Clinical Case Report

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Primary diffuse large B-cell lymphoma as a chest-wall mass

A case report

Qianwen Zhang, MS[a,b], Yuanrong Ju, MS[a], Tao Qu, MS[b], Tao Wang, MS[c,*], Xiaoqin Liu, MS[d]

Abstract

Rationale: Primary diffuse large B-cell lymphoma of the chest wall is extremely rare. A majority of the pleural lymphomas develop in patients with chronic tuberculous pyothorax. The underlying mechanism might be attributed to the sustained stimulation of chronic inflammation. Surgery followed by adjuvant chemotherapy can improve the outcome in some patients with lymphoma localized only in the chest wall. Thus, an early diagnosis of pyothorax-associated lymphoma is essential as it is a malignant, life-threatening condition.

Patient concerns: A 79-year-old male complained of left-side chest pain for more than 2 months, which was not alleviated with nitrates and aspirin. The patient presented an intermittent low fever, anorexia, and marasmus, accompanied by tuberculosis 40 years ago and chronic left-side pyothorax. Also, ANCA (antineutrophil cytoplasmic autoantibody)-associated vasculitis occurred for >3years.

Diagnosis: Computed tomography scan showed a solid mass in the left lateral chest wall. The patient underwent ultrasonic-guided biopsy of the lesion. A diagnosis of primary diffuse large B-cell lymphoma of the chest wall was established after histological examination.

Intervention: Due to advanced age and poor physical condition, the patient received CHOP chemotherapy at a reduced dose.

Outcomes: The patient died 5 days after the first cycle of chemotherapy with severe dyspnea and high fever.

Lessons: The chronic inflammation stimulation might result in the development of lymphoma in the chest wall of patients with long-term pyothorax, vasculitis, or other autoimmune diseases associated with malignancies. The fever, chest pain, or other nonspecific clinical symptoms in these patients should be under intensive focus as it might indicate the development of malignant lymphoma. Thus, histological examination in these patients is essential for accurate early diagnosis.

Abbreviations: α-HBDH = α-hydroxybutyrate dehydrogenase, ANCA = antineutrophil cytoplasmic autoantibody, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisolone, CT = computed tomography, DLBCL = diffuse large B-cell lymphoma, DNA = deoxyribonucleic acid, EBV = Epstein–Barr virus, IL-10 = interleukin 10, IL-6 = interleukin 6, LDH = lactate dehydrogenase, NSE = neuron-specific enolase, PAL = pyothorax-associated lymphoma, PCR = polymerase chain reaction.

Keywords: chest wall, diffuse large B-cell lymphoma, pyothorax-associated lymphoma

1. Introduction

Primary diffuse large B-cell lymphoma (DLBCL) of the chest wall is a rare disease. It often develops in patients with a prolonged history of pyothorax, and therefore, is speculated to be associated with pyothorax.[1–3] The pyothorax-associated lymphoma (PAL) is a non-Hodgkin's lymphoma that develops from chronic pyothorax usually resulting from artificial pneumothorax for the treatment of lung tuberculosis or tuberculous pleuritis. PAL was originally described as a distinctive clinicopathological entity in 1987, and currently, is listed as a distinct disease accompanied by primary effusion lymphoma (PEL) in the recent World Health Organization (WHO) classification for "Tumors of the Lung, Pleura, Thymus, and Heart."[4]

However, the mechanism underlying PAL has not yet been elucidated. The sustained stimulation of chronic inflammation or injury might be ascribed to PAL.[5–7] In addition, some lymphomas are often associated with vasculitis.

Chest pain is a common symptom of PAL but is unusual in cases of chronic pyothorax. A majority of the patients usually presented symptoms such as chest pain, fever, or marasmus for

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[a] Department of Respiratory and Critical Care Medicine, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, [b] Department of Respiratory, Weihai Municipal Hospital, Weihai, [c] Shandong Medical Imaging Research Institute Affiliated to Shandong University, Jinan, [d] Department of Pathology, Weihai Municipal Hospital, Weihai, Shandong, China.

