Original Article

Detection of rearrangement of anaplastic lymphoma kinase (*ALK*) and mutation of epidermal growth factor receptor (*EGFR*) in primary pulmonary lymphoepithelioma-like carcinoma

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Background: Primary pulmonary lymphoepithelioma-like carcinoma (LELC) is a distinct rare subtype of lung cancer. The prevalence of anaplastic lymphoma kinase (*ALK*) rearrangement and epidermal growth factor receptor (*EGFR*) mutation in primary pulmonary LELC had not been thoroughly investigated.

Methods: We investigated a cohort of 42 patients with primary pulmonary LELC and genotyped for *ALK* rearrangement and *EGFR* mutation. *ALK* rearrangement was detected by fluorescence in situ hybridization (FISH). *EGFR* mutational analysis of exons 18 through 21 was analyzed by TaqMan real-time polymerase chain reaction (PCR).

Results: Epstein-Barr virus-encoded RNAs (*EBERs*) showed positive signals in all 42 patients. By immunohistochemistry staining, all patients demonstrated positive expression of CK5/6 and P63, but almost all patients were negative for TTF-1 (34/34, 100%) or CK7 (34/35, 97.1%). None of the 42 patients had *ALK* rearrangement. Of 42 patients tested, only one patient (2.4%) harbored L858R mutation and gefitinib was applied to this case, however no objective response was observed and the progression free survival (PFS) time was only 1 month.

Conclusions: Primary pulmonary LELC is a unique histological subtype of lung cancer. *ALK* rearrangement and *EGFR* mutation are lack and they may not be the oncogenic driver gene in pulmonary LELC. Future efforts should be made to explore other oncogenic driver gene to guide targeted therapy in this rare disease to determine the optimal treatment.

Keywords: Pulmonary lymphoepithelioma-like carcinoma (LELC); anaplastic lymphoma kinase (*ALK*); epidermal growth factor receptor (*EGFR*); targeted therapy; Epstein-Barr virus (EBV)

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Introduction

Primary pulmonary lymphoepithelioma-like carcinoma (LELC) was first reported by Bégin *et al*. (1) in 1987. In the 2015 World Health Organization (WHO) Classification of Lung Tumors (2), LELC was moved to a group of "other and unclassified carcinomas" from large cell carcinoma. Histopathologically it is similar to nasopharyngeal lymphoepithelioma (3), which is a type of undifferentiated carcinoma with predominant lymphocytic infiltration most commonly occurred in Southern China, and had close relationship with Epstein-Barr virus (EBV) infection (4). Over the past 28 years since it was first reported, less than 300 cases have been reported in the literature. The state-of-art treatment for early stage disease is complete resection; whereas multimodality treatment strategy (surgery, chemotherapy, radiotherapy) applied in locally advanced disease, and palliative chemotherapy was used for metastatic disease. Compared with other types of non-small cell lung cancer (NSCLC), patients with pulmonary LELC had significantly better prognosis (5). However, due to the rarity of pulmonary LELC, treatment for advanced pulmonary LELC is still controversial.

