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Successful Chemo-Radiotherapy for Primary Anaplastic Large Cell Lymphoma of the Lung: A Case Report and Literature Review

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Conflict of interest: None declared

Patient: Male, 39
Final Diagnosis: Primary anaplastic large cell lymphoma of the lung
Symptoms: Hemoptysis • palpitation • shortness of breath
Medication: Cyclophosphamide • Doxorubicin • Vincristine • Prednisone
Clinical Procedure: Chemo-radiotherapy
Specialty: Oncology

Objective: Rare disease

Background: Primary anaplastic large cell lymphoma (ALCL) of the lung is an extremely rare disease. This disease is a great challenge for pneumologists due to its nonspecific clinical presentations and radiological findings. Appropriate invasive biopsy and immunohistochemistry are important for diagnosis. There is currently no standard treatment.

Case Report: We report a very rare case of primary pulmonary ALCL in a 39-year-old man. The clinical features, imaging, pathological findings, treatment outcomes, and prognosis, are described. Successful treatment outcomes were achieved after 6 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy followed by involved field radiotherapy of 54Gy/27f. The patient was disease-free after follow-up for 65 months.

Conclusions: Our study found that chemotherapy (such as CHOP) is recognized as the first-line regimen for primary ALCL of the lung. For patients with dyspnea caused by a mass blocking the main bronchus, chemo-radiotherapy may be a reasonable therapeutic option. The prognosis is better for patients with positive ALK staining. CD56(+), age older than 60 years, Ann Arbor stage III or IV, survivin expression, PS>2, and high serum LDH level and IPI scores are the poor prognostic factors of ALCL.

MeSH Keywords: Chemoradiotherapy • Lung Diseases • Lymphoma, Large-Cell, Anaplastic

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/896096

Background

Primary lymphoma of the lung is a rare subtype of extranodal malignant lymphoma. Only 0.4% of lymphomas occur in the lung [1] and non-Hodgkin lymphoma (NHL) occurs in the lung in only 0.3% of cases [2]. Marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type (MALT lymphoma) is the most common primary NHL in the lung. Anaplastic large cell lymphoma (ALCL) often involves the lymph nodes and skin, but only very rarely occurs in the lung [1,3,4]. Although there have been sporadic reports about primary ALCL of the lung, clinical features, optimal treatment, and prognostic factors have not been well defined. The objective of this article is to report a rare case and analyze primary ALCL of the lung.

Case Report

A 39-year-old Chinese man was admitted to West China Hospital of Sichuan University complaining of palpitation and shortness of breath for more than 6 months, with deteriorated concurrent hemoptysis not alleviated by anti-inflammation treatment. The patient did not have night sweats or skin rashes, with body temperature fluctuating from 37°C to 38°C. The patient had lost about 15 kg of body weight since his illness began, with no enlargement of lymph nodes, liver, or spleen found upon palpation. Decreased breathing sound was found in his right lung.

Chest computed tomography (CT) showed a soft tissue at the right hilum with enlarged hilum and mediastinum lymph nodes (Figure 1A). PET imaging revealed abnormally enhanced uptake of 18F-FDG in the right hilum mass, with a maximum SUV of 21.68. The maximum SUV of the enlarged lymph nodes was 3.95 (Figure 1B). Bronchoscopy detected a strip of neoplasm at the orifice of the right upper bronchus that obtruded into the lumen of the right main bronchus (Figure 1C, 1D). Immunohistochemical staining of tumor cells demonstrated: CD30(+), CD45/ LCA(+), EMA(+), Vim(+), PCK(–), CK7(–), CK20(–), TTF-1(–), NSE(–), CgA(–), Syna(–), S-100(–), HMB-45(–), PLAP(–), MPO(–), CD20(–), CD3ε(–), ALK-1(–), granzyme B(–), T1A-1(–), and CD56(–) (Figure 2A–2D). Polymerase chain reaction (PCR)

