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Case Report

Primary pulmonary anaplastic large cell lymphoma: case report and literature review

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Abstract: Primary anaplastic large cell lymphoma (ALCL) is a rare pulmonary malignancy. Due to its nonspecific clinical and radiologic manifestations, the disease presents a great challenge to pulmonologists. Appropriate invasive biopsy and immunohistochemistry are important for its diagnosis. Here, we report an ALCL case of a 27-year-old Chinese woman who presented to our hospital complaining of coughing for 10+ days and breath holding for 4-5 days after the event. Positive signs on physical examination were dull percussion sounds and decreased right lung breath sounds. Chest CT scans revealed central carcinoma and atelectasis of the right lung, pleural effusion, and lung mass. Pathology consultation showed a right main bronchial ALCL that involved the parabronchial lymph nodes but not the bronchial tangent. The patient discontinued treatment after right pneumonectomy and died two months later. Postoperative lung biopsy showed anaplastic tumor cells with large and multiple nuclei. The ALCL was characterized by the expression of T cell antigens, CD30 and ALK, as indicated by immunohistochemistry. We also reviewed the atypical cases of ALCL that were previously published. The results indicated that primary pulmonary ALCL is an extremely rare and easily misdiagnosed disease with non-specific clinical and imaging manifestations. Its diagnosis is based on biopsy and immunohistochemistry, and its prognosis is poor.

Keywords: Primary pulmonary anaplastic lymphoma, right pneumonectomy

Introduction

Anaplastic large cell lymphoma (ALCL), first proposed by German pathologists Stein et al. [1] in 1985, is a highly malignant and rare type of CD30 positive mature T-cell non-Hodgkin's lymphoma (NHL). ALCL often involves the lymph nodes and skin but very rarely the lungs [2-4]. Approximately 40-60% of patients with ALCL have a t(2;5)(p23;q35) translocation that expresses nuclear phosphorylated anaplastic lymphoma kinase (ALK), a chimeric protein with significant carcinogenic potential due to sustained activation of tyrosine kinase [5, 6]. According to the expression of ALK immune markers, ALCL can be classified as ALK positive or negative phenotype [7], of which the former is mostly seen in patients under 30 years old, often involving lymph nodes and extranodal sites. Compared to ALK-positive ALCL, ALK-negative ALCL is more commonly seen among the middle-aged and elderly, with a poor prognosis [8, 9]. As to primary pulmonary ALCL, it was first reported in the English literature by Chott in 1990 [10]. Although there have been several reports of primary pulmonary ALCL, its clinical features, optimal treatment, and prognostic factors have not yet been clearly defined [11]. ALCL has a broad morphologic spectrum with five or more variants of the disease [12, 13]. Due to the nonspecific clinical features, the diagnosis of ALCL is often a challenge. Misdiagnosis may be inevitable when only hematoxylin and eosin are used for histologic examination [14, 15]. To deepen the understanding of ALCL, we analyzed and compared the clinical records of 22 cases reported in previous studies so far [10, 16-29] and present one case of ALCL treated in our hospital, so as to summarize the clinical, radiological and pathologic characteristics of ALCL, as well as its diagnosis, treatment, and prognosis.