[*] Correspondence: Tao Wang, Shandong Medical Imaging Research Institute Affiliated to Shandong University, 324 Jingwu Weiqi Road, Jinan, Shandong 250021, China (e-mail: 1142555214@qq.com).

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months.[8–10] The nonspecific clinical symptoms may lead to a delay in the diagnosis, and the disease might be misdiagnosed as angina, nonspecific pleuritis, or another disease.

Patients with lymphoma are usually treated with chemotherapy or local irradiation. DLBCL is frequently treated using CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Interestingly, whether patients with lymphoma in the chest wall should undergo surgical resection is yet controversial. Surgery followed by adjuvant chemotherapy can provide a satisfactory outcome in some patients with lymphoma localized only in the chest wall. Subsequently, patients present a satisfactory prognosis especially when the diagnosis is made at a local stage suitable for surgical resection.[11,12]

Furthermore, the detection and early diagnosis of PAL is essential as it is a malignant, life-threatening condition.

Herein, we reported the case of a patient with a primary DLBCL of the chest wall and raised concern about the disease with respect to early diagnosis and appropriate treatment.

2. Case presentation

A 79-year-old Chinese male was admitted to the Department of Respiratory, Weihai Municipal Hospital on May 9, 2018, due to the left-side chest pain for >2 months, with constitutional symptoms including intermittent low fever, anorexia, and recent weight loss. The chest pain aggravated intermittently, and the patient visited the Department of Cardiology. While no dynamic change was detected in the ST-segment in electrocardiogram with aggravated left-side chest pain, the treatment with nitrates and aspirin did not have an obvious effect; however, the application of nonsteroidal anti-inflammatory drugs could relieve the pain. Also, other symptoms such as a cough, expectoration, or dyspnea were not observed. The patient suffered from tuberculosis, which was treated with streptomycin about 40 years ago; also, a chronic left-side pleural effusion was detected that had not been treated by drainage procedures such as closed thoracostomy or percutaneous catheter aspiration. In addition, the patient's previous chest computed tomography (CT) scan in 2015 displayed chronic encapsulated pleural effusion with pleural thickening in the left thoracic cavity (Fig. 1). The other past medical history included cerebral infarction 2 years ago and antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis with renal involvement that had been treated with prednisone acetate for >3 years.

The patient exhibited a poor general status, and the physical examination showed a palpable, immobile mass in the left lateral chest wall, measuring approximately 10 cm × 10 cm. The left thoracic cage was collapsed, the sound of breath was decreased in the left lung, and no positive sign was found in the physical examination of the heart and abdomen.

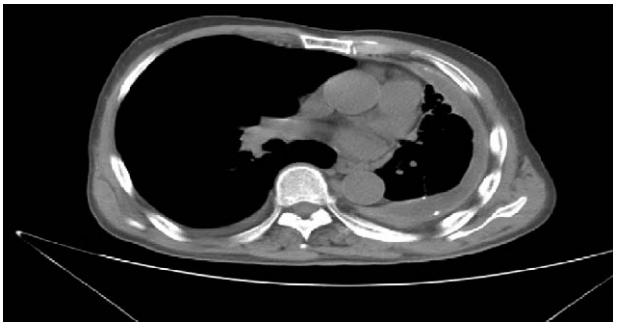

Figure 1. Computed tomography scan in 2015. The chronic encapsulated pleural effusion with pleural thickening in the left thoracic cavity. No mass was detected in the pleura or chest wall.

