



# Festered and Fenced-Lymphoepithelial Carcinoma Lung

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## Abstract

Lymphoepithelial carcinoma is an exceptionally discerned, primary pulmonary carcinoma with a distinct syncytial pattern of tumour evolution. Lymphoepithelial carcinoma incriminates centric or peripheral pulmonary parenchyma with equivalent predilection. Median age of disease emergence is 51 years to 57 years. Lymphoepithelial carcinoma lung occurs due to Epstein Barr virus (EBV) infection and malignant metamorphosis triggered by dysregulation of NFkB pathway, loss of type I interferon (IFN) genes and concordant signatures by APOBEC family of genes. Tumefaction is composed of enlarged, polygonal cells pervaded with abundant or variable eosinophilic cytoplasm, vesicular nuclei and prominent, eosinophilic nucleoli. Tumour cells are circumscribed by quantifiably variable lymphoid and plasma cell infiltrate. Tumour cells appear immune reactive to squamous epithelial cell biomarkers as CK5/6, p40 or p63 whereas in situ hybridization (ISH) for discerning Epstein Barr encoded small RNAs (EBER) appears optimal. Lymphoepithelial carcinoma lung requires segregation from neoplasms such as poorly differentiated adenocarcinoma, NUT pulmonary carcinoma, malignant melanoma, lymphoma confined to pulmonary parenchyma, metastatic undifferentiated carcinoma of nasopharynx or metastatic medullary carcinoma arising from breast of colon. Stage I and stage II neoplasms are subjected to comprehensive surgical extermination whereas stage II, stage III or advanced grade neoplasms may be managed with surgical eradication in combination with adjuvant radiotherapy or chemotherapy.

**Keywords:** Pulmonary Tumour; EBV; Lymphoid; Plasma Cells

**Abbreviations:** WHO: World Health Organization; EBV: Epstein Barr virus; FNAC: Fine Needle Aspiration Cytology; PET/CT: Positron Emission Computerized Tomography; IFN: Interferon; ISH: In Situ Hybridization; EBER: Epstein Barr Encoded Small RNAs; TTF-1: Thyroid Transcription Factor-1; CT: Computerized Tomography.

## Introduction

Lymphoepithelial carcinoma is an infrequently encountered, primary pulmonary carcinoma. As per

current classification of World Health Organization (WHO), tumefaction exemplifies a contemporary designation of subtype of poorly differentiated squamous cell carcinoma lung. Previously denominated as lymphoepithelioma-like carcinoma and categorized as an unclassified carcinoma, neoplasm is frequently concurrent to infection with Epstein Barr virus (EBV). Lymphoepithelial carcinoma characteristically exhibits a distinct syncytial pattern of tumor evolution. Neoplasm is accompanied by variable quantities of lymphoid and plasma-cellular inflammatory infiltrate. Neoplastic cells are permeated with abundant,

eosinophilic cytoplasm, vesicular nuclei and prominent eosinophilic nucleoli. Akin to conventional squamous cell carcinoma, tumefaction appears diffusely immune reactive to CK5/6, p40 or p63. Comprehensive surgical eradication is accompanied by favorable prognostic outcomes, in contrast to conventional squamous cell carcinoma lung.

The exceptionally discerned neoplasm configures 0.9% of primary pulmonary carcinomas. Commonly encountered within Asian population, lymphoepithelial carcinoma exhibits an equivalent gender predilection. Median age of disease emergence is 51years to 57years [1,2]. Lymphoepithelial carcinoma incriminates centric or peripheral pulmonary parenchyma with equivalent predilection. Notwithstanding, a characteristic concurrence within bronchial lumens is absent. Lymphoepithelial carcinoma lung occurs due to carcinogenesis induced by Epstein Barr viral infection. Subsequently, malignant metamorphosis is triggered by dysregulation of NFkB pathway along with loss of type I interferon (IFN) genes. Besides, genomic signatures by APOBEC family of genes appear concordant [1,2]. Majority (~80%) of neoplasms depict chromosomal deletions or mutations within TRAF3 gene. Besides, nearly 5% of simple somatic mutations may be confined within TRAF3 gene. Instances concurrent with cigarette smoking appear devoid of cytosine: guanine(C:G) to adenine: thymine(A:T) trans-version. In contrast to conventional non-small cell carcinoma lung, typical driver mutations within TP53, KRAS and EGFR genes or genomic translocation within ALK and ROS1 are exceptionally encountered [1,2].