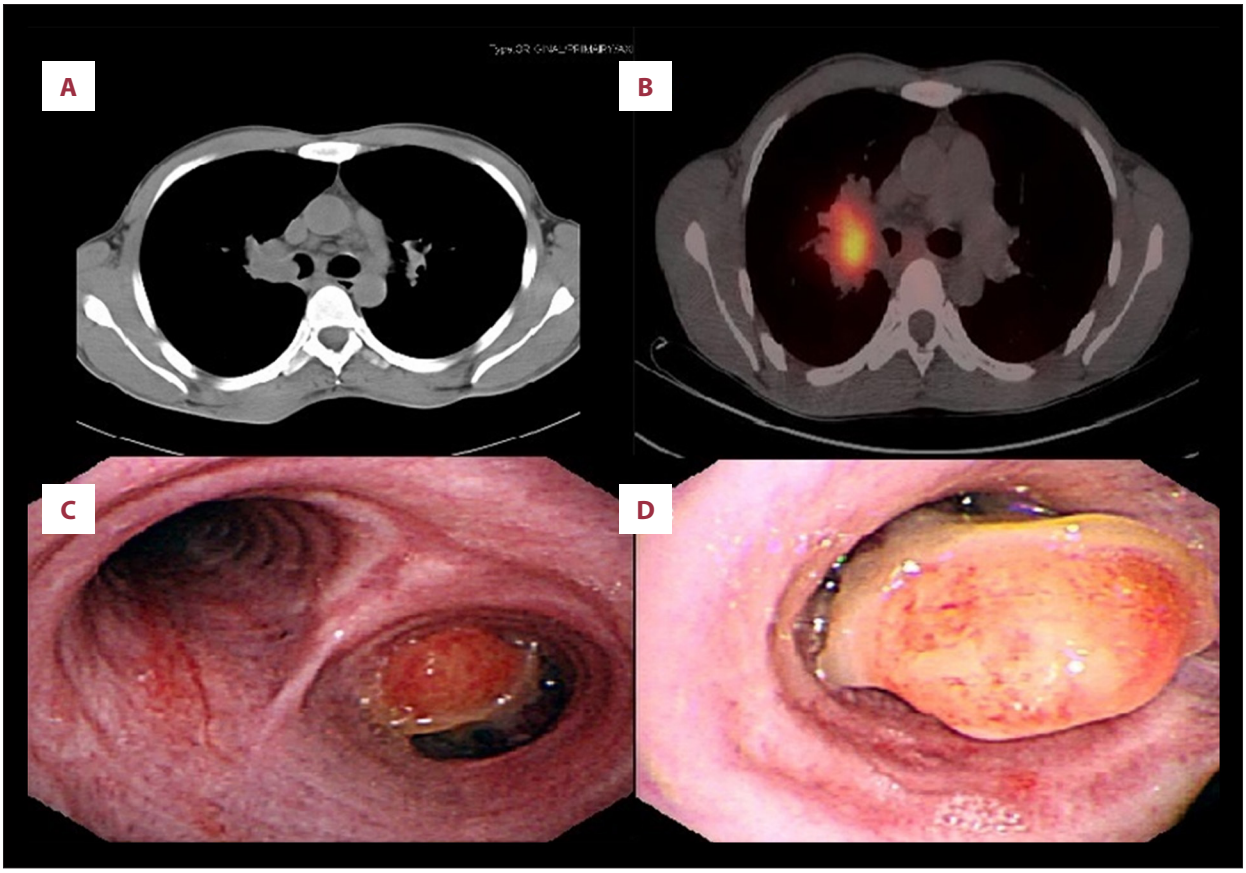

Figure 1. Chest CT scan displays a 3.1×2.8-cm soft-tissue-like mass at the right hilum, with enlargement of mediastinum and hilum lymph nodes, and invasion of adjacent upper lobe bronchus (**A**). PET/CT shows abnormal enhancement of 18F-FDG in the right hilum mass with a maximum SUV of 21.68 (**B**). Fiberoptic bronchoscopy shows a tube-like neoplasm at the orifice of right upper lobe bronchus and blocked the lumen of the right main bronchus (**C, D**).