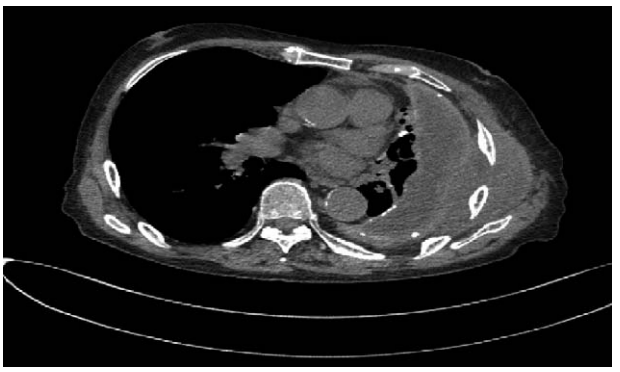

Figure 2. Computed tomography scan on May 3, 2018. A solid mass was seen in the left lateral chest wall, involving several ribs. Encapsulated effusion increased more than that in 2015.

The CT scan on May 3, 2018 (Fig. 2) revealed a solid mass in the left lateral chest wall, involving several ribs, and the left encapsulated effusion increased more than that in 2015. The three-dimensional reconstruction image showed an abnormality in the bone cortex of the anterior part of the left 5th rib, indicating the probability of a fracture (Fig. 3).

The laboratory examination displayed that the levels of serum LDH (lactate dehydrogenase, 1043.1U/L, reference: 0–250) and α-HBDH (hydroxybutyrate dehydrogenase, 985 U/L, reference: 76–196) were elevated, while the serum level of neuron-specific enolase (NSE) was 151.4 ng/mL (reference: 0–17) and the serum PCR (polymerase chain reaction) quantitation of EBV-DNA (Epstein–Barr virus deoxyribonucleic acid) was 5.0×10^4 (reference: 0–1000) IU/mL.

The routine blood test of the patient did not show any significant abnormality: white blood cells (WBCs) 6.32×10^9/L, neutrophils (NEUT) 4.79×10^9/L (NEUT%, 75.7), lymphocytes (LYMPH) 0.71×10^9/L (LYMPH% 11.2), monocytes (MONO) 0.81×10^9/L (MONO% 12.8), basophils% (BASO%) 0.2%,

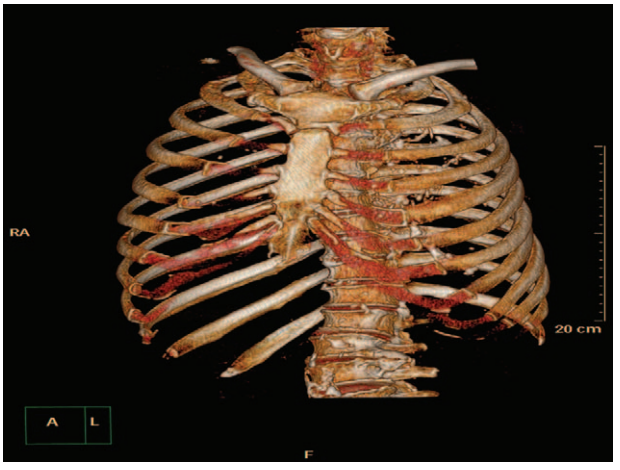

Figure 3. Three-dimensional image of ribs' reconstruction. The abnormality was observed in the bone cortex of the anterior part of the left 5th rib, which indicated the probability of fracture.

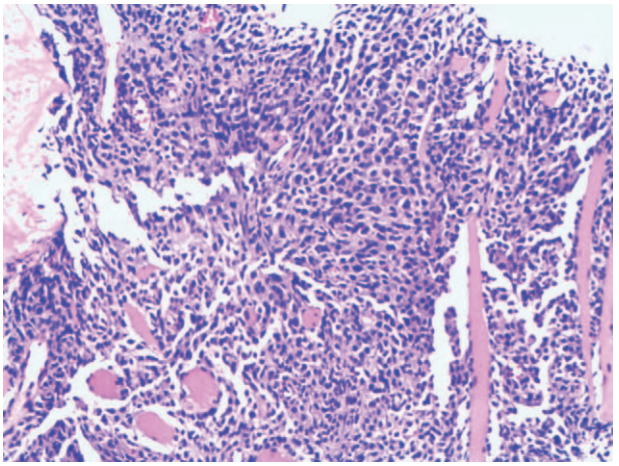

Figure 4. Hematoxylin and eosin (H&E) staining of histopathology (×100). The diffused proliferation of lymphoid cells was observed.

