Case Report

Lymphoepithelioma-like Carcinoma of Lung: An Important *Albeit* Uncommon Diagnosis

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Abstract

A 25-year-old young male presented with pain in chest and left shoulder for two months, dry cough, shortness of breath for one month and hoarseness of voice for 15 days. He was a non-smoker and served in the armed forces. Chest radiograph showed homogeneous opacity over the entire left hemithorax obliterating left costophrenic and cardiophrenic angles with a shift of mediastinum to the contralateral side. Contrast-enhanced computed tomography of chest and upper abdomen revealed a large mass lesion involving left upper lobe with minimal pleural effusion on the left. Bronchial washing cytology was positive for malignant cells. Endobronchial biopsy showed clusters, nests and small island of tumour cells infiltrating bronchial mucosa. Immunohistochemistry was focal positive for CK 5/6 and synaptophysin, strongly positive for pancytokeratin and Epstein-Barr virus, negative for thyroid transcription factor (TTF1) and CD 68; human leucocyte common antigen taken up by accompanying lymphoid cells confirmed the diagnosis of lymphoepithelioma like carcinoma. This variety of lung cancer is very rare, occurs mostly in Asians and has relatively better prognosis compared to non-small cell carcinomas. In young adults with lung mass; possibility of this uncommon variety of malignancy is high with a favourable outcome if diagnosed early and needs an aggressive clinical work-up. **[Indian J Chest Dis Allied Sci 2018;60:249-252]**

Key words: Lymphoepithelioma, Epstein-Barr virus, Carcinoma, Lung.

Introduction

Primary pulmonary lymphoepithelioma-like carcinoma (LELC), an uncommon variety of lung malignancy was first reported in 1987.[1] The unique characteristics of LELC that differentiates it from other histologic variants of lung cancer include no association with smoking, aetiopathogenic role of Epstein-Barr virus (EBV) in oriental population and affliction in younger individuals without any gender predilection. However, LELC has a better prognosis compared to non-LELC lung cancer.[1] This type of malignancy is usually found in the nasopharynx, and when present in the lung, was earlier considered to be a variant of large cell carcinoma of lung.[2] However, as per the latest World Health Organization classification of lung tumours, LELC comes under unclassified carcinomas.[3] Majority of these patients belong to oriental ethnicity with around two-thirds of cases reported from Southern China, Taiwan, and Hongkong.[1] However, to the best of our knowledge, till date only two case reports of pulmonary LELC have been reported in Indian literature.[4,5] Globally, around 300 cases have been reported out of which only 20 cases are from the Western world.[6] Prevalence of LELC in South-East Asia is estimated to be only 0.9% of all lung cancers.[1] Our case of pulmonary LELC is probably the third case reported from India.

Case Report

A 25-year-old young male, non-smoker, armed forces personnel, came to us with complaints of pain in chest and left shoulder for two months, dry cough and shortness of breath for one month and hoarseness of voice for the last 15 days. There was no significant past or family history. On examination, he was an average built individual with no other remarkable finding. Chest examination revealed decreased movements of the left hemithorax, decreased vocal fremitus, dull note on percussion and diminished vesicular breath sounds over the left mammary and axillary areas.

Chest radiograph (postero-anterior view) showed an opacity over the entire left hemithorax obliterating the left cardiophrenic and costophrenic angles with a shift of mediastinum to the right side (Figure 1). On ultrasonography of the chest, abdomen and pelvis; only positive finding was left-sided pleural effusion

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with underlying collapsed lung. Contrast-enhanced computed tomography of chest and upper abdomen revealed a mass lesion in the left upper lobe with a minimal left pleural effusion (Figure 2). Laboratory investigations did not reveal any abnormality. Sputum smear was negative for malignant cells and acid-fast bacilli. Pleural fluid was haemorrhagic in appearance, exudative in nature with a adenosine deaminase level of 4 U/L, negative for acid-fast bacilli on smear examination and negative for malignant cells on cytological examination.