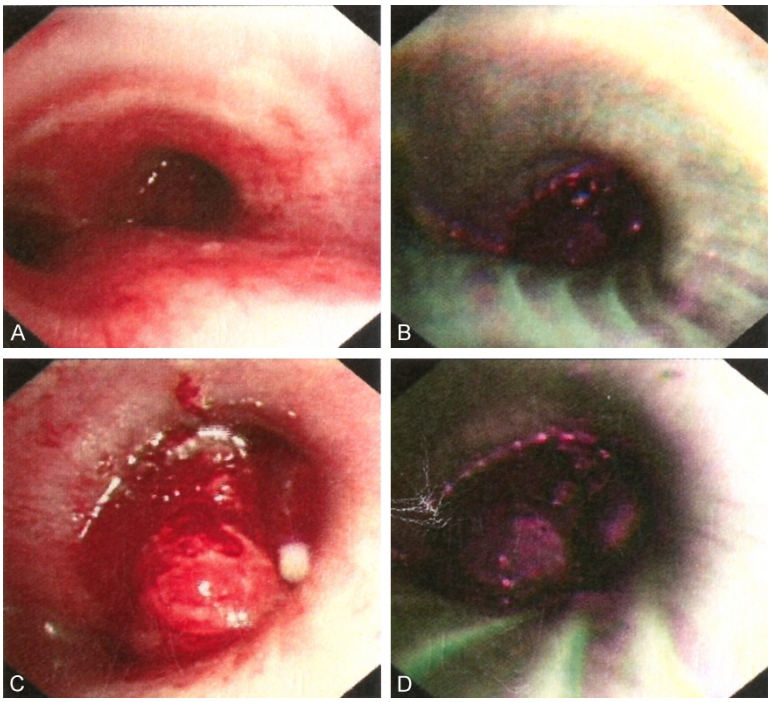

Figure 1. Fluorescence bronchoscopy findings. A: Bulging deformation; B: Fluorescence imaging: dark red coloring; C: The right main bronchus opening was completely blocked by the nodular mass, showing fresh hemorrhage and necrosis; D: Fluorescence imaging.

Case presentation

Here, we report a 27-year-old Chinese woman who presented to Jinan Central Hospital of Shandong University complaining of coughing for 10+ days and breath holding for 4-5 days. No enlargement of lymph nodes, liver, or spleen was observed upon palpation, except decreased right lung breath sounds. Fluorescence bronchoscopy revealed a bulging deformation, and the right main bronchus opening was completely blocked by the nodular mass, showing fresh hemorrhage and necrosis (**Figure 1**).

Bronchoscopic fine needle aspiration and cytopathological examination showed a large number of scattered round and oval tumor cells at low magnification, and a small number of mature lymphocytes admixed with malignant cells (**Figure 2A**). At high magnification, the tumor was composed of large and irregular cells with pleomorphic nuclei, dispersed distribution and increased cytoplasmic ratio. The tumor cells had hyperchromatic nuclei with abundant cytoplasm containing 1-2 basophilic nucleoli, with many cells having a prominent vesicular area in the cytoplasm (**Figure 2B**). Binucleated and multinucleated cells were also present and mitotic figures were easily identified.

Postoperative histopathologic findings of tissue samples showed that the tumor cells diffusely infiltrated and destroyed the bronchial wall mucosa and grew around the blood vessels. Most of the larger tumor cells were round or oval with basophilic vesicles in the cytoplasm and moderate amount of basophilic cytoplasm. ALCL cells contained pleomorphic nuclei that were generally roun, reniform or irregular with 1-2 prominent basophilic nucleoli; tumor cells were binucleated or multinucleated, with mitotic figures and coagulation necrosis. In addition, small lymphocytes were admixed with tumor cells in the case studied (**Figure 2C**).

Immunohistochemical staining of tumor cells demonstrated CK(-), CD30(+), ALK(+), EMA(+), T1A-1(+), EBV(-) and TTF-1(-), as shown in **Figure 3**. Combining clinical and pathologic findings, as well as the consultation of pathologists from the Department of Pathology, Shanghai Pulmonary Hospital, the patient was diagnosed with ALCL of the right main bronchus, which involved parabronchial lymph nodes but not the bronchial tangent. The patient underwent right pneumonectomy but was unable to receive follow-up treatment and died two months after surgery.

Discussion

Primary pulmonary lymphoma is a rare disease presenting as intrabronchial ALCL with acute atelectasis. Through searching relevant literature published in the Medline and PubMed databases since 1990 by using primary pulmonary ALCL as the keyword, a total of 22 full-text articles on ALCL patients were retrieved for analysis (**Table 1**).