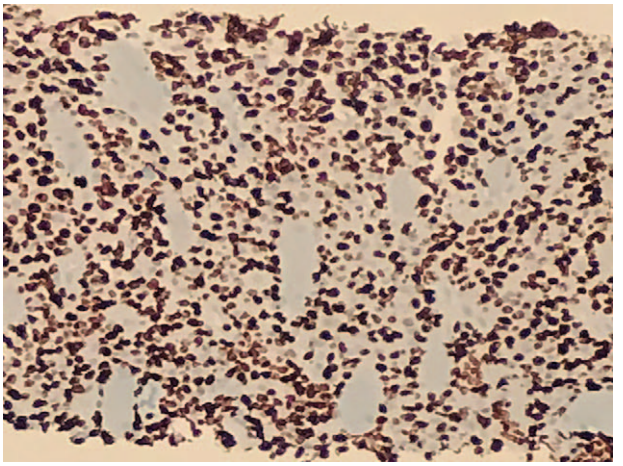

Figure 6. Immunohistochemistry of Ki-67 (+80%) (×100). The Ki-67 index was 80%.

eosinophils% (EO%) 0.1%, red blood cells (RBCs) 4.33×10^{12}/L, hemoglobin (HGB) 135 g/L, and platelets (PLT) 140×10^{9}/L. The level of serum urea nitrogen (8.2 mmol/L, reference: 3.2–7.1) and creatinine (163.5 μmol/L, reference: 36–100) indicated impaired kidney function, and the index of urine protein was 3+.

The patient underwent ultrasonic-guided biopsy of the chest-wall lesion under local anesthetic. The histopathology result was suggestive of DLBCL. The results of immunohistochemistry were provided as follows (Figs. 4–6): CK-pan(−), Vimentin (3+), LCA (3+), CD5 (seldom dispersed positive expression), c-Myc (+45%), CD20(3+), CD79α(1+), CD117(−), P63(dispersed weakly positive expression), P40(−), CK5/6(−), CD99(−), NSE(−), Desmin (−), CD34(−), S-100(−), CD3 (seldom dispersed positive expression), Bcl-2(1+), Bcl-6(−), CD10(−), MUM1(−)CD21 (−), CD23 (dispersed positive expression), and Ki-67 (+80%).

Interestingly, the abdominal CT scan and brain magnetic resonance imagining (MRI) were negative for metastasis.

Based on these findings, the lesion was diagnosed as primary DLBCL of the chest wall, and the patient was referred to the Department of Hematology. Due to the advanced age, poor physical condition, and comorbidities, the patient received CHOP chemotherapy with a reduced dose (cyclophosphamide 0.4 g, doxorubicin 20 mg, vincristine 4 mg, and dexamethasone10 mg/day for 7days). However, the patient died 5 days after the first cycle of chemotherapy with severe dyspnea and high fever.

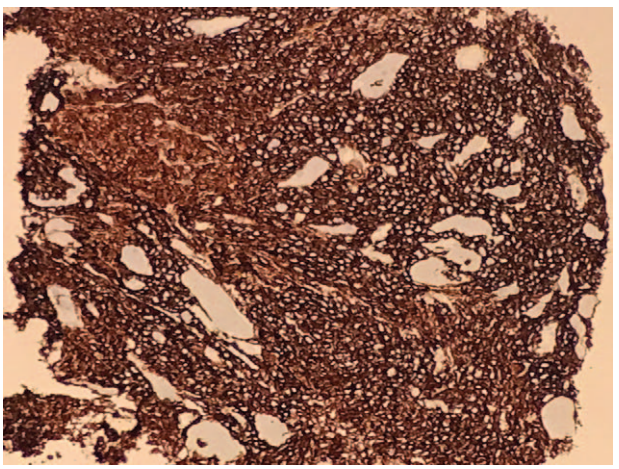

Figure 5. Immunohistochemistry of CD20 (3+) (×100). The staining was diffusely positive for CD20.