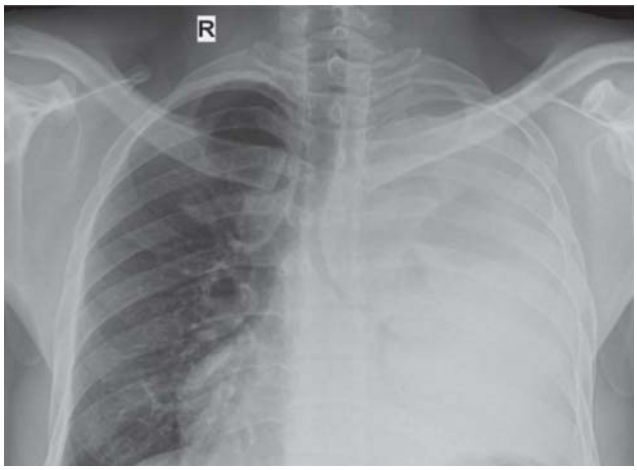

Figure 1. Chest radiograph (postero-anterior view) showing an opaque left hemithorax with obliteration of the left cardiophrenic and costophrenic angles and shift of the mediastinum to the contra-lateral side.

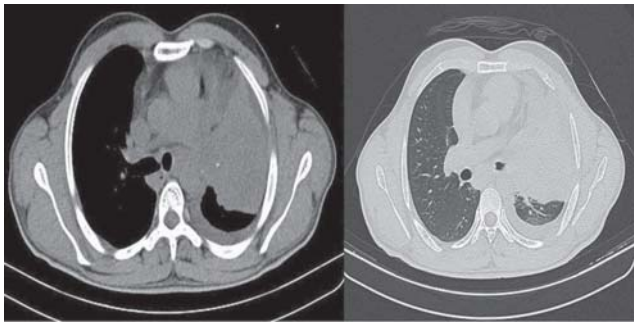

Figure 2. Computed tomography of thorax showing a large mass in the left upper lobe with minimal pleural effusion on the left.

On flexible bronchoscopy, there was sluggish movement of left vocal cord, a solitary mucosal nodule seen in the left main bronchus >2cm distal to the carina. Distal to the carina, there were multiple mucosal nodules seen in the left main bronchus, left upper lobe and lingula involved by a globular mass, almost completely occluding their lumen, overlying mucosa was unhealthy, friable, and bleeding on touch. There were multiple mucosal nodules seen at the lower end of the left main bronchus. The left upper lobe bronchus and lingula were almost completely occluded by a globular mass and the overlying mucosa was unhealthy, friable, and bleeded on touch

Endobronchial biopsy was done and bronchial washing taken from both the left upper lobe and lingula and smear cytology was positive for malignancy with clusters of well preserved malignant epithelial cells showing nuclear overlapping and crowding with prominent nucleoli. Histopathological examination showed clusters, nests and small islands of tumour cells infiltrating the bronchial mucosa. The malignant cells were medium sized, round to oval with vesicular to hyperchromatic nuclei, with no evidence of glandular formation, mucin secretion or squamous differentiation (Figure 3A). On immunohistochemistry, the tumour cells were strongly positive for pancytokeratin and EBV (Figure 3B); focal positive for CK 5/6 (Figure 3C) and synaptophysin and negative for thyroid transcription factor and CD 68. The human leucocyte common antigen stain was taken up by accompanying lymphoid cells and not the tumour cells (Figure 3D) that lead to a diagnosis of lymphoepithelioma-like carcinoma. This tumour is known to have a better prognosis with early surgical intervention. As of now, surgical facility is not available at our relatively new institution, patient was referred to a center experienced with thoracic surgical interventions. Subsequently, the patient was lost to follow-up.

Discussion

Primary pulmonary lymphoepithelioma-like carcinoma of lung with predominant lymphocytic

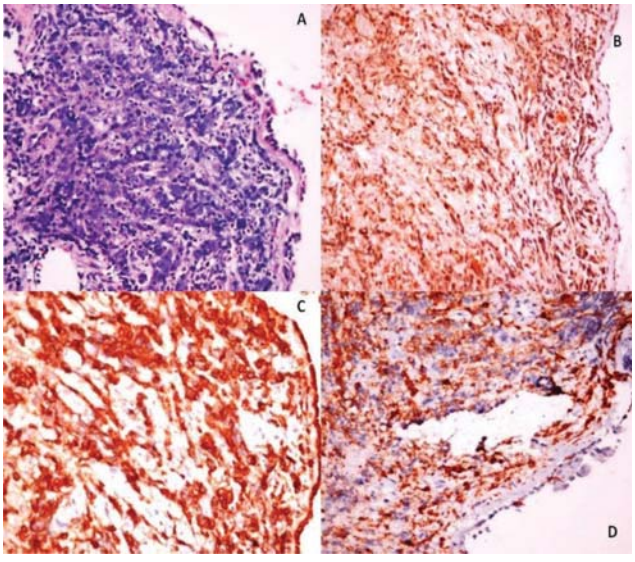

Figure 3. Photomicrograph showing (A) large tumour cells arranged in cords and small islands intermixed with lymphoid cells (Haematoxylin and Eosin, × 400); (B) on immunohistochemistry, tumour cells showed strong and diffuse positivity for Epstein-Barr virus; (C) for cytokeratin (magnification both B & C × 400); and (D) tumour cells are LCA negative, only accompanying lymphoid cells have taken LCA (magnification × 200).