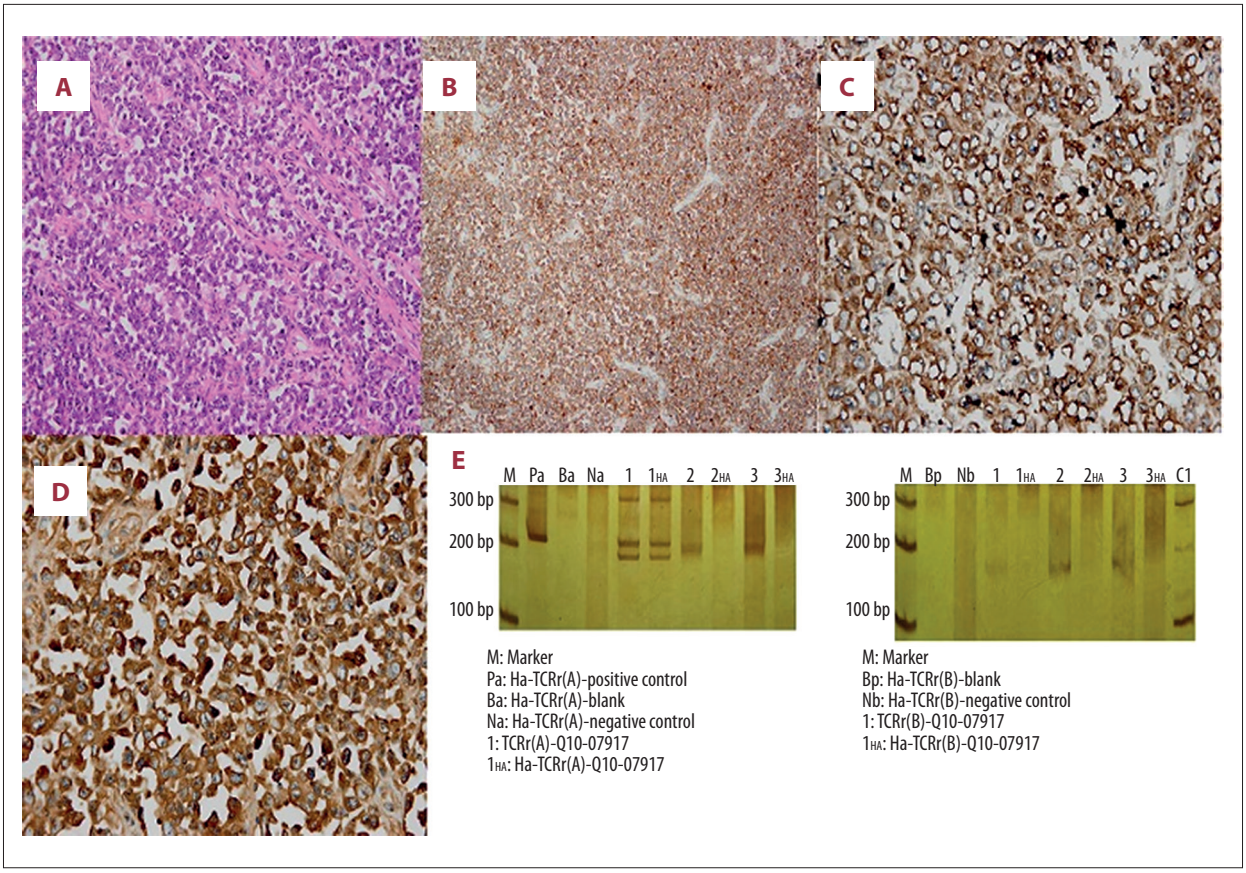

Figure 2. Monomorphic large tumor cells with abundant eosinophilic cytoplasm, round nuclei, and prominent nucleoli. Original magnification 200× (**A**). All tumor cells are strongly positive for CD45. Original magnification 100× (**B**). All tumor cells are strongly positive for CD30. Original magnification 400× (**C**). All tumor cells are strongly positive for CD30. Original magnification 400× (D). PCR assay detected clonal TCRγ rearrangement (**E**).