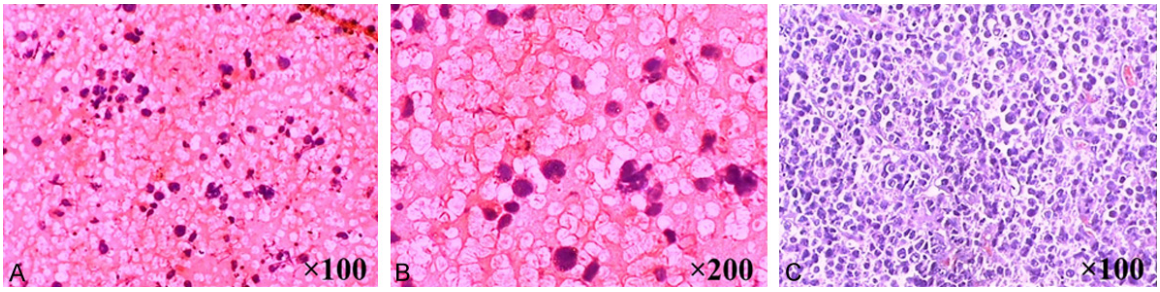

Figure 2. Cytopathological and histopathological findings. A: A large number of scattered, round and malignant tumor cells were observed (original magnification: ×100); B: The tumor cells were large and irregular in shape, with nuclear atypia and vesicular chromatin (original magnification: ×200); C: The tumor cells showed diffuse infiltration and perivascular growth (original magnification: ×100).

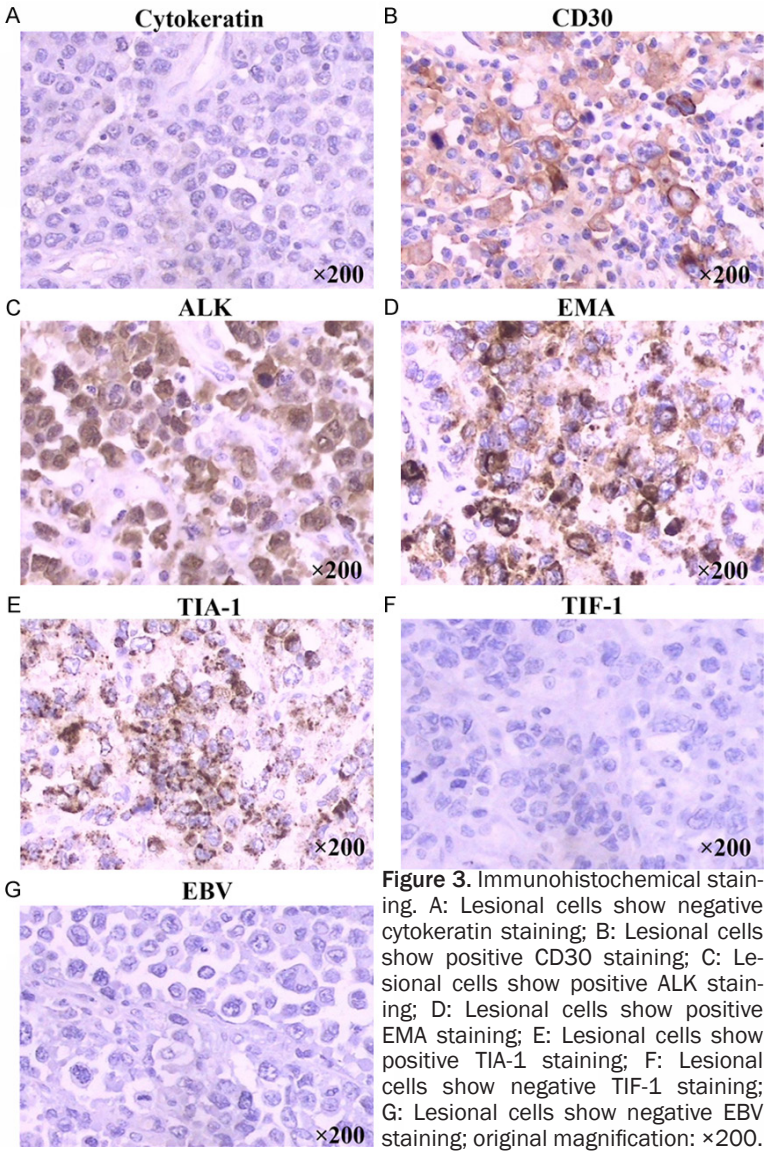

Figure 3. Immunohistochemical staining. A: Lesional cells show negative cytokeratin staining; B: Lesional cells show positive CD30 staining; C: Lesional cells show positive ALK staining; D: Lesional cells show positive EMA staining; E: Lesional cells show positive TIA-1 staining; F: Lesional cells show negative TIF-1 staining; G: Lesional cells show negative EBV staining; original magnification: ×200.

