Unusual presentation of pulmonary lymphoepithelioma-like carcinoma

Ryoko Oi¹, Hisashi Saji¹,², Hideki Marushima¹, Ichiro Maeda³, Masayuki Takagi³ & Haruhiko Nakamura¹

¹Department of Chest Surgery, St. Marianna University School of Medicine, Kanagawa, Japan.
²Department of Thoracic Surgery, Tokyo Medical University, Tokyo, Japan.
³Department of Pathology, St. Marianna University School of Medicine, Kanagawa, Japan.

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Abstract
Primary pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare malignant tumour with histological features similar to undifferentiated nasopharyngeal carcinoma. A close association is known to exist between pulmonary LELC and Epstein–Barr virus infection in Southeast Asian countries. We report a 69-year-old man with pulmonary LELC arising from a thin-walled cavity with a smooth inner surface and characterized by an unexpectedly rapid progression.

Introduction
Primary pulmonary lymphoepithelioma-like carcinoma (LELC), a rare kind of malignant tumour with histological features similar to undifferentiated nasopharyngeal carcinoma, was first reported by Begin et al. in 1987 [1] and classified as a subtype of large cell carcinoma according to the World Health Organization classification in 2015 [2]. Of particular interest is the close association between Epstein–Barr virus (EBV) infection and the occurrence of pulmonary LELC in Southeast Asian countries such as Taiwan, Southern China, and Hong Kong, and the significantly better prognosis of pulmonary LELC than other types of non-small cell lung cancer (NSCLC) [3].

Case Report
A 69-year-old man who had smoked 90 pack years of cigarettes was referred to our hospital for a detailed examination of an abnormality detected in a routine chest X-ray examination. Chest computed tomography (CT) showed a thin-walled cavity located in the left S9 area and a small 5-mm nodule in the visceral pleura of the left lower lobe (Fig. 1A, B). The 4-month follow-up CT showed no changes in these shadows (Fig. 1C, D), making the attending doctor classify the patient for annual chest X-rays. After 1 year and 6 months, the patient was referred specifically to our department for a detailed examination of the abnormal shadow on the chest X-ray. Chest CT revealed two round solid masses (17 and 15 mm) with a circumscribed border arising from a thin-walled cavity located in the left S9 area and in the visceral pleura of the left lower lobe, respectively, and one enlarged lymph node (20 mm) in the left hilum (Fig. 1E, F).

For pathological diagnosis, transbronchial needle aspiration of the hilar lymph node revealed a low-differentiated adenocarcinoma or squamous cell carcinoma. The levels of the specific tumour markers carcinoembryonic antigen (CEA), squamous cell carcinoma (SCC), cytokeratin 19 fragment (CYFRA), neuron specific γ- enolase (NSE), and pro-gastrin releasing peptide (Pro GRP) were not elevated. Neither brain contrast-enhanced magnetic resonance imaging (MRI) nor positron emission tomography–CT showed any metastatic lesions.

The patient then underwent left pneumonectomy with complete lymph node dissection, because of enlarged bulky lymph node (20 mm) in the left hilum (Fig. 1E). Grossly, the left lung showed two small solid masses in the left S6
area and the S9 area with a thin-walled cavity, respectively, with one enlarged lymph node in the left hilum (Fig. 2A). Microscopically, the tumour arose from a thin-walled cavity (Fig. 2B) and consisted of large atypical epithelial cells with extensive lymphocytic infiltration (Fig. 2C–E), and left hilar lymph node metastasis was confirmed. Despite the negative result for EBV-encoded small ribonucleic acid 1 (EBER1), the definitive diagnosis of this case was pulmonary LELC and pathologically staged as T3N1M0 IIIA. Adjuvant chemotherapy was not performed owing to pneumonectomy. Brain metastasis and multiple pulmonary metastases occurred 3 months postoperatively. Despite the administration of gamma knife and four courses of platinum doublet chemotherapy including carboplatin plus pemetrexed, the patient died 6 months after the surgical treatment.

**Discussion**

Primary pulmonary LELC, which is a rare malignant tumour constituting approximately 0.92% of all lung cancers, is an undifferentiated carcinoma and is known to have a close association with EBV infection in Southeast Asian countries [3]. A review of the literature has shown less than 300 cases reported with about 20 cases from the Western population. Previous studies of Chinese cases showed that pulmonary LELCs had a better prognosis than non-LELC lung cancers because of their good response to chemotherapy and irradiation, even though about 40% of the patients with pulmonary LELC had unresectable disease at diagnosis [3,4]. Most of the patients were young, women, and non-smokers, and most tumours were centrally located, in their early or locally advanced stages, and received multi-modality treatment. Almost all of the Chinese patients (>90%) had EBER-positive tumours. However, an association of pulmonary LELC with EBV infection has not yet been confirmed among Caucasians [5]. For Japanese patients, distant metastasis has not been observed at diagnosis, most tumours were peripheral, the proportion of male patients was higher, and the association of EBV with the tumours was less frequent. Therefore, these LELC might be thought as a subtype of LELCs in

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**Figure 1.** Chest computed tomography (CT) findings over the clinical course showed a thin-walled cavity in the left S9 area and a small 5-mm nodule in the visceral pleura of the left lower lobe at the first visit (A, B), no changes in the shadows at follow-up (C, D), and two round solid masses (17 and 15 mm) with a circumscribed border, and one enlarged lymph node (20 mm) in the left hilum at surgical treatment (E, F). The thin arrow shows the tumour in the left S6 area and one enlarged hilum lymph node. The thick arrow indicates the tumour in the left S9 area.
Southeast Asian. In Japan, there have apparently been no reports describing the rapid progression of pulmonary LELC as reported in the present case.

The radiological features of LELC have been described as non-specific. Recently, the CT findings of primary pulmonary LELC of the largest cohort of 41 patients have been reported [5]. Pulmonary LELC usually appears as a large, central, well-defined, and lobulated solid tumour with vascular or bronchial encasement and obstructive pneumonia, which is indistinguishable from other types of NSCLC. Here, we report a rare case of LELC presenting as a thin-walled cyst with a smooth inner surface and showing rapid tumour progression over several years. To the best of our knowledge, these unusual CT findings have never been reported to date.

Several reports have described the detection of EBV DNA in the blood of patients with pulmonary LELC, which is considered to be clinically significant. Thus, EBV DNA in the blood can be thought of as an effective surrogate tumour marker. Unfortunately, EBER was not detected in the tumours of the present case. Therefore, the association between the blood EBV DNA level and the clinical course was not clarified. The detailed demographic and clinicopathological features of LELC, including features associated with race and EBV DNA blood level, should be carefully clarified.

Disclosure Statements
No conflict of interest declared. 
Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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