Clinical Case Report

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Primary pulmonary lymphoepithelioma-like carcinoma in non-endemic region

A case report and literature review

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Abstract

Rationale: Pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare type of lung squamous cell carcinoma. In situ hybridization test for Epstein–Bar virus-encoded RNA (EBER) is generally used for distinguishing it from other lung cancers. Although plasma EBV DNA quantification has been widely used as a tumor biomarker in nasopharyngeal carcinoma (NPC), only a limiting number of studies have suggested that plasma EBV DNA quantification may be used as a tumor marker in pulmonary LELC patients.

Patient concerns: We report two female patients diagnosed as poorly differentiated squamous cell carcinoma, subsequently, their further histological examinations showed that tumor cells were EBER positive and plasma EBV DNA was detectable.

Diagnoses: Two patients was diagnosed with advanced pulmonary LELC.

Interventions: The patients were treated with chemotherapy and chemoradiotherapy respectively.

Outcomes: Both patients responded well to our treatment, in accordance with their decreased EBV DNA level.

Lessons: Pulmonary LELC is a rare type of lung cancer which is sensitive to chemoradiotherapy, especially in late staged patients.

Abbreviations: EBER = Epstein–Bar virus-encoded RNA, EBV = Epstein–Barr virus, EGFR = epidermal growth factor receptor, LELC = lymphoepithelioma-like carcinoma, NPC = nasopharyngeal carcinoma, NSCLC = non small cell lung cancer, PET-CT = positron emission tomography-computed tomography.

Keywords: chemoradiotherapy, epidermal growth factor receptor, Epstein–Bar virus DNA, pulmonary lymphoepithelioma-like carcinoma

1. Introduction

Lymphoepithelioma-like, carcinoma (LELC) was reported firstly by Regaud and Schmincke to describe tumor from mucous surface of nasopharynx. However, LELC can also occur in extra-nasopharyngeal sites, especially the foregut-derived organs, such as lung, stomach, salivary gland, and thymus. They share similar histopathological characteristics with undifferentiated nasopharyngeal carcinoma (NPC) in morphology and molecular markers, especially in the presence of Epstein–Bar virus-encoded RNA (EBER). Since the first primary pulmonary LELC reported by Begin in 1987, EBV infection was detected in most of the reported cases, most of which were East Asians, especially the population with resident history in southern China. EBER is regarded as the most important differentiation test between pulmonary LELC and other primary lung malignancies. However, cases from non-Asian countries have demonstrated that most patients have EBV-negative diseases, which suggests that the association between EBV and pulmonary LELC, especially in the Western population need further investigation. The majority of pulmonary LELC patients receive complete resection, as well as chemotherapy and radiotherapy based on their clinical stage.[1,2] Comparing to other non-small cell cancer (NSCLC), pulmonary LELC is more sensitive to chemotherapy and radiotherapy, which is similar to EBV associated NPC.

2. Case presentation

2.1. Case 1

A 64-year-old female patient initially presented with dysphagia after meal, coughing and hemoptysis. Chest computed tomography (CT) revealed a mass in the inferior lobe of left lung which surrounded the esophagus and extended to left hilus. She had been working as a farmer for 50 years, and had never been to southern China. The patient had no smoking history. CT-guided needle biopsy of the pulmonary lesion confirmed the diagnosis of poorly differentiated squamous cell carcinoma, immunohistochemistry (IHC): PCK(+), CK5/6(+), P40(+), CK(−), TTF-1(−), NapsinA(−), CgA(−), Syn(−), CD56(−), ALK(±), Ki67 (Li:20%), tumor cells stained positively for EBV on in-situ hybridization studies (Fig. 1A and B). The peripheral blood extracellular EBV DNA level was 1.81×10^3 copies/mL (normal

