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Case Report

ALK-negative anaplastic large cell lymphoma primarily involving the bronchus: a case report and literature review

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Abstract: Anaplastic large cell lymphoma (ALCL) is a mature T cell lymphoma with characteristic morphologic, immunophenotypic and cytogenetic features. Current WHO classification includes anaplastic lymphoma kinase (ALK)-positive and ALK-negative variants. ALCL rarely presents with obstructive symptoms of the main airway. In addition to reporting a HIV-associated bronchial ALK-negative ALCL in a 44 year-old female, our literature review identified eight cases of bronchial ALCL with several interesting clinicopathological features, including: 1) a female predominance (67%); 2) two thirds of patients younger than 18 years old; 3) uniformly presented with respiratory symptoms and progressed to respiratory failure; 4) the tumor involving the main airways; 5) often with localized disease at the initial presentation. This unusual presentation of ALCL may pose as a diagnostic pitfall and delay the treatment.

Keywords: Anaplastic large cell lymphoma, anaplastic lymphoma kinase, bronchus, respiratory failure, HIV

Introduction

Anaplastic large cell lymphoma (ALCL) is a CD30+ mature T cell lymphoma with characteristic morphology and immunophenotype. According to the current WHO classification, there are two variants: ALCL, ALK (anaplastic lymphoma kinase)-positive (ALCL, ALK+) and ALCL, ALK-negative (ALCL, ALK-), which have many similar features. Both variants show modest male predominance and involve both lymph nodes and extranodal sites. ALCL, ALK+ is more often seen in the first three decades of life and by definition, carries a translocation of the ALK gene and over-expresses the ALK protein [1]. In comparison, ALCL, ALK- is usually in middle-aged group with a worse prognosis [2].

Among extranodal presentations, rare ALCL cases have been reported to present with respiratory complaints and later a bronchial mass was found. Up to date, there were 8 such cases reported in the English literature [3-10]. All of the eight reports are single case report, and so far no review is available about clinical

and pathological features of this rare presentation. In addition to reporting one case of bronchial ALCL in an HIV patient, our literature review identified some interesting clinical features of bronchial ALCL.

Case report

The patient was a 44-year-old female with a history of HIV infection for 11 years. She presented with shortness of breath, fevers, night sweats, and quickly progressed to acute respiratory failure. Imaging showed narrowing of the proximal left lower lobe pulmonary artery and surrounding metabolically active left hilar lymphadenopathy. No additional sites of involvement were identified. Flexible bronchoscopy identified a protruding endobronchial lesion at the left main bronchus. The lesions were biopsied for histologic examination.

The biopsy showed tiny fragments of soft tissue with a proliferation of medium-to-large sized neoplastic cells, which are dispersed in a background of mixed reactive inflammatory cells.