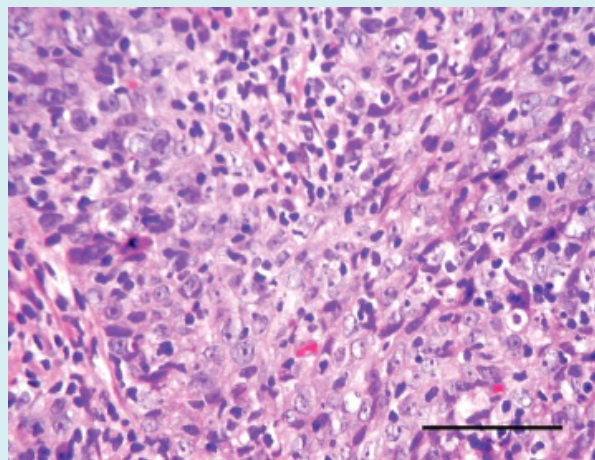
Lymphoepithelial carcinoma lung is intensely concurrent with Epstein Barr viral (EBV) infection. History of cigarette smoking is absent. Lymphoepithelial carcinoma

lung is devoid of specific clinical manifestations. Nearly ~33% subjects appear asymptomatic. Commonly discerned respiratory symptoms appear as cough with expectoration or pain confined to thoracic cavity [1,2]]. Cytological examination exhibits spindle shaped cells configuring enlarged, cohesive cellular clusters commingled with a population of small lymphocytes. Tumour cell nuclei appear elliptical, pleomorphic and are permeated with prominent nucleoli. Smears appear reminiscent of malignant melanoma or synovial sarcoma [3,4].

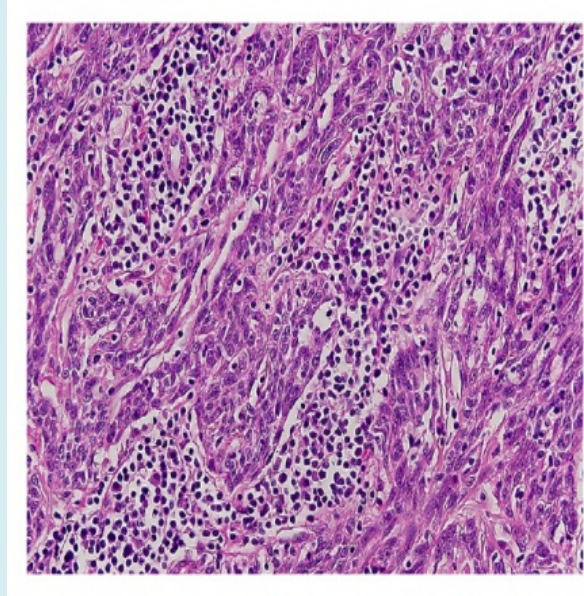
Grossly, neoplasm is confined to peripheral pulmonary parenchyma, in contrast to central parenchyma. Generally, association with bronchial tree is absent. Tumefaction is well circumscribed and demonstrates an irregular perimeter [3,4].

Upon frozen section and low power magnification, neoplasm may simulate lymphoid tissue. The epithelial component appears reminiscent of histiocytic cells [3,4]. Upon microscopy, tumefaction exhibits a distinct syncytial pattern of tumour evolution. Tumefaction is comprised of enlarged, polygonal cells pervaded with abundant or variable eosinophilic cytoplasm, vesicular nuclei and prominent, eosinophilic nucleoli.