3. Discussion

Primary malignant lymphoma originating from the pleura is uncommon, comprising of only about 2.4% of the primary chest wall tumors.[13] Intriguingly, 4/250 patients with lymphoma presented isolated chest-wall lesions.[14] Reportedly, DLBCL is the most common subtype of primary lymphoma of the chest wall.[15] A majority of the pleural lymphomas develop in patients with chronic tuberculous pyothorax or a history of artificial pneumothorax, and most cases of this disease are reported in Japan,[16] while a few were documented in Western countries.[17] The study by Aozasa et al[18] revealed that the patients receiving artificial pneumothorax experienced a significant increase in the risk of development of pleural lymphoma (relative risk = 4.92, $P < .05$). Thus, chronic nonhealing inflammation was suggested to be caused by artificial pneumothorax in the pleural cavity, which in turn, resulted in the development of pleural lymphoma.

Pyothorax-associated lymphoma (PAL) is a non-Hodgkin's lymphoma that develops in the pleural cavity after a prolonged history of pyothorax resulting from pulmonary tuberculosis or tuberculous pleuritis,[4] and it occurs in 2% of the patients between 22 and 55 years after the onset of tuberculosis. Moreover, the study by Nakatsuka et al,[19] reviewed 106 patients with PAL assimilated through a nationwide survey in Japan. These patients, aged 46 to 82 (median, 64) years and a male/female ratio of 12.3:1, had a 20- to 64-year (median, 37-year) history of pyothorax originating from artificial pneumothorax for the treatment of pulmonary tuberculosis (80%) or tuberculous pleuritis (17%). The most common symptom at the time of admission was chest and/or back pain (57%) and fever (43%). The serum NSE level was occasionally elevated (3.55–168.7; median 18.65 ng/mL), thereby suggesting a putative diagnosis of small-cell lung cancer. PAL showed a diffused proliferation of large cells of B-cell type (88%) histologically and EBV-positive in 70% of the patients by the in-situ hybridization study.

Although the pathogenesis of PAL has not yet been elucidated, chronic inflammation has been considered as a significant cause. The chronic stimulation of B cells at the site of chronic inflammation results in the production of cytokines such as interleukin 6 (IL-6) and interleukin 10 (IL-10), inducing a local immunosuppressive environment that plays a critical role in neoplastic cell growth.[5–7,16,17,20] The production of IL-10, an immunosuppressive cytokine, might contribute to the development of overt lymphoma. The present study suggested that immunosuppressive cytokine plays a role in the lymphomagenesis of immunocompetent patients.[21]

Other mechanisms comprise antecedent autoimmune disease and EBV infection. Moreover, several studies found that PAL is strongly associated with the latency III form of the EBV infection.[1–3,22–24] Reportedly, malignant lymphoma has been associated with antecedent autoimmune diseases.[4] In some patients, vasculitis occurred during or prior to malignancies that were hematological rather than solid tumors. The malignancies with vasculitis were predominantly hematological (myelodysplastic syndromes and lymphoid), and non-Hodgkin's lymphomas were often associated with vasculitis than Hodgkin's disease.[25] Baecklund et al[26] revealed that the risk of lymphoma is substantially increased in a subset of patients with severe rheumatoid arthritis. High inflammatory activity is a major risk determinant rather than the treatment.