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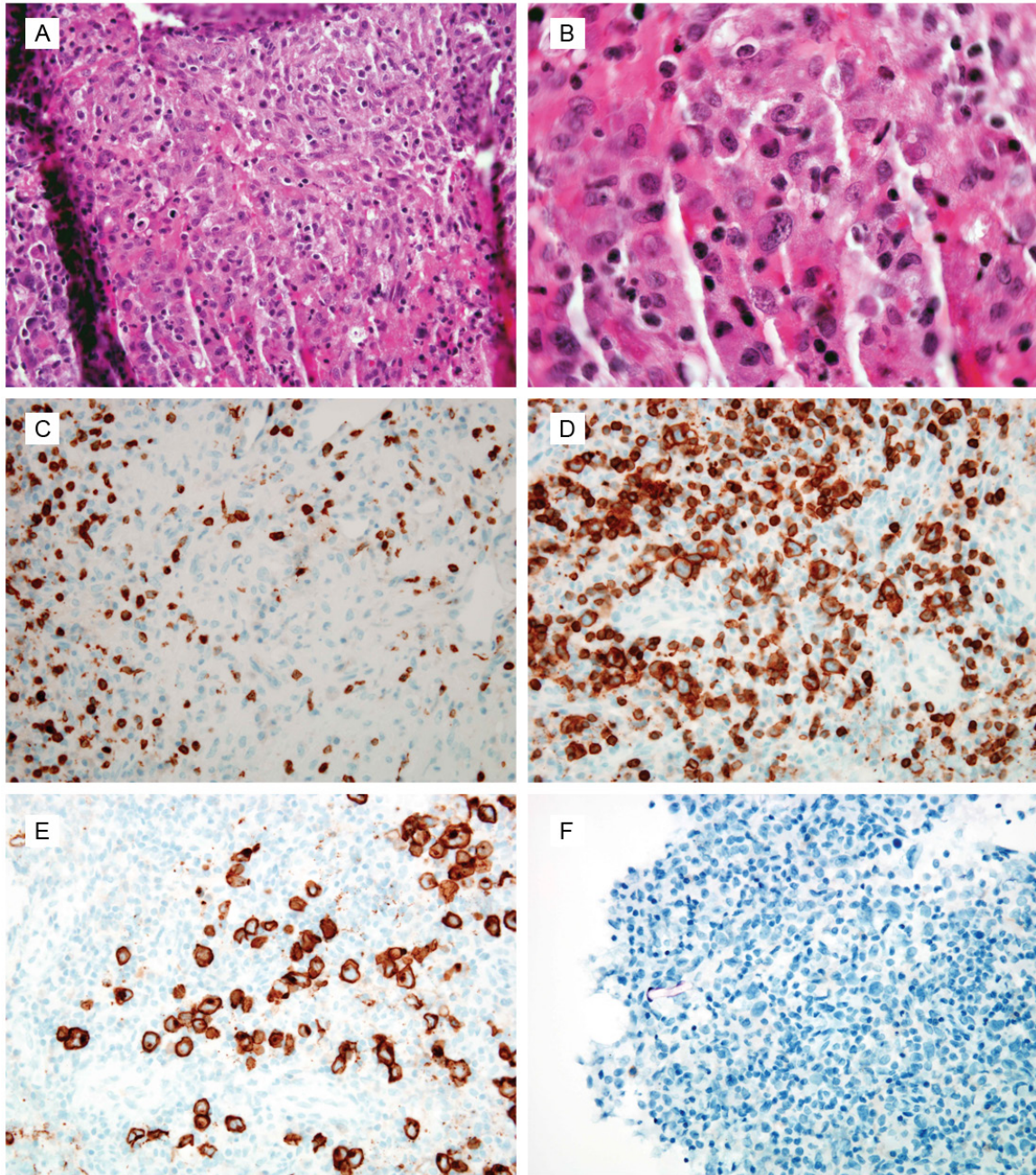


Figure 1. Anaplastic large cell lymphoma, ALK negative from left main bronchus. (A, B): The neoplastic cells are large in size, with moderate amount of eosinophilic cytoplasm, vesicular chromatin. Occasional “hallmark cells” are seen. The neoplastic cells are negative for CD3 (C), and positive for CD5 (D), CD30 (E). ALK-1 is negative (F).

The neoplastic cells had moderate amount of granular, eosinophilic cytoplasm, coarse chromatin, single to several nucleoli. Occasional kidney-bean shaped nuclei were seen, resembling “hallmark cells” (Figure 1A, 1B).

Immunohistochemistry revealed the neoplastic cells were positive for CD45, supporting a hematolymphoid origin. The cells were negative

for CD3 (Figure 1C), but positive for several other T cell makers, including CD2, CD4 (data not shown), and CD5 (Figure 1D). The expression of CD7 was down-regulated (data not shown). Pan B cell markers were all negative. CD30 was strongly positive (Figure 1E). CD15 only highlighted smaller-sized neutrophils (data not shown). ALK-1 immunostain was negative (Figure 1F). The overall findings were consis-

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Table 1. The summary of clinicopathologic features of nine cases of bronchial / tracheal ALCL

