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CASE REPORT

Rare case of primary pleural lymphoma presenting with pleural effusion

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Abstract

Primary pleural lymphoma is rare and has been described in association with human immunodeficiency virus (HIV) infection or pyothorax. We report a rare case of primary pleural lymphoma in a 73-year-old man who presented with chest pain and no history of HIV infection or pyothorax. Chest imaging showed pleural thickening and pleural effusion. Thoracoscopic pleural biopsy was performed. Histopathological and immunohistochemical examinations conformed to that of a diffuse large B-cell lymphoma. Physicians should be aware of this rare location of primary lymphoma and implement thoracoscopy as soon as possible.

Introduction

Pleural involvement by malignant lymphoma is common; during the development of the disease process about 16% of patients with non-Hodgkin's lymphoma (NHL) present with or subsequently develop pleural involvement.[1] However, primary pleural lymphoma is extremely rare, accounting for only 7% of all lymphomas.[2] It has been reported that the most common NHL arising in the pleura is diffuse large B-cell lymphoma (DLBCL), accounting for approximately 30% of the total number of NHL and showing an increasing trend.[3] In recent years, an in-depth study of DLBCL revealed that it was highly invasive. DLBCL has obvious heterogeneity in clinical presentation, morphological features, genetic characteristics, immune phenotypes, and other aspects. More and more evidence suggests that DLBCL is not an independent disease. We report a very rare case of primary pleural DLBCL diagnosed at the Shandong Provincial Hospital Respiratory, and review the literature. We also discuss pleural lymphoma based on the literature.

Case report

A 73-year-old man presented with a one-month history of left chest pain. A month previous the patient had persistent, paroxysmal, and increasing chest pain on the left side with no obvious cause. He occasionally coughed without hemoptysis, fever, night sweats or weight loss. The patient was an ex-smoker with a prior history of cerebral infarction. He had no past medical history of close contact with individuals with tuberculosis. In addition, he reported no previous history of allergy or other medical history. Before admission, a computed tomography (CT) scan of the thorax showed pleural thickening and moderate pleural effusion on the left side, without lymph node swelling in the mediastinum (Figs 1~2). To define the causes of pleural effusion, the patient was admitted to the local hospital. A thoracic drain was inserted into the left pleural cavity, which drained about 1500 mL yellow exudate. A provisional diagnosis was made, and tuberculous pleurisy was suspected. After two weeks of treatment with isoniazid and rifampicin, the pleural effusion continued

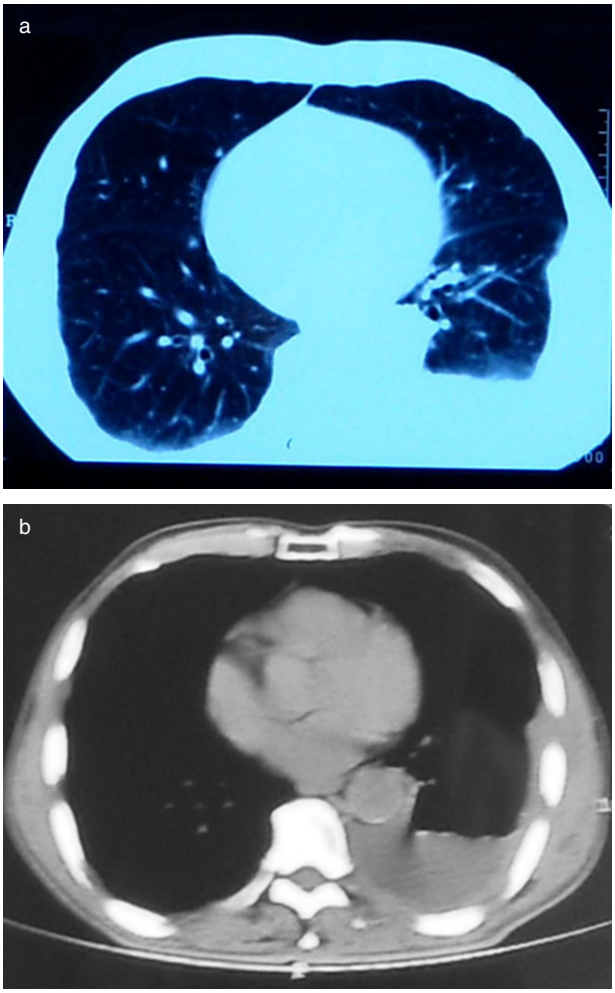

Figure 1 Computed tomography of the chest reveals (**a**) pleurisy and (**b**) pleural effusion in the left pleural cavity.