Tumour cells are circumscribed by variable quantities of lymphoid and plasma cell infiltrate. Lymphoid and plasmacytic inflammatory infiltrate may be scanty and histologically simulates foci of non-keratinizing squamous cell carcinoma. Besides, foci of granulomatous inflammation and focal keratinization may be discerned. Tumefaction may delineate lepidic pattern of tumour invasion. Mitotic activity is variable [3,4].



**Figure 1:** Lymphoepithelial carcinoma delineating syncytia of enlarged, polygonal cells imbued with abundant, eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli. Tumour cells are enmeshed by small lymphocytes and plasma cells [5].



**Figure 2:** Lymphoepithelial carcinoma demonstrating clusters of enlarged, polygonal cells incorporated with abundant cytoplasm, vesicular nuclei and prominent nucleoli. A dense exudate of small lymphocytes and plasma cells encompass neoplastic cells [6].

TNM staging of non-small cell carcinoma lung as per American Joint Committee on Cancer 8th Edition [3,4].

### Primary Tumour

- TX: Primary tumour cannot be assessed or tumour discerned by malignant cells encountered within sputum or bronchial washings although non visualized upon imaging or bronchoscopy.
- T0: No evidence of primary tumour.
- Tis: Carcinoma in situ, squamous cell carcinoma in situ, adenocarcinoma in situ or a 'pure' lepidic pattern with tumour magnitude  $\leq 3$  centimetres.
- T1mi: Minimally invasive adenocarcinoma  $\leq 3$  centimetre diameter with a predominantly lepidic pattern and  $\leq 5$  millimeters depth of invasion.
- T1a: Tumour  $\leq 1$  centimetre magnitude OR exceptionally, a superficial, spreading tumour of variable magnitude with tumour invasion confined to bronchial wall which extends proximal to main bronchus.
- T1b: Tumour magnitude  $> 1$  centimetres and  $\leq 2$  centimetres.
- T1c: Tumour magnitude  $> 2$  centimetres and  $\leq 3$  centimetres.
- T2: Tumour magnitude  $> 3$  centimetres and  $\leq 5$  centimetres or tumour incriminates main bronchus irrespective of distance to carina in the absence of involvement of carina. Tumour invades visceral pleura OR is associated with atelectasis or obstructive pneumonitis which extends to hilar region and confined to partial or

comprehensive (100%) pulmonary parenchyma.

- T2a: Tumour magnitude  $> 3$  centimetres and  $\leq 4$  centimetres along with minimally a singular aforesaid features.
- T2b: Tumour magnitude  $> 4$  centimetres and  $\leq 5$  centimetres.
- T3: Tumour magnitude  $> 5$  centimetres and  $\leq 7$  centimetres or tumour directly invades parietal pleura, chest wall OR tumour confined to superior sulcus, phrenic nerve or parietal pericardium or presence of disparate tumour nodule within singular pulmonary lobe.
- T4: Tumour magnitude  $> 7$  centimetres or tumour of variable magnitude with invasion into diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body or carina or presence of disparate tumour nodule within an ipsilateral, different pulmonary lobe.

### Regional Lymph Nodes

- NX: Regional lymph nodes cannot be assessed.
- N0: Regional lymph nodes metastasis absent.
- N1: Tumour metastasis into ipsilateral peribronchial, ipsilateral hilar or intrapulmonary lymph nodes along with direct tumour extension into lymph nodes.
- N2: Tumour metastasis into ipsilateral mediastinal or subcarinal lymph nodes.
- N3: Tumour metastasis into contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or

supraclavicular lymph nodes.

### Distant Metastasis

- M0: Distant metastasis absent
- M1a: Distant metastasis with disparate tumour nodules within contralateral pulmonary lobe, pleural nodules, pericardial nodules, malignant pleural effusion or malignant pericardial effusion
- M1b: Distant metastasis into singular extra-thoracic metastasis confined to singular organ or singular non regional lymph node
- M1c: Distant metastasis into multiple extra-thoracic sites confined to singular organ or multiple organs.