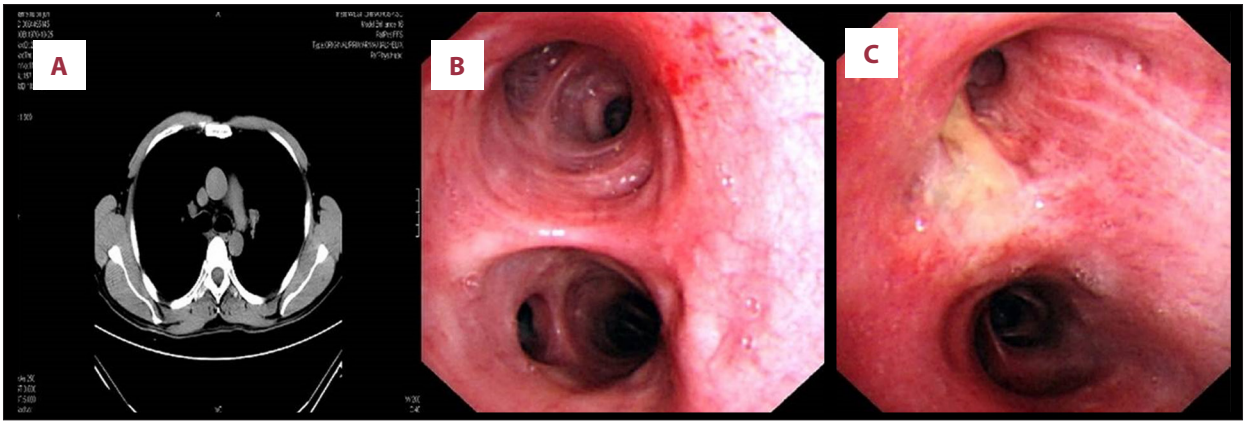

Figure 3. At the completion of treatment, CT (**A**) and bronchoscopy (**B, C**) both showed disappearance of the tumor.

assay was performed, which demonstrated clonal TCRγ gene rearrangement but no rearrangement of IgH gene (Figure 2E).

Combining the clinical and pathological findings, the patient was diagnosed with primary anaplastic large cell lymphoma of the right lung, stage IIEB, with international prognosis index (IPI) score 3 (intermediate to high risk). The patient was treated with 6 cycles of CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy, followed by involved field radiotherapy of 54Gy/27f. Chest CT scan and fiberoptic bronchoscopy were performed after treatment completion, and both demonstrated complete remission of disease

Table 1. Reported cases of primary anaplastic large cell lymphoma of the lung.