Epidermal growth factor receptor (*EGFR*) is a protein that helps regulate cell growth. Abnormalities in the *EGFR* gene can lead to the development of NSCLC (6). *EGFR* mutations are more often found in the adenocarcinoma. In the western country, about 15% NSCLC patients have an *EGFR* mutation; however, in Asian countries this number is as high as 40-50% (7). Recently, studies have found that echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (*EML4-ALK*) fusion gene plays an important role in the pathogenesis of lung cancers, and *ALK* fusion gene can be found in nearly 5-8% of NSCLC patients (8). Patients with NSCLC who have sensitizing *EGFR* mutation responded better to *EGFR* tyrosine kinase inhibitors (TKIs) such as gefitinib or erlotinib (9), and patients with the *ALK* rearrangement were sensitive to *ALK* TKIs such as crizotinib (10). Testing for *EGFR* gene mutations and *ALK* rearrangements are routine for NSCLC patients in clinical practice now (11,12). However, only few genotype studies have been done in pulmonary LELC, and till now no targeted therapy has been shown effective in the treatment of these patients. Tam *et al*. (13) observed that *EGFR* mutations were uncommon in LELC (1 of 11 patients were positive) and Chang *et al*. (14) reported that 17.4% of patients with lung LELCs harbored *EGFR* mutations. As we previously reported (5), we analyzed *EGFR* mutations in 11 patients with LELC of the lung, but all patients were wild-type. All these data suggested that *EGFR* target therapy may not be an encouraging treatment for patients with advanced LELC of the lung (14). The *EML4-ALK* expression profile in pulmonary LELC was only reported in 11 patients by Wong *et al*. (15) but no patients had observed this fusion gene. Thus, in this relatively large cohort of patients with pulmonary LELC, we investigated the prevalence of *EGFR* mutation and *ALK* rearrangement, trying to explore the future targeted therapy in primary pulmonary LELC.

Materials and methods

Ethics, consent and permissions

Approval to review, analyze, and publish the data in this study was given by the Sun Yat-sen University Cancer Center Research Ethics Board. Written informed consent for the collection of medical information was obtained from all patients at their first visit.

Patients

We retrospectively investigated a cohort of 42 patients who were diagnosed with primary pulmonary LELC and treated in Sun Yat-sen University Cancer Center from January 2008 to April 2014. Pulmonary LELC was diagnosed according to criteria described by the WHO (2). We excluded undifferentiated carcinomas without lymphoid infiltrates and EBV-encoded RNAs (*EBERs*) staining in our study. All patients underwent endoscopic examination of the nasopharynx or PET-CT scan to rule out metastatic LELC from the nasopharynx.

We collected the clinical data from patients' medical records. We focused on patients' gender, age, symptoms, smoking status, tumor size, staging and treatments. Pathologic or clinical staging was performed according to the American Joint Committee on Cancer (AJCC) staging system (the 2007 TNM classification of malignant tumors) (16). Tumor assessment was based on Response Evaluation Criteria in Solid Tumors after at least two cycles of chemotherapy (17).

Immunohistochemistry staining

Immunohistochemical staining with CK5/6 (DAKO), CK7 (DAKO), P63 (Santa Cruz), and TTF-1 (DAKO) was

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Table 1 Patients' characteristics

Characteristics	Number (n=42) (%)
Gender	
Male	22 (52.4)
Female	20 (47.6)
Age (years)	
>60	7 (16.7)
≤60	35 (83.3)
Smoking history	
Yes	13 (31.0)
No	29 (69.0)
Stage	
I	10 (23.8)
II	5 (11.9)
IIIA	12 (28.6)
IIIB	4 (9.5)
IV	11 (26.2)
Treatment approach	
Surgery alone	7 (16.7)
Surgery + chemotherapy	28 (66.7)
Chemotherapy alone	7 (16.7)
Disease progression at last follow-up	
Yes	8 (19.0)
No	34 (81.0)

carried out and evaluated according to the manufacturer's instructions.

In situ hybridization (ISH) of Epstein-Barr virus-encoded RNAs (EBERs)

EBERs were detected using the EBV Probe In Situ Hybridization Kit (DIG-AP, A300K.9901, PanPath Company, Amsterdam, Netherlands) as described in previous reports (18). Briefly, the process included the following steps: (I) deparaffinization and dehydration of the paraffin sections using xylene and a series of graded ethanol; (II) pretreatment with 0.4% pepsin for 10 minutes; (III) hybridization with digoxigenin-conjugated EBV (*EBERs*) probe at 37 ℃ for three hours; (IV) signal detection using peroxidase-conjugated anti-digoxigenin antibody and 3,3'-diaminobenzidine (DAB); and (V) counterstaining the sections with hematoxylin solution. The positive signals were brownish-yellow and localized within the nuclei.