As can be seen from **Table 1**, among patients of known age, the male to female ratio was 10:9, and the median age was 37.8 years old (age range: 9-68 years old, with gender and age not mentioned in 4 cases). Among them, there were 4 children (<18 years old) with a median age of 14 years. The clinical manifestations were non-specific, including cough, dyspnea, hemoptysis, fever, shortness of breath, weight loss, pruritus, and body surface mass. X-ray findings included nodules (2/17), masses (9/17), vacuolar consolidation (1/17), pleural effusion (6/17), vacuoles (2/17), cystic lesions (1/17), and airway involvement of bronchus (3/17), which are not different from other widespread diseases. Of the 23 reported cases, 9 underwent surgery; 2 had a history of HIV infection, and the rest had no reported HIV status. HIV infection is known to be associated with a 15-fold increased risk of various malignancies, including those of the hematopoietic system, compared to other T-cell lymphomas [30]. Other studies have shown that most HIV-associated ALCL is an ALK-negative variant [31], which is similar to the case in this paper. Imaging examinations and/or bone marrow biopsies were performed in 17 patients (which was not men-

Table 1. Reported cases of primary pulmonary ALCL since 1990

Reference	Age/sex	presentation	Chest radiology	Immunohistochemistry	Diagnostic intervention	Chemotherapy	Radiation	Outcome
Chott et al. [10]	57/M	NA	NA	CD30(+) pleomorphic large cell	surgical	NO (NM)	YES	died at 2 months[1]
Chadburn et al. [16]	40/M	NA	NA	CD30(+)EMA(+)CD3(+)CD45(+)CD43(+)CD45RO(+)CD20(-) CD15(-) Abundant, large and round or oval cell, acidophilic cytoplasm	NA	YES (CHOP)	NO	died 3 months after diagnosis
Rush et al. [17]	27/F	cough, pruritus weight loss	LUL, nodule	CD30(+)CD15(-)EMA(-) CD20(-)CD3(-)CD45RO(+)CD45RB(-) anaplastic large cell, relatively monomorphic large cells with vesicular nuclei, multiple inconspicuous nucleoli, and pale gray cytoplasm	wedge biopsy	YES (NM)	YES	NED at 100 months
Rush et al. [17]	38/F	nonproductive cough	RUL, cystic	CD30(+)CD15(-)EMA(-)CD20(-)CD3(-)CD45RB(+)CD45RO(-) large cells with pleomorphic nuclei, large cells with pleomorphic nuclei, one or more prominent nucleoli, and abundant eosinophilic cytoplasm	surgical resection	YES (NM)	NO	NED at 51 months
Rush et al. [17]	34/M	Dyspnea multiple erythematous skin lesions and mass	LLL, endobronchialmass	CD30(+)CD15(-)EMA(+)CD20(-)CD3(-)CD45RB(+) CD45RO(+) large cells with pleomorphic nuclei, one or more prominent nucleoli, and abundant eosinophilic cytoplasm	left pneumonectomy	NO (NM)	YES	alive at 42 months
Rush et al. [17]	66/M	Sepsis, HIV	bilateral nodules	CD30(+)CD15(-)EMA(-)CD20(-)CD3(+)CD45RB(-)CD45RO(+) Relatively monomorphic large cells with vesicular nuclei, multiple inconspicuous nucleoli, and pale gray cytoplasm	NA	NO	NO	antibiotics died at 21 days
Rush et al. [17]	58/F	Acute dyspnea	intratracheal mass	CD30(+)CD15(-)EMA(+)CD20(-)CD3(-)CD45RB(+)CD45RO(-) relatively monomorphic large cells with vesicular nuclei, multiple inconspicuous nucleoli, and pale gray cytoplasm	surgery	YES (NM)	YES	died after 6 months
Kim et al. [18]	NA	NA	NA	CD30(+)EMA(+)ALK(+)	NA	YES (CHOP)	NO	disease free at 34.5 months
Kim et al. [18]	NA	NA	NA	CD30(+)EMA(+)ALK(+)	NA	YES (CHOP)	NO	died at 5 months
Guerra et al. [19]	9/F	dry cough, chest pain, progressive breathlessness, intermittent fever	left upper lobe mass	CD30(+)CD43(+)ALK(+)LCA(+)CD3(-)CD20(-) Abundant cytoplasm, enlarged round pleomorphic nuclei	lobectomy	YES (DVMP)	NO	alive at 4 years
Cermagic et al. [8]	46/M	NA	NA	CD30(+) vimentin(+) ALK(-) LCA(+) large cells with pleomorphic nuclei, prominent nucleoli, and abundant atypical mitotic figures	NA	YES (NM)	NO	NA
Yang HB et al. [21]	28/F	productive cough fever, SOB	RUL, RML mass, pleural effusion	CD30(+)ALK(-)CD3(+)CD20(-)CD43(++), large cells with multiple nuclei	lobectomy	YES (CHOP)	NO	alive at 6 months
Yang HB et al. [21]	17/F	cough hemoptysis	RUL, RLL consolidation, cavitation	CD30(+)ALK(+)CD3(+)CD20(-)CD34(-) cells with large and multiple nuclei	endobronchial biopsy	YES (CHOP)	NO	alive at 6 months
Yang SL et al. [22]	13/F	cough, chest pain, breathlessness, mass of body surface	LLL, pleural effusion	CD30(+)ALK(+)EMA(+)CD3(+)CD34(+)CD20(-)CD68(-) cells with large nuclei, prominent nucleoli, eosinophilic cytoplasm, atypical mitotic figures	chest wall tumour excision	YES (CHOP)	NO	2 cycles complete remission. follow-up
Tian XL et al. [23]	NA	NA	RML, RLL, consolidation, cavitations	CD30(+)ALK(+)LCA(+)CD20(-)CD34(-)cells with large and irregular nuclei, one or more prominent nucleoli, atypical mitotic figures	NA	NO	NO	unfavourable prognosis

