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A patient with CXR abnormality

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Case History

A fifty-five years old housewife was referred to the respiratory clinic of Tseung Kwan O Hospital for chest X-ray (CXR) abnormality in June 2013. She was a non-smoker and non-drinker. Her past medical history included hypertension, diabetes mellitus and obesity. She complained of cough for one month with whitish sputum and weight loss. Physical examination was unremarkable except finger clubbing. CXR of this patient showed a round mass with well-demarcated border in right middle lobe. (Figures 1, 2) Computer tomography (CT) thorax showed a 5.5cm well-defined mass in the right middle lobe with enlarged right para-tracheal, para-carinal and subcarinal lymph nodes. (Figures 3, 4) Blood tests were unremarkable except elevated *alkaline phosphatase (ALP)* to 175 U/L. Heat stability index suggested that the ALP was of bone in origin. Sputum for AFB and cytology were negative. Bronchoscopy showed no endobronchial lesion. Transbronchial bisopy showed a focus of elongated and plump epithelial tumor cells admixed with lymphocytes within the peribronchial lung parenchyma. These anaplastic tumor cells showed high nucleocytoplasmic ratio, hyperchromasia and prominent nucleoli. They were demonstrated to be positive for EBV-encoded RNA (EBER) by in-situ hybridization. The diagnosis was lymphoepithelioma-like carcinoma (LELC).

Since LELC shares similar histological features with metastatic nasopharyneal carcinoma, the patient was referred to otorhinolaryngologist to rule out nasopharyneal carcinoma. Physical examination by otorhinolaryngologist showed symmetrical nasopharynx with no mass, normal

larynx, hypopharynx and tongue base. There was no palpable cervical lymph node. Epstein-Barr virus viral capsid antigen IgA (EBV VCA IgA) was 80. Positron emission tomography (PET) scan was performed and showed that the nasopharynx was unremarkable. There was a malignant neoplasm, most likely bronchogenic carcinoma, in right middle lobe with tumour invasion into the adjacent pleura and oblique fissure. Nodal metastases to mediastinal region was present. A mildly hypermetabolic node was seen in right lower jugular region, which was suspicious of nodal metastasis. There was no hypermetabolic focus to suggest liver, adrenal or axial bony metastasis. The patient was reviewed by the otorhinolaryngologist. Since clinically there was no palpable cervical lymph node, ultrasound guided fine needle aspiration (FNA) was booked for the mildly hypermetabolic right lower jugular node. Ultrasound performed by radiologist showed a 0.5 x 0.5 x 1.0cm (W x AP x L) lymph node with fatty hilum in lower right jugular region. The lymph node was surrounded by arteries and internal jugular vein and there was no safe access for FNA, and hence the procedure was not done.

The patient was referred to cardiothoracic surgeon for further management. Mediastinoscopy showed small bilateral paratracheal and enlarged subcarinal lymph nodes. Pathology of these lymph nodes did not show evidence of malignancy. Right thoracotomy with right middle lobe lobectomy was performed. A tumour of size 5 x 3.5 x 5cm was resected. Subcarinal lymph node metastasis and visceral pleural penetration were present. The diagnosis of stage IIIA T2aN2 lymphoepithelioma-like carcinoma was made. The patient subsequently completed chemotherapy (Vinorelbine and carboplatin) and radiotherapy. Till her last follow up in early 2016, 30 months after lobectomy, there was no evidence of disease recurrence. No palpable cervical lymph node was found during follow up and the ALP level also returned to normal.

Discussion

Epidemiology

Lymphoepithelioma-like carcinoma (LELC) was first reported by Begin et al in 1987. It is an uncommon but distinct form of non-small cell carcinoma of lung. (1) Under World Health Organization histological classification of tumours of lung, LELC was classified under large cell carcinoma. (2) Around 200 cases were reported in the literature till 2012. Majority of the cases were ethnically Orientals, mainly from Taiwan, Southern China and Hong Kong. There were no more than 20 cases from the Western populations. (3) LELC represented 0.9% of primary lung cancers. (1) When the patients' characteristics of LELC were compared with that of other lung cancers, the mean age was reported to be 10 years younger. The youngest reported case was an 8-year-old child. LELC showed greater tendency to occur in non-smokers. 69% of LELC patients were non-smokers. (1)

Histological features

Tumour cells of LELC consist of undifferentiated carcinoma cells with ill-defined cytoplasmic borders arranged in syncytial sheets and nests. The stroma showed thick fibrous bands contain large numbers of reactive lymphoplasmacytic cells and other inflammatory cells. (1) Histologically, it is indistinguishable from undifferentiated nasopharyngeal carcinoma. Differential diagnoses include NPC with lung metastasis and Non-Hodgkin's lymphoma. It is clinically important to exclude these diagnoses. LELC of lung is strongly associated with Epstein-Barr virus (EBV) infection. However, this relationship is only observed in Asians but not in Caucasians. The presence of EBV in LELC has been demonstrated by polymerase chain reaction (PCR) for EBV DNA, in situ hybridization (ISH) for EBV DNA, EBV-encoded small nuclear RNA (EBER) by ISH and immunohistochemistry for EBV-associated proteins. (1) 17.4% of patient with LELC of lung presented with EGFR mutation (4) but no EML4-ALK expression was observed (5).