Mutational analysis of EGFR

Mutational analysis of the *EGFR* (exons 18 through 21) was carried out using TaqMan real-time polymerase chain reaction (PCR) as described in previous studies. Briefly, tissue sections of 10-µM thickness microdissected from formalin-fixed paraffin-embedded surgically resected tumor specimens were examined by microscopy after hematoxylin and eosin staining, and only tissue samples with greater than 80% tumor content were selected for the study. To obtain genomic DNA, the QIAamp DNA FFPE tissue kit (Qiagen, Hilden, Germany) was used according to the manufacturer's instructions. The *EGFR* mutations were analyzed using a Real Time PCR Detection Kit for the Analysis of *EGFR* Gene Mutations (GP Medical Technologies, Beijing, China), to detect two specific in-frame deletion mutations in exon 19 (A: E746-A750del B: L747-P753ins S del) and two point mutations in exon 21 (C: L858R D: L861Q) of the *EGFR* gene. The TaqMan PCR and genotyping analysis were performed on ABI7500 Real Time PCR System (Applied Biosystems, Life Technologies Corporation, Carlsbad, CA). Data were analyzed with SDS2.0.software (Applied Biosystems) according to the manufacturer's instructions.

ALK rearrangement determination

Determination of *ALK* rearrangement status was done by FISH using Vysis *ALK* Break Apart FISH Probe Kit (Abbott Molecular, Inc.) according to the manufacturer's instructions. This commercial kit includes orange and green-colored break apart probes which flank, respectively, the 5 and 3 sides of the translocation breakpoint within the *ALK* gene. If *ALK* is not rearranged, the two probes overlap in a fused or yellow signal; *ALK* rearrangement is characterized by spatial separation of the green and red probes or by an isolated orange signal. Criteria that need to be met for a break apart FISH assay to be considered positive for *ALK* rearrangement include: at least 15% of the cells counted to harbor signals of translocation; separation of the green and red signals by at least two signal diameters; and at least 50 cells counted (19).

Results

The clinicopathologic characteristics of 42 patients with pulmonary LELC are presented in *Table 1*. The female to male ratio was about 1:1, and the median age at diagnosis was 51 years (range, 29-67 years). Only 13 (31.0%) patients were smokers. Seventeen patients (40.5%) had no symptoms at the time of diagnosis, and were found to have LELC by regular checkups. Other patients had mild cough (10 patients), chest pain (7 patients), or bloody sputum (8 patients). Twenty-seven of 42 patients had stage I-IIIA (64.3%), and only 15/42 patients (35.7%) were in stage IIIB or IV.

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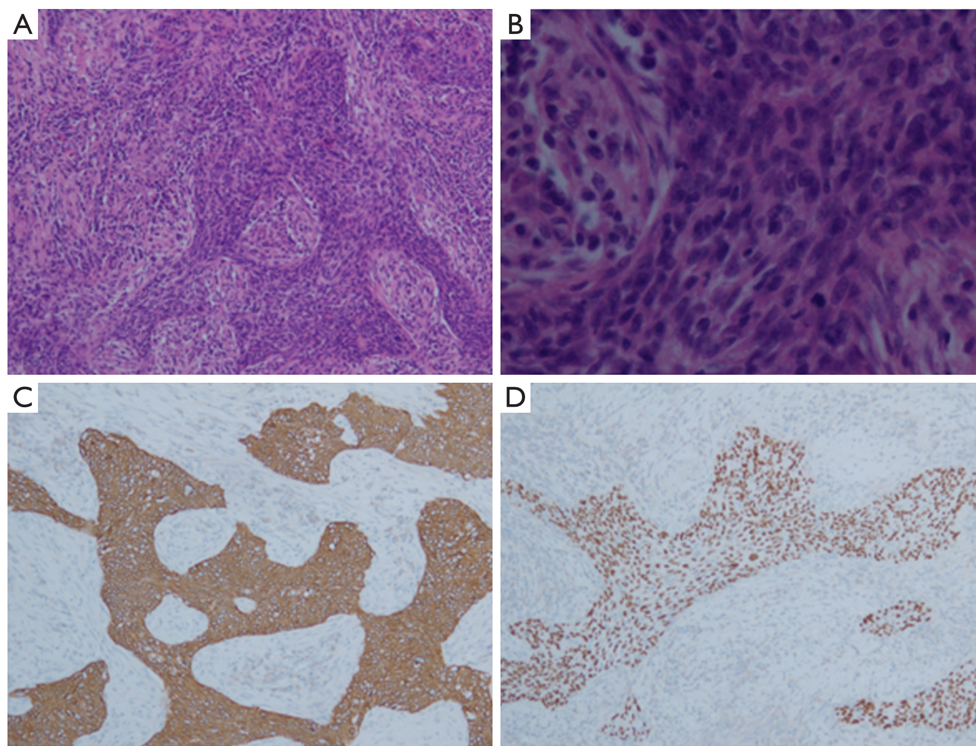

