 expression occurs more often in mantle cell lymphomas than in low-grade MALT lymphomas [12]. However, positive CD20 and CD43 expression is characteristic of mantle cell lymphomas. Thus, recognition of MALT lymphoma remains problematic in many circumstances and mantle cell lymphoma is less likely to be diagnosed [13]. Therefore, this patient could be an aberrant phenotype of lung MALT lymphoma or a phenotype of other B cell lymphomas.

Conclusions

Differentiating between lymphocytic interstitial pneumonia and MALT lymphoma of the lungs is difficult based solely on clinical manifestations and chest imaging. Therefore, histopathologic examination is essential for a definitive diagnosis. Even so, recognition of lung MALT lymphoma and LIP remains problematic in many circumstances, thus, doctors should be cautious in making a diagnosis.

Disclosure of conflict of interest

None.

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