Author	Age/ sex	Presentation	Location	Immunohistochemistry*	Therapy			Prognosis
					Chemotherapy	Radiation	Surgery	
Yang et al. [5]	28/F	Cough, shortness of breath, fever	RUL, RML	CD30(+), CD3(+), CD43(+)	CHOP	NO	YES	CR, alive at 3 mos
Yang et al. [5]	17/F	Cough, fever	RUL, RLL	CD30(+), CD3(+), ALK(+)	CHOP	NO	NO	CR, alive at 6 mos
Zhang et al. [6]	18/M	Dyspnea, cough, palpitation, fever	Mediastinum	ALK(+)	CHOP	YES	NO	NA
Barthwal et al. [l7]	23/M	Cough, fever, weight loss, breathlessness	LUL	CD30(+), ALK(+)	YES**	NO	NO	Died at 5 mos
Han et al. [8]	55/M	Cough, night sweating	LUL	CD30(+), CD3(+)	CHOP	NO	NO	NA
Cerimagic et al. [9]	46/M	NM	NM	CD30(+), vimentin(+) LCA(+)	YES	NO	NO	NA
Guerra et al. [10]	NM	Cough, chest pain, fever	Left bronchus	NM	YES***	NO	NO	CR, alive at 36 mos
Rush et al. [11]	27/F	Cough, sweats, pruritus	LUL	CD30(+), CD45RO(+)	YES(NM)	YES	NO	NED 100 mos
Rush et al. [11]	38/F	Cough	RUL	CD30(+), EMA(+)	YES(NM)	NO	YES	NED at 51 mos
Rush et al. [11]	34/M	Dyspnea	LLL, endobronchial	CD30(+), EMA(+) CD45RB(+), CD45RO(+)	YES(NM)	YES	YES	Alive at 42 mos
Rush et al[11]	66/M	Sepsis, HIV	Bilateral nodules	CD30(+), CD3(+), CD45RO(+)	NO	NO	NO	Died at 21 days
Rush et al. [11]	58/F	Acute dyspnea	Intratracheal	CD30(+), EMA(+), CD45RB(+)	YES(NM)	YES	NO	Died at 6 mos
Chott et al. [12]	68/M	NM	NM	ALK(+)	YES(NM)	YES	NO	Died at 4 mos
Chott et al. [12]	57/M	NM	NM	ALK(+)	NO	YES	NO	Died at 2 mos
Kim et al. [13]	NM	NM	NM	CD30(+), EMA(+), ALK(+)	CHOP	NO	NO	CR, NED at 34.5 mos
Kim et al. [13]	NM	NM	NM	CD30(+), EMA(+), ALK(+)	CHOP	NO	NO	Died at 5 mos

M – male; F – female; NM – not mentioned; LLL – left lower lobe; LUL – left upper lobe; RLL – right lower lobe; RUL – right upper lobe; RML – right middle lobe. * Only shows the positive expression antigens. CHOP – cyclophosphamide, doxorubicin, vincristine, and prednisone; ** Dexamethasone, cyclophosphamide, doxorubicin, vincristine, and etoposide; *** Doxorubicin, vincristine, 6-mercaptopurine, and prednisone. NED – no evidence of disease; mo – months. NA – not available.

(Figure 3). The patient had been followed up for 65 months and remained disease free.

Discussion

Primary ALCL of the lung is a rare neoplasm. We conducted a systematic search of Medline and PubMed databases to identify all reports that contained primary anaplastic large cell lymphoma

(ALCL) of the lung, and only 10 reports were identified (published between 1990 and 2015), as shown in Table 1 [5–13].

Anaplastic large cell lymphoma (ALCL) is a special type of non-Hodgkin's lymphoma, which was first described and reported by Stein et al. in 1985 [14]. This disease is typically characterized by large lymphoid cells with abundant cytoplasm and pleomorphic, often horseshoe-shaped, nuclei, exhibiting strong, uniform expression of CD30 [15]. The diagnosis of ALCL was made

according to the World Health Organization (WHO) classification [16]. However, the diagnosis of primary pulmonary lymphoma is currently based on criteria proposed by Cordier et al. [17]. These criteria include: 1) definite histopatholoical diagnosis of lymphoma; 2) disease limited to the lung, with or without hilar and mediastinum lymph node involvement; and 3) no occurrence of lymphoma within tissues or organs other than the bronchus. Our patient showed typical histopathology of ALCL, while fulfilling the above criteria of primary pulmonary lymphoma; therefore, he was diagnosed as having primary ALCL of the lung.