Figure 1 Histopathologic examination revealed nests of epithelial tumor cells separated by abundant lymphocytes in hematoxylin and eosin-stained tissue samples (A,B). Immunohistochemistry staining showed positive expression of (C) cytokeratin 5/6 and (D) P63 (original magnification, ×100 in A, C, D, and ×400 in B).

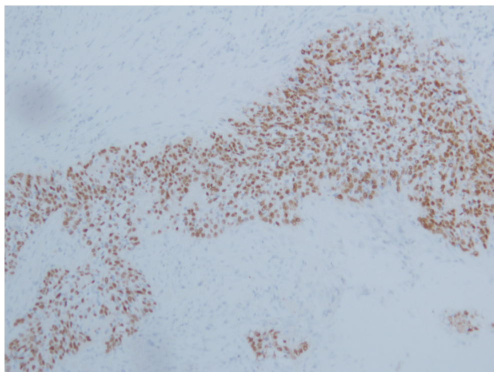

Figure 2 *In situ* hybridization for Epstein-Barr virus-encoded RNAs (EBERs) is illustrated. EBERs were positive in the nuclei of large neoplastic cells but not in the surrounding lymphocytes (original magnification, ×100).

All specimens were from primary tumors. Pulmonary LELC was characterized by undifferentiated carcinoma cells with ill-defined cytoplasmic borders arranged in syncytial sheets and nests. The tumor cell nuclei were round, oval or elongated, with mildly irregular nuclear borders, vesicular chromatin and distinct nucleoli. The stromal tissue septa contained large numbers of reactive lymphoplasmacytic cells and other inflammatory cells (*Figure 1A* and *B*). By immunohistochemical staining, all patients demonstrated positive expression of CK5/6 (*Figure 1C*) and P63 (*Figure 1D*), but almost all patients were negative for TTF-1(34/34, 100%) or CK7 (34/35, 97.1%). ISH for EBERs showed positive signals in all 42 patients (*Figure 2*). Of 42 patients tested, only one patient (2.4%) harbored EGFR L858R mutation (*Figure 3A*) while others were all EGFR wild-type. None of the 42 patients had *ALK* rearrangement (*Figure 3B*).