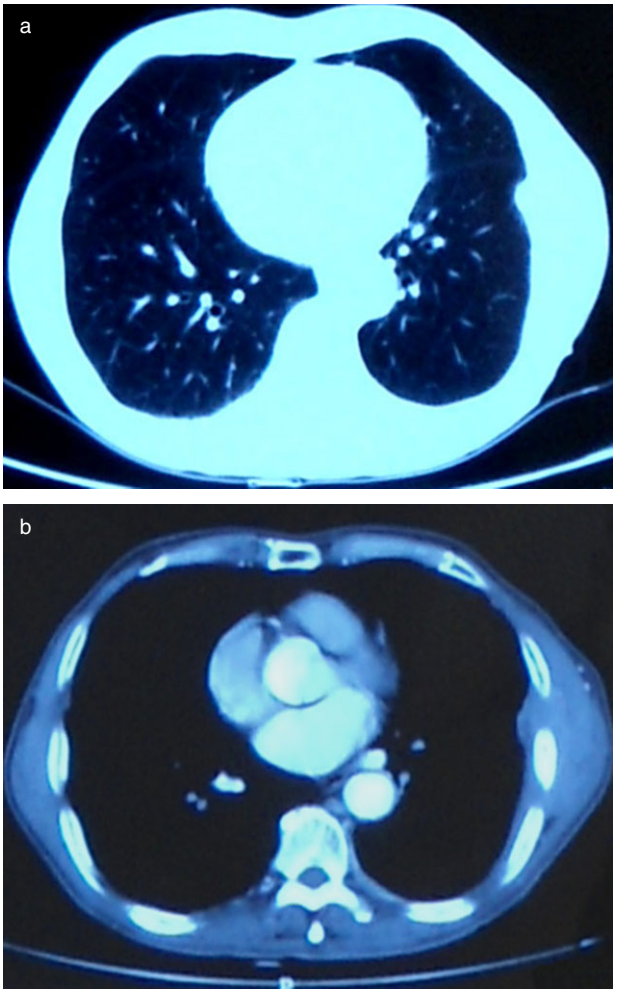

Figure 2 After drainage of pleural effusion, computed tomography demonstrates (**a**) left pleural thickening, nodular changes, and (**b**) no enlarged lymph nodes in the mediastinum.

to increase, and there was no relief of the chest pain. In order to make a further diagnosis and treatment, the patient was transferred to our department.

On physical examination the patient displayed: a temperature of 36.7°C; pulse rate of 102 beats/minute; respiratory rate of 20 breaths/minute; and blood pressure of 138/92 mm Hg. Chest examination revealed diminished breath sounds on the lower zone of the left hemithorax. No palpable lymphadenopathy was found. Hepatosplenomegaly was not present. The laboratory workup showed normal hepatic and renal functions, as well as a normal blood count. Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV) test results were negative. Erythrocyte sedimentation rate was 25 mm/hour. The tumor markers resulted in a serum neuron-specific enolase (NSE) level of 20.73 ng/mL. Tuberculosis antibody and mycobacterium γ- interferon tested were negative. Pleural fluid routine examination resulted in: a pale yellow and turbid appearance without clots; Rivalta test 1 + ; nucleated cell count of 5546 × 10 ∧ 6 /L; mononuclear cells accounted for 98%; multinucleated cells accounted for 2%; eosinophil was 1.00 × 10 ∧ 6 /L; and erythrocyte was 2.00 × 10 ∧ 9 /L. Pleural fluid biochemistry revealed: a protein content of 27.77 g/L; glucose content of 5.78 mmol/L; lactate dehydrogenase level of 650 u/L; and an adenosine deaminase level of 17.68 U/L. Carcinoembryonic antigen of pleural effusion was 0.84 ng/mL, carbohydrate antigen 125 was 951.30 U/mL, and non-small cell lung cancer-associated antigen was 7.84 ng/mL. The effusion was sterile and the Ziehl-Nielsen stain revealed no acid-fast bacilli.