infiltration typically affects younger population and mean age of the patients is 10 years younger compared to non-LELC lung malignancies.[1] The youngest patient reported with LELC is an eight-year-old girl.[1] However, age of the patients varies from 9 years to 74 years.[7] There is no clear gender predilection in contrast to other histologic variants of lung carcinomas with a male predominance. Only 25%–30% of LELC cases are smokers, suggesting possibility of alternative aetiological factors.[1,7] Our patient also presented at a young age of 25 years and was a non-smoker. In patients with LELC, the most common symptoms are cough (47%), haemoptysis (30%), followed by chest pain, dyspnoea, weight loss, night sweats, joint pain and fever. Interestingly, asymptomatic presentation has also been reported in 22% patients.[1]

Epstein-Barr virus infection may have a major role in tumourigenesis of LELC. EBV association is demonstrated only in tumours of respiratory and digestive systems, like lung, salivary gland and stomach. It is pertinent to note that EBV association of lung and salivary gland in LELC is limited to Asian population only. No such ethnic predisposition is documented for thymic and gastric LELC.[1] A subset of pulmonary squamous cell carcinomas and adenocarcinomas may have EBV expression.[8]

Radiologically, it is not possible to differentiate LELC from non-small cell carcinomas. However, LELC tumours are more likely to present as poorly circumscribed peripheral nodule of size 3.5cm or less with no lymphadenopathy.[9] However, it has been observed that LELC tumours may be central, large in size, associated with peri-vascular nodal spread and vascular encasement.[10] The differential diagnosis of LELC include poorly-differentiated carcinoma, malignant melanoma; close mimickers being metastatic nasopharyngeal carcinoma and non-Hodgkin's lymphoma.

Immunohistochemistry may help to differentiate between non-Hodgkin's lymphoma and LELC. Magnetic resonanace imaging and CT of neck together with nasopharyngeal biopsy may be required to rule out nasopharyngeal LELC.[11] In fact, primary pulmonary LELC has been mis-diagnosed as undifferentiated adenocarcinoma based on percutaneous trans-thoracic needle biopsy and the diagnosis was revised to LELC on surgically resected samples. Therefore, histopathological confirmation on biopsy through excision or surgical resection has been proposed as the sine *qua non* for the diagnosis of LELC.[12]

The largest cohort of LELC patients has been reported from China in a retrospective study.[7] Most of the patients were diagnosed at an early stage and they received multi-modality treatment. In this study, the median follow-up time was 31.6 months (range 3.6-121.8 months). The 2- and 5-year overall survival rate was, 88% and 62%, respectively.[7] Tumour necrosis affecting 5% or more of the tumour and recurrence of tumour are associated with poor prognosis; whereas under-expression of p53 and c-erb B2 in tumour cells and the presence of CD8-positive cytotoxic T-lymphocytes are the markers for a better survival.[13]

Patients with LELC have a more favourable prognosis compared to non-small cell carcinomas. Most of the patients present early (39% stage 1, 14% stage 2); metastases tend to develop less frequently (15%) and later in natural history of the disease.[1] However, LELC being a rare tumour, there is no standardised treatment protocol. Surgery appears to be the unequivocal management in the early stages.[11] In our patient also, there was no evidence of any distant metastases, and hence, the patient was considered for surgical resection.

In a study with 10 patients of advanced stage LELC where surgery was not possible, chemotherapy with fluorouracil (5FU)/leucovorin/cisplatin combination was administered along with local radiotherapy and the response was encouraging.[14] Epidermal growth factor receptor and anaplastic lymphoma kinase mutation expression is rare in LELC. Therefore, tyrosine kinase inhibitors or crizotinib is not effective in these tumours.

In a recent study,[6] it was found that LELC with positive PD-L1 (programmed cell death ligand 1) expression had significantly better progression free survival. Potential of anti-PD-1/PD-L1 targeted therapies in this rare malignant condition needs to be explored.[6]

To conclude, in young adults with a lung mass, the possibility of an uncommon type of malignancy, like LELC should always be kept in the differential diagnosis. It needs to be reiterated that these malignancies have favourable outcomes if diagnosed early and calls for a proactive clinical work-up.

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