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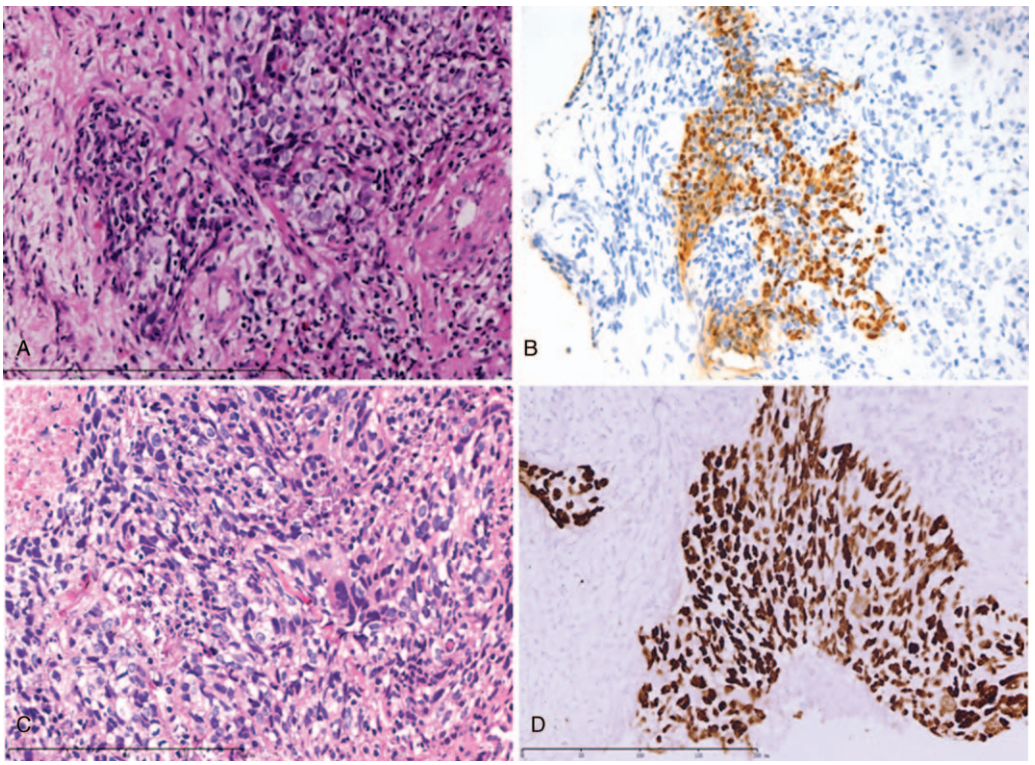

Figure 1. Histology of 2 patients. (A) and (B): Case 1, (C) and (D): Case 2. (A and C) The tumor cells have a seemingly syncytial pattern of growth and a marked lymphocytic infiltration (original magnification ×40); (B and D) the tumor cells are positive for EBER by in situ hybridization (original magnification ×40). EBER = Epstein–Bar virus-encoded RNA.

limit <400 copies/mL). Her brain and bone scan revealed no metastasis or a primary nasopharyngeal carcinoma. The patient was staged as cT2N3M0. Subsequently, she received 2 cycles of induction chemotherapy with paclitaxel liposome and carboplatin (TC regimen Paclitaxel liposome 135 mg/m^2 d1, carboplatin AUC = 5 d1), and the hemoptysis stopped afterwards. Chest CT scan showed that the primary lesion and metastatic lymph nodes shrank significantly and EBV DNA level was undetectable after induction chemotherapy (Figs. 2 and 3). She received another 2 cycles of concurrent chemotherapy and chest intensity-modulated radiation therapy (IMRT) (60 Gy/30F) to the primary lesion and metastatic lymph nodes. The patient was discharged from hospital with close follow-up. No recurrence has been detected so far.