As was shown in *Table 1*, multimodality treatment was applied in 66.7% of patients. Most chemotherapy regimens were platinum-based (cisplatin or carboplatin combined with pemetrexed, gemcitabine, or docetaxel). Of note, *EGFR* TKI gefitinib was applied in that patient with *EGFR* L858R mutation, but no objective response was observed and the PFS was only 1 month. None of those 42 patients received *ALK*-targeted therapy crizotinib due to lack of *ALK* rearrangement. At a median follow-up time

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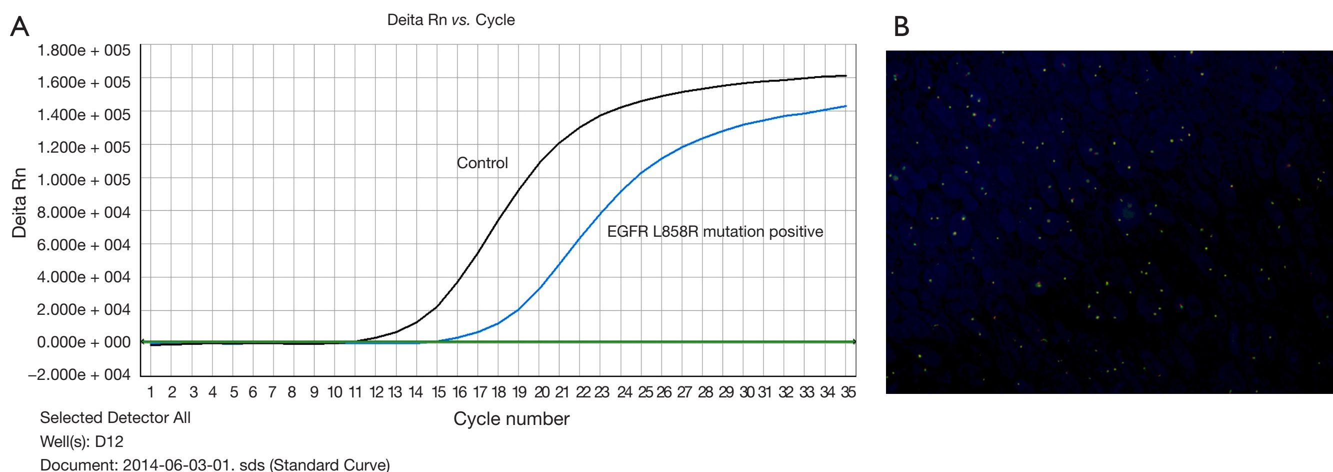

Figure 3 (A) EGFR L858R mutation was demonstrated in one patient; (B) this patient had no ALK rearrangement.

of 12 months (range, 1-67 months), 8 patients had disease progression at a median of 10 months (range, 1-40 months). All patients were alive at the time of data analysis.

Discussion

Pulmonary LELC is a rare histological type of lung cancer and the incidence in previous reports is approximately 1% of all lung malignancies (14). Its clinical and pathological features are different from other histological types of NSCLC. Smoking was considered to be a major cause of lung cancer. However, only 31.0% of LELC patients in this study had a smoking history, which suggested that smoking might not play an important role in the tumor genesis of LELC (5). Nearly half of our patients were asymptomatic when they were diagnosed with pulmonary LELC, whereas others present with symptoms similar to those observed in other lung cancers, such as cough, chest pain, bloody sputum, etc.

In this study, all patients had positive expression of CK5/6 and P63, while almost without expression of TTF-1, indicating the nature of pulmonary LELC is more likely to be squamous cell carcinoma rather than adenocarcinoma. As was mentioned above, LELC is histopathologically identical to the nasopharyngeal lymphoepithelioma, suggesting chemotherapy drugs which were sensitive to nasopharyngeal carcinoma (NPC) such as paclitaxel/docetaxel, 5-fluorouracil, capecitabine and cisplatin may be effective in LELC. In our cohort, 12 patients received paclitaxel/docetaxel-based therapy (alone or combined with cisplatin), and 4/12 (33.3%) patients got PR, and 5/12 (41.7%) got SD. Ho *et al*. (20) reported their experience in five patients with advanced or metastatic pulmonary LELC treated with single agent capecitabine as salvage chemotherapy. Disease control was obtained in three of five patients, especially with exceptionally durable stable disease (14.8 months) in one patient, suggesting the potential clinical activity of capecitabine in pulmonary LELC. Recently, more and more studies have found that gemcitabine can induce lytic EBV infection in B-cell lymphomas, and addition of ganciclovir to gemcitabine can enhance the therapeutic efficacy for EBV-driven tumors (21). As previously reported, all Chinese pulmonary LELC patients had positive *EBERs*, confirming the consistent association of EBV in Chinese patients with pulmonary LELC, and suggesting a possible etiologic role of EBV (4). Thus, combination of ganciclovir and gemcitabine-based chemotherapy could be further investigated in the treatment of pulmonary LELC.