Malignant mesothelioma was initially suspected. In order to confirm the diagnosis, a thoracoscopy was performed on the third day of hospitalization. The patient was placed in a lateral decubitus position, with the involved side upward. After skin sterilization, an incision was made on the posterior axillary line. Subsequently, blunt dissection was performed in

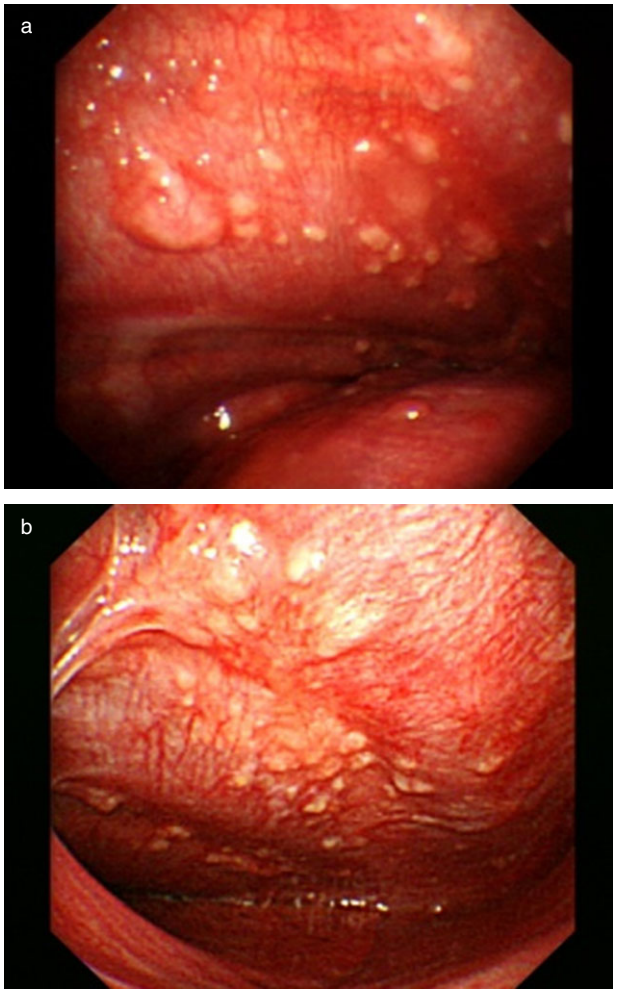

Figure 3 Thoracoscopic view of the patient shows (**a**) there are multiple nodules of varying sizes on the visceral, (**b**) parietal pleura with widespread congestion and edema.

order to enter the pleural space. The thoracoscope was then inserted, and the pleural cavity was inspected after about 800 mL of pleural fluid was completely drained. During the operation, multiple and varied nodules were seen; hyperemia and edema was widespread in the visceral and parietal pleura (Fig 3). Multiple biopsies of the lesions were performed. Pathological examinations (Figs 4, 5) showed diffuse large B-cell lymphoma (GCB type). Immunohistochemical studies revealed CD79α +, CD20 +, CD10 +, Bcl-6 +, κ +, CD3 -, CD38 -, CD138 -, λ -, MPO -, Ki-67 + (90%), and Mum-1 -. Neck, abdomen, and bone emission CT showed no abnormalities. A bone marrow biopsy was morphologically normal. A final diagnosis of primary pleural DLBCL was made. The patient received six cycles of cyclophosphamide, pirarubicin, vincristine, and prednisolone (CHOP) chemotherapy. Currently the patient has had no recidivation and continues follow-up by our department.

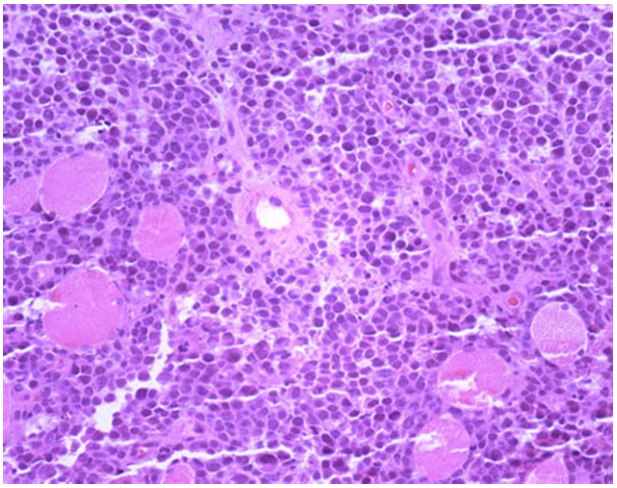

Figure 4 Pathological findings of the pleural tumor show heterotypic large-sized cells, round or ovoid nucleus, rich translucent cytoplasm, granular chromatin, multiple nucleoli, and nuclear fission is easy to see (hematoxylin and eosin staining, magnification × 400).