Tian XL et al. [23]	NA	NA	RUL, onsolidaftion, pleural effusion	CD30(+)ALK(+)LCA(+)CD20(-)CD34(-) cells with large and irregular nuclei, one or more prominent nucleoli, atypical S figures	Breast operation	NO	NO	unfavourable prognosis
Kim et al. [24]	68/M	dyspnea, and upper respira tory symptoms	NA	CD30(+)CD43(+)CD3(+)ALK(+)EMA(+)	NA	YES (CHOP)	NO	alive at 8 months
Xu et al. 13[25]	44/F	Cough, chest pain	Left bronchus	CD30(+), CD5(+), CD3(-)ALK(-)	NA	YES (DDEVP)	NO	alive at 6 months
Meyyappa DR [26]	50/M	SOB	RUL, RML	CD30(+), CD3(+), EMA(+), ALK(+)CD56(+)LCA(+)	NO	YES (CHOP)	NO	NA
Barthwal et al. [27]	23/M	cough, SOB fever	LUL	CD30(+), ALK(+)	NA	YES (DCDVE)	NO	alive at 8 months
Zhang et al. [28]	18/M	SOB, cough	Mediastinum	ALK(+)CD30(+)	NA	YES (CHOP)	YES	NA
Han et al. [29]	55/M	Cough, night sweat	LUL	CD30(+)CD3(+)CD45(+)ALK(+)CD8(+)Vimentin(+)	NA	YES (CHOP)	NO	NA
Patient in this paper	27/f	Cough, productive cough, breathlessness,	the main bronchus atelectasis of right lung pleural effusion	ALK(+)CD30(+)EMA(+)CD3(-)CD20(-)LCA(-)vimentin(+) cells with large and irregular nuclei, one or more prominent nucleoli, atypical mitotic figures	Right pneumonectomy	NO	NO	died at 2 months after operation

LLL = Left lower lobe; LUL = left upper lobe; RLL = right lower lobe; RUL = right upper lobe; RML = right middle lobe; SOB = shortness of breath; NED = no evidence of disease; NA = not available. [1]At the time the report was published.