Clinical features and diagnosis

Clinical presentations of LELC include cough (47%), chest pain (13%), dyspnoea (5%),

weight loss (5%), night sweat (3%), joint pain (3%) and fever (2%). 22% of patients were asymptomatic. (1) The most frequent site of metastasis is local lymph node. Occasionally hematogenous metastasis occurs and most commonly to skeletal system. (6) Most cases were presented in early resectable stages. (1) In a study investigating the CT features of LELC of the lung, it was found that LELC tumours were significantly larger and more centrally located when compared with other non-LELC non-small cell lung cancer. The same study also noted LELC tumours were associated with well-defined borders, fewer spiculated borders and increased peribronchovascular nodal metastases and vascular encasement. (7) Staging of LELC uses the same TNM System as other non-small cell carcinoma.

Treatment and prognosis

For treatments of LELC, they are mostly similar to those for NSCLC. (8) There was evidence showing for the patients with stage IIIA disease who underwent complete resection, adjuvant chemotherapy was correlated with a significantly better prognosis. (3) Patients with LELC had a significantly better 5-year survival than those with non-LELC. One study showed that the 5-year survival rate for LELC stage II-IV patients was over 60%. (9) There were a few factors significantly associated with better overall survival. These include early tumor stage, normal serum lactate dehydrogenase level, normal serum albumin level, absence of lymph node metastasis and having complete resection of tumour. (3) The poor prognostic factors include tumour recurrence and necrosis. (9)

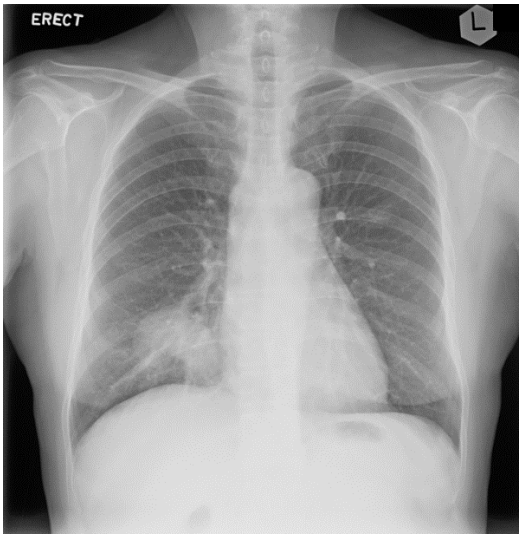

Figure 1

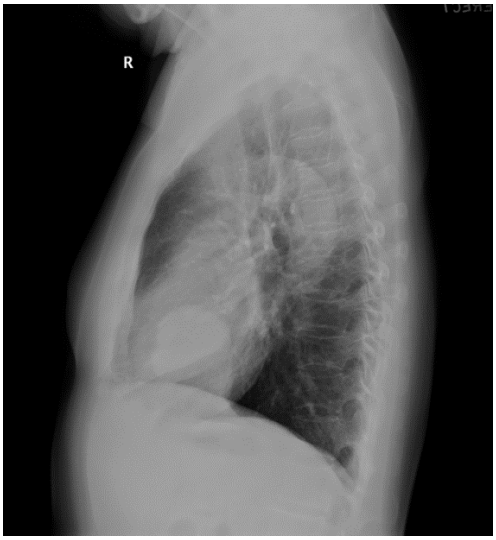

Figure 2

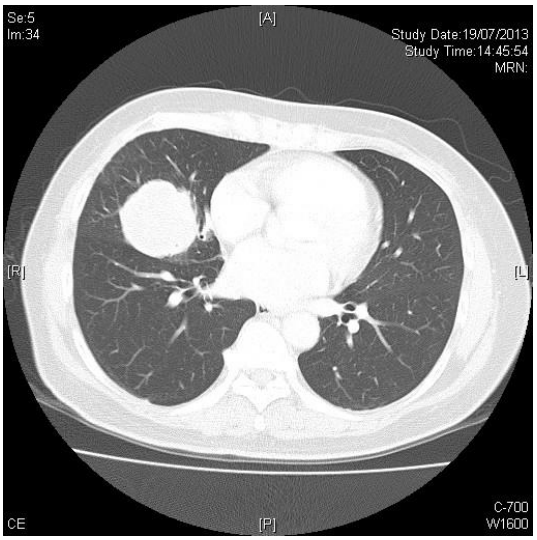

Figure 3

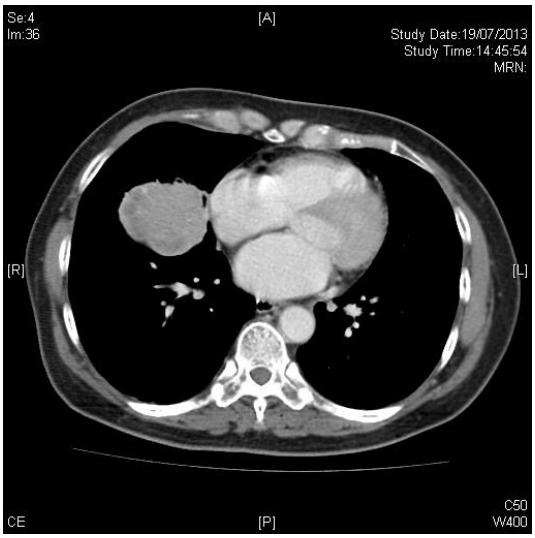

Figure 4

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