No.	Age/Gender	Tumor location	Respiratory Failure	Systemic Disease	HIV Status	ALK IHC	Follow-Up	Ref.
1	28/M	LMB	Yes	No	N/A	N/A	DFS 5 mo	Kim et al, 1998
2	17/F	LMB	Yes	N/A	N/A	Pos	N/A	Bhalla et al, 2003
3	23/M	LMB	Yes	Yes*	Pos	Pos	Expired in 5 mo	Barthwal et al, 2005
4	9/F	LMB	Yes	No	Neg	Pos	DFS 48 mo	Guerra et al, 2006
5	7/F	LMB	Yes	N/A	N/A	Neg	Expired in 6 mo	Kuperman et al, 2006
6	16/F	Trachea	Yes	No	N/A	Pos	DFS 25 mo	Khodadad et al, 2011
7	13/F	RMB	Yes	No	N/A	Pos	DFS 108 mo	Pavlov et al, 2012
8	16/M	RMB	Yes	No	N/A	Pos	DFS 6 mo	Zhang et al, 2012
9	44/F	LMB	Yes	No	Pos	Neg	DFS 6 mo	Current

ALK: Anaplastic lymphoma kinase; DFS: disease free survival; F: female; IHC: immunohistochemistry; LMB: left main bronchus; M: male; mo: months; N/A: not available; Ref: reference; RMB: right main bronchus. *The disease involved supraclavicular and axillary lymph nodes, right thigh and bone marrow.

tent with a mature T cell lymphoma, most favor ALCL, ALK-.

The patient was treated with cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone. She had been in remission up to 6 months.

Discussion

It is extremely rare for ALCL to initially present with respiratory symptoms. Our review of English literature had identified eight cases [3-10], summarized in **Table 1**. Including the current case, there were 9 patients in total with 3 male and 6 female (male to female ratio of 1:2). The median age was 16 years (ranging from 7 to 44 years). Sixty-seven percent of the group was < 18 years old. The sites of main airway involvement include the left main bronchus in 6 cases (67%), the right main bronchus in 2 cases (22%), and the trachea in 1 case (11%). All of the cases initially presented with respiratory symptoms and later progressed to respiratory failure. Seven cases had imaging studies and/or bone marrow biopsies to evaluate systemic involvement, six cases (86%) of which showed no evidence of systemic disease. Six of eight cases (75%) reported ALK immunoreactivity in the neoplastic cells. Two cases, including the current one, had a prior history of HIV infection [5]. HIV test was negative in Case #4 and the rest six cases did not report HIV status. The median duration of follow-up was 6 months (ranging from 5 to 108 months), during which six patients were in remission. On the other hand, Case #3 and #5 did not achieve initial remission and the patients passed away 5 and 6 months after the diagnosis, respectively.

It is known that HIV infection is associated with increased risks of developing various malignancies, including hematopoietic malignancies, among which a 15-fold risk of developing T-cell lymphoma has been reported [11]. ALCL is the second most common subtype of T-cell lymphomas in HIV patients [12]. Interestingly, one study showed the majority of the HIV-associated ALCL are ALK-negative variant [13]. Our case is the first reported HIV-associated ALCL, ALK-presented as a bronchial mass.

In summary, the initial bronchial involvement of ALCL was associated with some interesting clinicopathologic features: 1) There is a female predominance, in contrast to male predominance in the general ALCL group; 2) Majority of the patients are less than 18 year-old; 3) The patients uniformly present with obstructive symptoms of respiratory tract and usually develop respiratory failure; 4) The primary neoplasm is in the bronchus or the trachea; 5) At the initial presentation, majority of the cases have only localized disease.

Even though limited by the number of cases available, our analysis suggested that this group of ALCL have unusual presentation and could pose as a diagnostic challenge. It is especially true in the youth, for whom non-malignant respiratory diseases are much more common. On the other hand, a timely diagnosis is critical to avoid disease progression and complications from respiratory failure, which had been reported in all the nine cases. The author hopes this review could draw attention to and help our understanding of this rare presentation of ALCL. In addition, bronchial ALCL need be con-

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sidered in the differential diagnosis if airway obstruction is suspected, especially in a young patient.

Disclosure of conflict of interest

None

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