2.2. Case 2

A 30-year-old woman presented with symptoms of persistent coughing, chest pain, and aypnia for 2 months. Chest CT showed a 2.5 cm mass near left hilus of the lung with pleural invasion and multiple lesions in the liver. The patient was non-smoker without resident history in southern China. Her positron emission tomography-computed tomography (PET-CT) showed multiple hypermetabolic sites in the liver, kidneys, and bones, in addition to the mass and other small nodules in the left lung. No abnormal lesion was observed in the head and neck region. CT-guided needle biopsy of the left lung mass revealed a non-keratinizing carcinoma with necrosis, IHC: P63(+), PCK(+), CK5/6(+), P40 (+), CK7(−), TTF-1(−), NapsinA(−), CgA(−), Syn(−), CD56(−), ALK(−), EGFR(−), Ki67(Li:70%), EBER (+) (Fig. 1C and D). In addition, EBV DNA level was 3.33×10^5 copies/mL in the plasma. She was diagnosed with poorly differentiated squamous cell carcinoma cT2N2M1. The patient received chemotherapy with docetaxel and cisplatin (DP regimen docetaxel 75 mg/m^2 d1, cisplatin 75 mg/m^2 d1-d2). After 4 cycles of DP chemotherapy, her CT scan showed that the mass in the left lung shrunk and plasma EBV DNA level decreased significantly (Figs. 2 and 3). Unfortunately, the patient suffered from severe febrile neutropenia after her fifth DP chemotherapy. After supportive treatment, she recovered and refused further treatment. According to her follow-up CT scan a month after discharged from hospital, the lesions remains stable.

The ethics committee of Union Hospital, Tongji Medical College approved the case. All participants provided informed consent.

3. Review of literature and discussion

Pulmonary LELC is a rare type of lung cancer. Most patients come from East Asia, especially the southeastern China, which is an endemic region of nasopharyngeal carcinoma. This finding suggests that EBV may be an important carcinogenic factor. However, there is no obvious correlation between EBV and pulmonary LELC among Caucasian population,[3] and reports of pulmonary LELC from non-endemic region of China are rare.

Most pulmonary LELC were poorly differentiated squamous cell carcinoma.[4] Liang et al reported high level of CK, CK5/6, and p63 expression detected by IHC in 145 patients, which

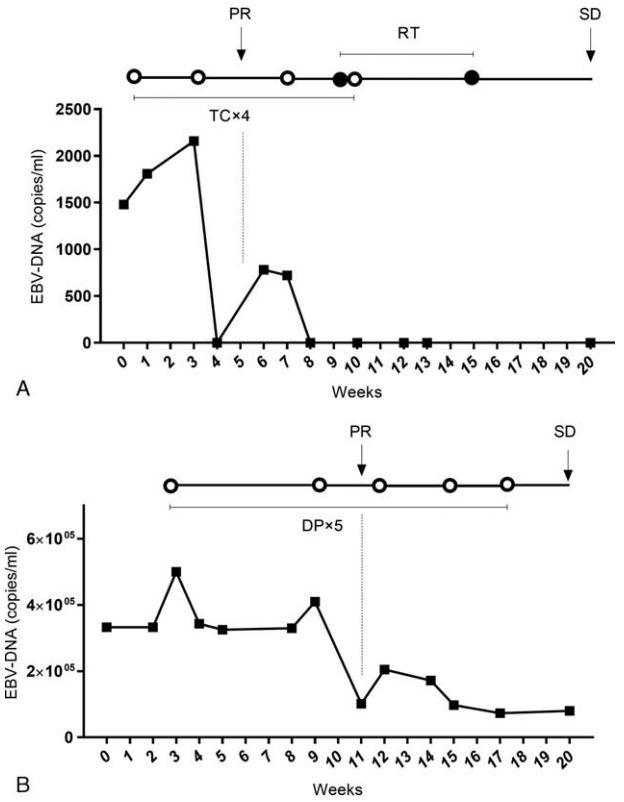

Figure 2. Correlation between plasma EBV DNA level and treatment EBV DNA level of the 2 patients decreased after chemotherapy and radiotherapy. DP = docetaxel+cisplatin, response evaluation based on RECIST 1.1), PR = partial response, RT = radiation therapy, SD = stable disease, TC = paclitaxel+carboplatin.

indicates that pulmonary LELC may originate from epithelial tissue and belongs to the category of squamous carcinoma. In situ hybridization for EBER is generally regarded as the most important differentiation test. The result of the EBER test in a recent report consisting of 36 Chinese patients shows that all of them are positive for EBER, similar to a previous report with 94% (30/32) positivity. In our cases, CK5/6 and p40 were both positive, which is consistent with previous reports.