For anaplastic large cell lymphoma originating in the lung, or with its first biopsy obtained from the lung, the differential diagnoses should consider a spectrum of primary or metastatic tumors commonly encountered in the lung: Hodgkins disease, and lymphomatoid granulomatosis. The diagnosis of ALCL is based on typical histopathology and immunohistochemistry staining, and the strong immunoreactivity with CD30 is key to its diagnosis [5,11]. In our case, the tumor cells were characterized by pleomorphic large cells and consistent expression of CD30. Also, the tumor cells demonstrated positivity for CD45 and LCA, suggesting hematopoietic and lymphoid tissue tumors. The negativity for MPO, CD20, granzyme B, T1A-1, and CD56 in a tumor may exclude diagnoses of myeloid leukemia, diffuse large B-cell lymphoma, and NK/T-cell lymphoma. The negativity for CKs, TTF-1, NSE, CgA, and Syna excluded diagnosis of neuroendocrine carcinoma. The negativity of S-100 and HMB-45 does not support melanoma, and negative tumor PLAP also excludes diagnosis of germ cell tumor. Considering all these findings, we made the diagnosis of anaplastic large cell lymphoma in our case. Based on the tumor cell immunotyping, ALCL may arise from either T phenotype or null phenotype. The cytogenetic feature of ALCL is the possession of translocation, which causes fusion of the nucleophosmin gene (NPM1) with anaplastic lymphoma kinase (ALK), and results in the abnormal expression of ALK protein [2,5]. Thus, ALCL can also be classified into ALK-positive and -negative subtypes according to ALK expression [18]. In addition, PET/CT is accurate for baseline staging and yields important prognostic information for determining the most appropriate initial treatment of lymphoma [19]. In our case, PET/CT allowed precise delineation of the extent of disease for determining the initial treatment, and better defined the radiation field.

Presently, there is no standard treatment for primary ALCL of the lung. Combination chemotherapy based on anthracycline (such as CHOP) is usually the first-line regimen for ALCL (1, 5). Among the 16 patients reported with primary ALCL of the lung (5–13), half of the patients who received only CHOP regimens, and all the patients who were managed with surgery and chemotherapy, reached complete remission; 5 patients were managed with chemo-radiotherapy and 2 young patients (aged 27 and 34) were alive after follow-up for 100 and 42 months, but 2 older patients (aged 58 and 68) died at 6 and 4 months. Our patient received chemotherapy with CHOP regimen combined with local radiotherapy. Complete response (CR) of the tumor was achieved, and the patient was disease-free after follow-up for 65 months. The tumor location of a patient reported by Rush et al. [11] was similar to that in our patient and they both developed the symptom of breathing difficulty. After chemo-radiotherapy, their symptoms of dyspnea were quickly relieved, and both of them achieved ideal treatment outcome.

It is generally considered that ALCL prognosis is better than that of the other large cell lymphomas [20]. ALK is an important prognostic marker for ALCL. The prognosis is better for patients with positive ALK staining [5]. ALK(+) ALCL typically occurs in younger patients and has a more favorable prognosis, with 5-year survival rates of 70% to 90% in comparison with 40% to 60% for ALK(+) ALCL. [21]. CD56 is an independent prognostic factor in ALCL, and CD56(+) cases showed a significantly worse prognosis overall, as well as in both ALK-positive and ALK negative subgroups [22]. In addition, age older than 60 years, Ann Arbor stage III or IV, survivin expression, PS>2, and high serum LDH level and IPI scores are also poor prognostic factors in ALCL [22–24].

Conclusions

ALCL of the Lung is a very rare disease. Because the clinical presentations and radiological findings are nonspecific, appropriate invasive biopsy and immunohistochemistry are important for diagnosis. There remains controversy about optimal therapy. Chemotherapy (such as CHOP) is recognized as the first-line treatment for ALCL. We found that if a patient has difficulty in breathing because of a mass blocking the main bronchus, concurrent chemo-radiotherapy is an effective method to relieve the symptoms of dyspnea. Our patient was disease-free after follow-up for 65 months. Age at onset, staging, survivin expression, PS, serum LDH level, IPI scores, and immunotyping such as ALK and CD56, but not site of tumor, are prognostic factors of ALCL.

Conflict of interest

The authors have no conflicts of interest to disclose.

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