### Prognostic Staging of Non-Small Cell Carcinoma Lung as per American Joint Committee on Cancer 8th Edition

- ✓ Occult carcinoma: TX, N0, M0
- ✓ Stage 0: Tis, N0, M0
- ✓ Stage IA1:T1mi, N0, M0 OR T1a, N0, M0
- ✓ StageIA2:T1b,N0,M0
- ✓ StageIA3:T1c, N0,M0
- ✓ Stage IB:T2a, N0, M0
- ✓ StageIIA:T2b, N0, M0
- ✓ Stage IIB: T1a, T1b, T1c, N1, M0 OR T2a, T2b, N1, M0 OR T3, N0, M0
- ✓ Stage IIIA:T1a, T1b, T1c, N2, M0 OR T2a, T2b, N2, M0 OR T3, N1,M0 OR T4, N0, N1, M0
- ✓ Stage IIIB: T1a, T1b, T1c,N3, M0 OR T2a, T2b, N3, M0 OR T3,T4, N2, M0
- ✓ Stage IIIC: T3, T4, N3, M0
- ✓ Stage IVA: Any T, any N, M1a OR any T, any N, M1b
- ✓ Stage IVB: Any T, any N, M1c

Lymphoepithelial carcinoma appears immune reactive to various squamous epithelial cell biomarkers as CK5/6, p40 or p63. In situ hybridization (ISH) for Epstein Barr encoded small RNAs (EBER) is optimal for neoplastic assessment. An estimated 90% of incriminated Asian subjects may delineate concurrent infection with Epstein Barr virus (EBV) whereas the virus appears absent in implicated individuals of European descent. Lymphoepithelial carcinoma lung appears immune non-reactive to CK7, thyroid transcription factor-1(TTF-1), CD56, synaptophysin or chromogranin [7,8].

### PD-L1 Levels are Significantly Elevated.

Lymphoepithelial carcinoma lung requires segregation from neoplasms such as poorly differentiated adenocarcinoma, NUT pulmonary carcinoma, malignant

melanoma, lymphoma confined to pulmonary parenchyma, metastatic undifferentiated carcinoma of nasopharynx or metastatic medullary carcinoma arising from breast of colon. Upon radiography, tumefaction appears as a solitary, well defined, lobulated tumefaction exceeding > 1 centimetre magnitude. Computerized tomography (CT) of thoracic cavity is recommended in order to categorize the tumour [7,8]. Fine needle aspiration cytology (FNAC) with cogent immunohistochemistry may appropriately discern the neoplasm. Besides, fibre-optic bronchoscopy followed by histological evaluation of surgical tissue samples may be adopted for cogent neoplastic detection [7,8]. Endoscopic examination along with or in absence of radiographic imaging of nasopharynx may be optimally performed in order to exclude metastasis arising from lymphoepithelial carcinoma of nasopharynx. Upon positron emission computerized tomography (PET/CT), tumefaction exhibits an enhanced uptake of 18F- fluorodeoxyglucose (18F -FDG). Neoplasm expounds homogenous density and may display vascular enhancement [7,8]. Stage I of lymphoepithelial carcinoma is optimally and primarily alleviated with surgical eradication. Stage I and stage II neoplasms may be subjected to comprehensive surgical extermination. Alternatively, stage II, stage III or advanced grade neoplasms may be managed with surgical extermination in combination with adjuvant radiotherapy or chemotherapy [7,8]. Chemotherapeutic drugs as PD-L1 inhibitors appear as potential, contemporary agents which may beneficially adopted for disease alleviation [7,8]. Lymphoepithelial carcinoma lung is accompanied by superior prognostic outcomes, in contrast to conventional squamous cell carcinoma.

### Factors Contributing to Favorable Prognostic Outcomes Emerge as

- Preliminary tumour stage
- Absence of regional lymph node metastasis
- Neoplasms treated with comprehensive surgical resection
- Elevated expression of pd-l1 or wild type p53 [7,8].

### Factors Contributing to Adverse Prognostic Outcomes Appear as

- Tumour reoccurrence
- Emergence of tumour necrosis
- Enhanced levels of serum epstein barr viral (EBV) capsid antigen [7,8].

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