Another theory is trauma to the thorax. Fujimoto et al[27] reported a patient with EBV-associated DLBCL that was developed in the chest wall after a polyethylene terephthalate surgical mesh was implanted during surgery for squamous cell lung carcinoma. Thus, surgical implants were speculated to cause localized, long-standing inflammation that might enable EBV-transformed B-cells to escape from host immune surveillance, in turn, leading to lymphomagenesis. Atoini et al[28] reported another patient with a history of blunt trauma with swelling and rib fracture developed with DLBCL in the chest wall after 41 years. Thus, it was proposed that chronic post-traumatic inflammation leads to tumor proliferation.

In the current study, the patient with chest pain as the main complaint developed DLBCL of the chest wall after 40 years of tuberculous pleuritis. According to the mechanisms described above, the chronic inflammation due to the prolonged history of chronic tuberculous pleuritis and ANCA-related vasculitis, an autoimmune disease, might account for the pathogenesis. In addition, the quantitation of elevated serum EBV-DNA indicated that EBV infection might play a role in the pathogenesis. The high level of serum NSE, which originally suggested a putative diagnosis of small-cell lung cancer, indicated the development of PAL.

The overall prognosis of PAL was poor with a 5-year survival of 21.6%.[19] The stage of malignancy and histopathological diagnosis exert a major impact on the treatment and prognosis of PAL. Chemotherapy is the primary treatment for DLBCL, with or without chest-wall involvement, and the most common regime is CHOP. Lymphoma commonly responds to chemotherapy; however, in patients with PAL, the treatment might be challenging due to persistent pyothorax. Intriguingly, whether patients with lymphoma only in the chest wall should undergo surgical resection is yet controversial. Thus, it is suggested that surgical resection could be used in the diagnosis and management of some selected extranodal locations.[12] Because tumor burden is a critical predictor for survival in patients with lymphoma, surgery as front-line therapy in patients with resectable early stage DLBCL has been proposed.[12]

Based on the current reports, surgical resection and adjuvant chemotherapy might improve the prognosis.[11,12] Romagurea et al[11] reported that surgical debulking is associated with improved survival in stage I-II DLBCL. In the study by Luh et al[1], a patient with DLBCL that was developed from a prolonged pyothorax of the left lower chest wall remained free of local recurrence or metastasis at 9 months after surgical resection without further chemotherapy. The study by Hsu et al,[12] demonstrated that 3/4 patients with isolated chest wall lymphoma, treated with resection and adjuvant chemotherapy remained disease-free during the follow-up period; the maximum duration was 171 months. Thus, it is indicated that patients have a satisfactory prognosis after diagnosis at a local stage suitable for surgical resection.

In the current case, the outcome of the patient with respect to physical condition and comorbidities was not adequate. Failure to diagnose accurately in an early stage might partially account for the poor prognosis. Therefore, early and accurate diagnosis is essential. In patients with a prolonged history of pyothorax, a pleural soft-tissue mass adjacent to the margin of a coexistent empyema cavity suggested the presence of PAL; especially, in patients with fever or chest pain. An elevated serum NSE level in patients with chronic pyothorax may be an indicator of PAL development.[29] Similarly, it is necessary to consider the possibility of malignant lymphoma when pleural masses were observed in patients with the antecedent autoimmune disease, occasionally in the absence of preceding inflammatory disease.

4. Conclusions

The sustained stimulation of chronic inflammation or injury might result in the development of lymphoma of the chest wall in patients with long-term pyothorax or thoracic trauma. Vasculitis or other autoimmune diseases were associated with malignancies. Thus, a long-term follow-up and regular examination in these patients is essential. Taken together, the awareness of this rare entity, together with histological examination is imperative for accurate early diagnosis. The unexplained fever, chest pain, or other non-specific clinical symptoms in these patients should be under intensive focus as it might indicate malignant lymphoma development.

Author contributions

Conceptualization: Qianwen Zhang, Yuanrong Ju, Tao Qu, Tao Wang.
Data curation: Qianwen Zhang.
Formal analysis: Qianwen Zhang.
Resources: Xiaoqin Liu.
Writing – original draft: Qianwen Zhang.
Writing – review & editing: Yuanrong Ju.

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