tioned in the remaining 6 cases) to assess systemic symptoms. The patients' lesions were found to be located in the bronchi and lungs, and definite diagnostic interventions included wedge biopsy in 7 cases, transbronchial lung biopsy in 3 cases, resection of chest wall mass in 4 cases, and thoracic surgical biopsy in the rest. ALK was negative in 4 cases and positive in 12 cases. According to the 2016 revision of the WHO classification, ALCL can be classified into four types: ALK-positive ALCL, ALK-negative ALCL, primary skin ALCL, and breast implant-associated ALCL [20]. Here we report a case of ALK-positive ALCL, which was finally diagnosed as primary pulmonary ALCL. Immunohistochemistry showed that all the 23 cases (100%) had a positive expression of CD30, while there were 12 cases with EMA expression, 15 cases with ALK expression, 13 cases (100%) with negative expression of CD20, and 6 cases (100%) with negative expression of CD15. Expression of CD3(+) was detected in 15 of 23 (65%), CD45 RO expression was found in 4 of 6 (67%), and highly expressed CD43 was determined in 3 cases (100%). Immunohistochemistry showed that tumor cells could express one or more T-cell associated antigens [32], but all expressed CD30. A positive correlation of ALK was detected in 60-85% of all the cases, and ALK expression was truly specific for the detection of ALCL. In addition, most patients showed overexpressed EMA. In our case, the patient's immunohistochemical results showed positive ALK and EMA, which is consistent with previous reports. Patients with young age, early diagnosis, and timely appropriate treatment have a good prognosis. Therefore, early diagnosis requires appropriate invasive biopsy [21].

With the extensive application of immunohistochemical markers for pathologic diagnosis in recent years, reports on ALCL have gradually increased, but there is no consensus on standard treatment of the disease. Most studies on adult ALCL treatment focus on anthracyclines (such as CHOP and MACOP)-based chemotherapy combined with immunotherapy, while lymphocytic leukemia protocols such as LNH-92 [33] and Burkitt lymphoma regimen B-NHL-BFM-90 [34] are used in the treatment of pediatric ALCL. Murthy et al. reported a large study on ALCL, showing that the 5-year overall survival rate decreased gradually with age. At present, chemotherapy combined with immunotherapy is mostly used [35]. Hematopoietic stem cell transplantation has also been reported to be a good cure for ALCL. Chemotherapy is currently the first choice for primary pulmonary lymphoma; radiotherapy is rarely used, and surgical treatment is an important approach [23]. In our report, the patient received a right pneumonectomy.

As mentioned earlier, primary pulmonary ALCL is extremely rare. From admission to post-operative pathologic diagnosis took one month. The patient was initially diagnosed with lung cancer by clinicians in combination with imaging examinations and bronchoscopy forceps biopsies, and finally with primary pulmonary ALCL by post-operative pathological examination and immunohistochemistry. Although NHL was highly suspected by cytological examination in this paper, it was not accepted at the initial diagnosis and was diagnosed as lung cancer due to the lack of histopathologic tissue and the absence of immunohistochemistry. Misdiagnosis is common, given the lack of documentation of bronchial brush cytology in the literature as well as the non-specific clinical manifestations of primary pulmonary lymph nodes. The case reported by Meyyappa was similar to the one in this paper, with a high suspicion of ALCL on bronchoscopy fine needle aspiration cytology. Due to the limitations of cytopathology, therefore, there is no specificity for the diagnosis of ALCL. The final diagnosis still depends on histopathologic examination and immunohistochemistry. Early diagnosis requires invasive inspection to obtain pathological specimens, and surgical or bronchoscopy or CT-guided biopsy can be used to diagnose primary pulmonary lymphoma. In terms of diagnostic technique, surgery is not the first choice for diagnosis of primary pulmonary NHL unless it is for therapeutic purposes. Unfortunately, this case failed to undergo postoperative chemotherapy and radiotherapy and died two months later.

The research of Guzik [36] showed that surgical treatment can significantly improve patient prognosis if radical resection is possible. His work showed that there was no evidence of generalized disease during the follow-up period in patients treated with radical resection and prosthesis implantation. Guzik also argued that

surgical treatment should be performed when radical tumor resection is possible, and that radiotherapy and chemotherapy should be employed only in palliative treatment when radical resection is inapplicable. Surgical procedure may play a more significant role in the treatment rather than merely for histologic confirmation.

Conclusion

ALK-positive primary pulmonary ALCL is a very rare disease with nonspecific clinical and imaging manifestations. Therefore, appropriate invasive biopsy and immunohistochemistry are necessary for the diagnosis of ALCL. Our case highlighted that ALCL has unusual presentations and can pose a diagnostic challenge.

Disclosure of conflict of interest

None.

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