In patients with advanced NSCLC, progress has been made in identifying patients whose disease is caused by specific genetic alterations. This has enabled the development of therapies targeted against different oncogenic drivers, in particular in the *EGFR* mutations and *ALK* rearrangements. To our knowledge, this study is the largest cohort to date reporting prevalence of *EGFR* mutation and *ALK* rearrangements in primary pulmonary LELC.

Mutation in *EGFR* tyrosine kinase domain encoded by exons 18-21 is involved in both pathogenesis and progression of lung cancer (6). *EGFR* TKIs (erlotinib, gefitinib) are now the standard of care in patients with advanced/metastatic NSCLC harboring sensitizing *EGFR* mutations. An earlier study on the detecting *EGFR* mutations among different histological subtypes of NSCLC demonstrated a low incidence

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(1/11, 9.1%) of *EGFR* mutations in pulmonary LELC (13). Chang *et al*. (14) found that *EGFR* mutations were identified in eight out of 46 pulmonary LELC patients (17.4%), among which there were three patients with mutations in exon 21, two with mutations in exon 20, one with mutation in exon 19, and one with mutation in exon 18. Studies had shown that in-frame deletion in exon 19 and L858R mutation in exon 21 are predominant mutations in lung cancer (22,23). In our cohort, among 42 detected patients, only one (2.4%) patient harbored EGFR L858R mutation in exon 21, but responded poorly to EGFR TKIs treatment and PFS was only one month. In all, these results indicated that *EGFR* mutation is uncommon and maybe not an oncogenic driver gene for primary pulmonary LELC which should be further investigated (24).

Rearrangement or fusion of the *ALK* gene, which ultimately gave rise to the oncogenic *ALK* fusion kinase, was identified as a driver oncogene of lung cancer in 2007 (25). The first *ALK* fusion identified in NSCLC was *EML4-ALK*, although other fusion partners for *ALK* in NSCLC have since been discovered (26), along with several *EML4* variants (27). *ALK* rearrangement was also a known oncogenic driver in tumors such as anaplastic large cell lymphoma and inflammatory myofibroblastic tumor (28). It is estimated that *ALK* rearrangements occur in around 5-8% of NSCLC cases depending on the population selection (8). The *ALK* inhibitor crizotinib and ceritinib were approved for advanced or metastatic NSCLC with *ALK*-rearrangement (29,30). In our study, we used *ALK* break apart FISH probe to detect *ALK* rearrangement. One of the major advantages of the break apart FISH assay was that this method does not rely on knowledge of all *ALK* fusion partners, an important benefit since some remain to be discovered (19). A further advantage of the technique was highly sensitive and specific. However, in this cohort, none of 42 patients with pulmonary LELC had *ALK* rearrangement, which is consistent with previously report (15). Thus, we concluded that *ALK* rearrangement was possibly not a driver gene and *ALK*-targeted therapy might not be favorable for pulmonary LELC.

In conclusion, primary pulmonary LELC is a special histological subtype of lung cancer with rare EGFR mutation and lack of *ALK* rearrangement. Whether EGFR-targeted therapy is effective in pulmonary LELC patients harbored with EGFR mutations should be further studied. Conventional cytotoxic chemotherapy is still a backbone treatment in advanced stage primary pulmonary LELC. Future efforts should be made to explore other oncogenic driver gene to guide targeted therapy in this rare disease to determine the optimal treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.
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