Discussion

Primary pleural lymphoma is very rare and has been sparsely reported.[4] Two types of primary pleural lymphoma have been described in the previous literature: primary effusion lymphoma (PEL) in patients with HIV, and pyothorax-associated lymphoma (PAL).[5,6] It has been reported that PEL is strongly associated with human herpes virus-8 infection and sporadically with EBV infection, but PAL is strongly associated with EBV infection. Most cases of pleural primary lymphoma reported in the literature have been from Japan, and indicate that as high as 2.2% of patients are associated with chronic pyothorax.[7,8] In 1987, Iuchi *et al*. first confirmed the

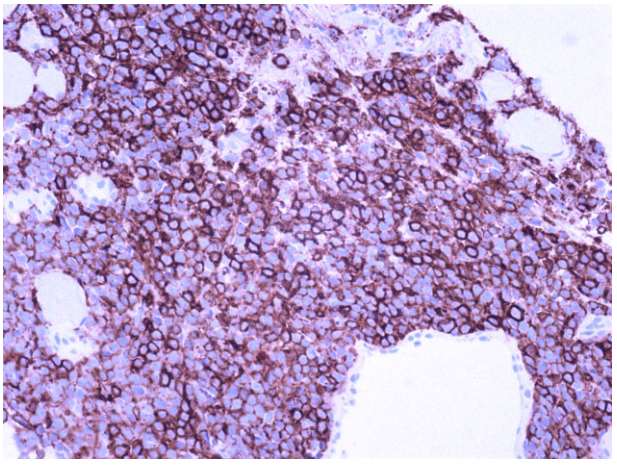

Figure 5 Immunohistochemistry staining showing CD20 positivity of the neoplastic cells (original magnification×400).

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Table 1 Summary of features of primary pleural DLBCL reported in the literature

Case No.	Age	Gender	Initial symptoms	Associated pyothorax	Radiographic finding	Diagnostic procedures	Treatment
1	69	M	Shoulder pain, abdominal pain	No	Pleural effusion (left)	Thoracoscopic biopsy	C/T
2	77	F	Chest pain, dyspnea	No	Pleural effusion (right), pleural thickening	Open thoracotomy	C/T
3	12	F	Cough, fever	Yes	Pleural effusion (left), pleural thickening	Open thoracotomy	SR+C/T
4	71	M	Cough, hemoptysis, dyspnea	Yes	Pleural effusion (right)	Thoracoscopic biopsy	C/T
5	71	F	Chest pain, fever	Yes	Pleural effusion (left)	Open thoracotomy	C/T
6	66	M	Chest pain, fever	Yes	Pleural tumors, pleural effusion (right)	Open thoracotomy	SR +C/T + RT
7	68	M	Back pain	Yes	Chest wall calcification, pleural tumors, pleural effusion (right)	Open thoracotomy	C/T + RT
8	81	M	Chest pain, dyspnea	Yes	Pleural tumors, pleural effusion (right)	CT-guided percutaneous biopsy	SR +C/T + RT
9	58	M	Chest pain, dyspnea	No	Pleural tumors, pleural effusion (left)	Open thoracotomy	no record
10	20	M	Chest pain, fever, weight loss	No	Pleural tumors, pleural effusion (left)	CT-guided percutaneous biopsy	C/T
11	80	M	Chest pain	No	Pleural tumors	Open thoracotomy	C/T + RT
12	63	F	Asymptomatic	No	Pleural effusion (right)	Open thoracotomy	C/T

CT, computed tomography; C/T, chemotherapy; DLBCL, diffuse large B-cell lymphoma; RT, radiation therapy; SR, surgical resection.

relationship between chronic tuberculous pyothorax and pleural malignant lymphoma, naming it PAL.[9] Later, they retrospectively analyzed 37 cases of PAL, and the results showed that 32 cases were B-cell type.[10] In an observational study, Shuman *et al*. reported 71 cases of lymphoma with pleural lesions, in which there were no cases of lymphoma with pleural change alone.[11] In our case, there was no history of chronic pyothorax, and investigations for HIV and mycobacterium species were negative.