Epidermal growth factor receptor (EGFR) mutations are the major carcinogenic mechanism in non-tobacco induced lung cancers. The EGFR mutation frequency in Caucasian NSCLC patients is 15%, while East Asian patients nearly 50%.[5] However, EGFR mutation status varies even in Asian population. Liang et al reported 15 patients underwent mutational analysis of EGFR and all of them had wild type. Tam et al reported that 1 of 11 patients with EGFR mutation, while Liu et al investigated a total of 32 patients but no mutation in axons 19 and 21 was detected.[6–8] Liu et al reported 19 patients underwent surgery without EGFR mutation. Lately, Chang et al[9] reported that 17.4% (8/46) pulmonary LELC patients with EGFR mutations, but none was classical mutation site such as L858R in exon 21. Comparing to previous reports that nearly half of NSCLC patients in East Asian have EGFR mutations, pulmonary LELC patients with EGFR mutation is very rare.

EML4-ALK fusion gene in pulmonary LELC is not very common. Wong et al[10] investigated a total of 11 patients, but none of them were identified with the fusion gene. A large cohort study reported lately shows that 1.8% (2/113) patients with EGFR mutation but none (0/113) with ALK fusion gene. However, PD-L1 over-expression was detected in 74.3% (84/113) patients.[11] In our cases, no ALK fusion gene and EGFR mutation were detected. Collectively, these results indicate that pulmonary LELC possesses a distinguishable genetic profile, especially among different ethnics.

Generally, pulmonary LELC manifests as centrally located tumors with frequent lymph node involvement, as well as bronchial and vascular encasement invasion. In addition, peribronchovascular nodal spread is common.[12] Hoxworth et al[13] reported 3 early-staged cases without lymphadenopathy, while lesions in all patients manifest as poorly circumscribed peripheral nodules. To our knowledge, this difference could be explained as a reflection of clinical course. Forty-one patients from eastern China reported by Ma et al[14] shown that radiological differentiation and diagnosis of pulmonary LELC based on imaging might be difficult. In these cases, all the masses located around the hilus of the lung with mediastinal invasion, which was similar to the imaging features of most central lung squamous carcinoma.

Plasma EBV DNA copy number quantification has been proven to be a useful tumor marker for diagnosis, prognosis, prediction of recurrence, and therapeutic response in NPC patients.[15,16] Thus far, few results have been reported in pulmonary LELC patients. Ngan et al[17] observed the variation pattern of circulating EBV DNA in pulmonary LELC patients with detectable EBV DNA at initial diagnosis. In their cases, plasma EBV DNA profile correlated with treatment and clinical course, especially in patients with recurrence. Patients sensitive to the treatment had persistently decreased EBV DNA level. Furthermore, they also found that patients with high pretreatment plasma EBV DNA level had lower overall survival rate. In these cases, the plasma EBV DNA copies decreased significantly after induction chemotherapy, and both maintained at undetectable level after effective local and systemic treatment. So far, both our patients are in stable condition after the treatment, which is verified by imaging and EBV DNA level. Therefore, we believe that variation of plasma EBV DNA copy quantification in the plasma could be used as a useful tumor marker in pulmonary LELC.

Currently, there is no standard treatment for pulmonary LELC. Chan divided patients into 2 categories, operable or inoperable. Two patients without metastatic disease received surgery and adjuvant chemotherapy with progression free survival (PFS) of 18 and 20 months, respectively. Seven patients received chemotherapy, 5 achieved PR (71.4%) and 2 had PD (28.6%) with OS ranging from 5 to 26 months.[18] However, 2 operable patients' condition deteriorated rapidly 1 year after surgery, emphasizing chemotherapy could be an important treatment even in the early stage of the cancer. Lately, the result of a series of 32 pulmonary LELC patients received surgical resection showed that they had a significantly better 5-year survival than non-LELC patients.[1] Thus, optimizing therapy for this rare type of lung cancer requires more cases and further investigation.