The pathogenesis of primary pleural lymphoma is not yet elucidated, but may be related to the chronic inflammatory stimulation of B-cells in the pleural cavity caused by long-standing pleural disease.[4,8,12] Whether a result of genetic factors or acquired immunodeficiency, chronic pleural inflammation leads to the uncontrolled proliferation of B-cell lymphocytes, and can eventually result in the occurrence of pleural lymphoma.[13]

Primary pleural lymphoma has diverse and clinical manifestations but a lack of specificity, such as chest pain, dyspnea, cough, or fever. The patient was admitted to our hospital because of left chest pain, accompanied by a cough, consistent with previous reports.[14] The CT manifestation of primary pleural lymphoma, in addition to pleural effusion and thickening, mainly occurs from self-pleural nodules protruding into the lungs or along the pleura infiltrating growth patch or nodular shadows.[11,15] The CT appearance of our patient revealed pleural effusion on the left side, consistent with previous studies reported in the literature. Pleural effusion in patients with lymphoma can develop as a result of a variety of mechanisms, including pleural infiltration by a tumor, mediastinal lymph nodes with obstruction of the thoracic duct, or tumor obstruction of the lymphatics draining the pleura.[4,16] A diagnosis of primary pleural lymphoma is ultimately based on histopathological evidence. To our knowledge, thoracic surgery or thoracoscopic biopsy, are the methods of choice for undiagnosed pleural effusion.[17] According to cases reported so far, although any type of lymphoma can involve the pleura, diffuse large B cell is the most frequent type.[1,8]

A literature search using PubMed with the key words "pleura," "pleural," "lymphoma," "primary," and "DLBCL" found only twelve documented cases. The pertinent features of those cases and ours are summarized in Table 1. Our case probably represents the first reported case of lymphoma in China based on pleural primary lesions.

Harris *et al*. first proposed the concept of DLBCL in a study combined with clinical data.[18] The World Health Organization defines DLBCL as the hyperplasia of diffuse large B cell malignant tumor, where the tumor cell nucleus is equal to or greater than the normal phagocytic cell nucleus, or more than twice the normal lymphocyte.[19] DLBCL is the most common type of malignant lymphoma, an aggressive and rapidly progressing lymphoma in which the gastrointestinal tract is the most common site of invaded parts; however, primary pleural DLBCL is rare.[20] Although the cause of most DLBCL remains unknown, some studies show that immunosuppression is a high risk factor.[21] Most cases of DLBCL are primary, but can

develop and transform from other low invasive lymphomas. The clinical manifestations of primary pleural DLBCL are related to the lesion and invasion. Most patients experience respiratory and systemic symptoms at first, usually characterized by coughing, chest pain, dyspnea, and a low fever.

Dispute remains over the choice of first-line treatment for patients with primary pleural DLBCL.[22,23] Because of the high heterogeneity of clinical pathology, patients need individualized treatment. Currently, chemotherapy is the most frequent treatment method used, and can improve the survival and prognosis of patients, with a complete remission rate of about 35%. In 1972, the first patient with advanced DLBCL was successfully cured using CHOP treatment, and since then it has been the standard treatment.[24] In recent years, with the development of molecular targeted drugs, CD20 (+) and the application of rituxan in combination with CHOP (R-CHOP) chemotherapy has become a new method of DLBCL therapy. Pfreundschuhd *et al*. reported six-year follow-up results of the MInT experiment study, and confirmed that compared with chemotherapy alone, the addition of the anti-CD20 monoclonal antibody rituximab to CHOP chemotherapy could significantly improve survival rate.[25] Wilson *et al*. published similar results.[26] However, another study showed that rituxan plus CHOP had no curative effect.[27]

Whether there are differences in curative effect and long-term prognosis of combination chemotherapy for different primary sites of DLBCL has not yet been systematically reported.[28,29] Peyrad *et al*. conducted a multi-center clinical study, in which 150 patients were treated with R-CHOP chemotherapy.[30] Results showed a median survival of 29 months, with an actuarial two-year survival rate of 47%. Twelve patients (12/52) died of treatment-related toxicity, the most common side effect of chemotherapy being bone marrow toxicity. In a number of recent clinical studies using CHOP or R-CHOP program-based combination chemotherapy in the treatment of DLBCL, the complete response rate was 35~50%, and the total effective rate was 80~90%, further illustrating that DLBCL shows high invasiveness and a poor prognosis.[31] After diagnosis, our patient received six treatments of CHOP chemotherapy, and to date has had no relapse.

We report a very rare case of primary pleural DLBCL with no history of persistent pyothorax. What makes this case illustrative is the rarity of its location. Primary pleural DLBCL has complicated clinical manifestations and imaging features, and a laboratory examination has no specificity; therefore, it is difficult to differentiate from pleural mesothelioma or pleural metastatic tumors. Pleural thickening, patches or nodules from the pleura protruding into the lungs, and symptoms, signs, and therapeutic effects are not obvious in imaging techniques; therefore, an accurate diagnosis can only be made by thoracoscopy.

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Disclosure

No authors report any conflict of interest.

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