In conclusion, we reported 2 cases of pulmonary LELC from region with low incidence of EBV infection. These cases are EBER positive, thus emphasizing that EBV may be an important carcinogenic factor in this type of lung cancer in Asian population. A remarkable finding in the case is that variation of the plasma EBV DNA level in both patients is consistent with their clinical course. Comparing to other NSCLC; pulmonary

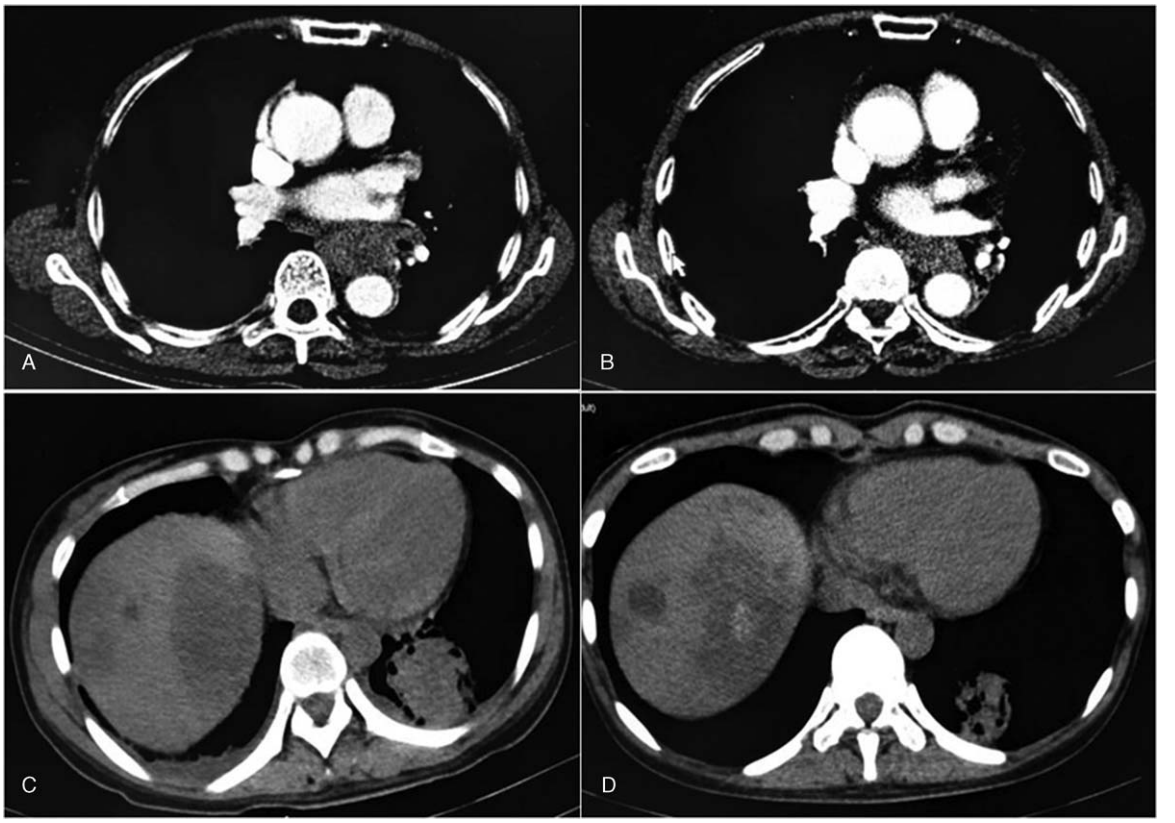

Figure 3. Chest CT of 2 patients. Case 1: (A) a mass in the inferior lobe of left lung (B) after 2 cycles of TC chemotherapy, the mass shrunk significantly. Case 2: (C) a mass near left hilus of the lung with pleura invasion (D) CT scan after 2 cycles of DP chemotherapy showed that the mass in the left lung shrunk significantly. CT = computed tomography, DP = docetaxel+cisplatin, response evaluation based on RECIST 1.1), TC = paclitaxel+carboplatin.

LELC is more sensitive to chemoradiotherapy, especially in late staged patients.

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