# A Rare Double Pathology- Coexistent Large Cell Neuroendocrine Cell Carcinoma of the Lung with Basal Cell Carcinoma of the Skin

**Muhammad Redzwan S. RASHID ALI, MRCP(UK)*, Arfian IBRAHIM, MRCP(UK)*, Giri Shan RAJAHRAM, MRCP(UK)**, Kunji Kannan SIVARAMAN KANNAN, MRCP(UK)***

*Department of Respiratory, Hospital Queen Elizabeth, Kota Kinabalu, Sabah, Malaysia, **Department of Internal Medicine, Hospital Queen Elizabeth, Kota Kinabalu, Sabah, Malaysia

## INTRODUCTION

Large cell neuroendocrine cell carcinoma (LCNEC) is a relatively uncommon, poorly recognised and underestimated high-grade tumour that is part of the neuroendocrine cell tumours (NET) of the lung group. It is usually associated with a dismal outcome even at an early stage. It has a reported prevalence of 2.9% of all surgically resected lung cancers. Its association with other subtypes of extra thoracic carcinoma is even rare but has been reported in case series. We report a rare occurrence of double carcinoma pathology in a patient who was diagnosed with large cell neuroendocrine cell carcinoma (LCNEC) and was separately diagnosed with basal cell skin carcinoma.

## CASE REPORT

A 64 year old diabetic and hypertensive lady, an ex-smoker of 10 pack years, presented with a 1 month history of swelling on her upper back and left arm associated with generalised lethargy, loss of appetite and loss of weight.

She was pink, BP 125/70 mmHg, Pulse Rate: 83 bpm, Respiratory Rate 18 breaths and afebrile. Air entry was reduced over left lung field. There was three soft tissue subcutaneous mass, measuring 4 x 2.5 cm (left lateral aspect of forearm), 3.5 x 3.0 cm (posterior aspect of forearm) and 3.0x 2.5 cm (lumbar region). It was mobile, firm, and non-tender with mild signs of erythema over the skin.

Blood panels were normal except she had Hb of 8.4g/dl (normochromic, normocytic). Chest radiograph revealed a well-rounded suspicious mass at the left lung hilum. She underwent an Excisional biopsy of the lumbar mass and was planned for a subsequent Computed Tomography (CT) Thorax a week later while awaiting for the results. CT Thorax was reported as large enhancing predominantly enhancing hypodense mass arising from left hilar region measuring 7.1 x 5.8 x 7.2 cm suggestive of bronchogenic carcinoma with evidence of liver, kidney and bone (rib) metastases. The biopsy results were interpreted as basal cell carcinoma (incompletely excised).

In view of the rarity of metastatic basal cell carcinoma to the lung, she was referred for a CT guided biopsy of the hilar mass and rib lesion 3 weeks later. The biopsy revealed malignant cells, mild pleomorphic dense chromatic nuclei with moderate cytoplasm. Keratin pearls and typical pseudorosette are not seen. Mitoses are present. Tumour cells positive for CK7, CK 20 and synaptophysin. Chromogranin and CK5/6 focally positive. TTF-1 is negative. Features are suggestive of large cell neuroendocrine carcinoma (LCNEC).

She was referred to the Oncologist and was deemed to have two separate double pathology, which is concurrent metastatic Stage 4 LCNEC and basal cell carcinoma. She was offered palliative radiotherapy for the lung mass and rib metastases and subsequent chemotherapy as per treatment of small cell lung cancer (Etoposide with Carboplatin) as it was the more aggressive cancer out of the two. The patient agreed for radiotherapy fractions but declined further chemotherapy and subsequently succumbed three months later.

## DISCUSSION

The above case illustrates the rare occurrence of a double carcinoma pathology or synchronous tumour, namely the large cell neuroendocrine carcinoma (LCNEC), which is a part of the Neuroendocrine tumours of the lung (NET) and basal cell skin carcinoma. This is the second such case reported in the literature.

*Neuroendocrine Tumours of the Lung*

Neuroendocrine tumours (NET) of the lung was initially classified in 1972 according to Arrigoni classification based on aggressiveness and the grade of the tumours into typical carcinoid (TC), atypical carcinoid (AC) and small cell lung carcinoma (SCLC)[1]. In 1990's, other authors also identified a fourth high grade neuroendocrine tumours called large cell neuroendocrine carcinoma/intermediate cell carcinoma (LCNEC)[2].

In 1999, World Health Organization (WHO) classified LCNEC as a variant of large cell carcinoma. In this schema, large cell carcinomas are classified into four types based on neuroendocrine morphology as determined by light microscopy and neuroendocrine differentiation demonstrable by immunohistochemistry and/or electron microscopy into

*This article was accepted: 14 August 2014*
*Corresponding Author: Muhammad Redzwan S Rashid Ali, Hospital Queen Elizabeth, Respiratory Department, Hospital Queen Elizabeth, Karung Berkunci 2029, 88586 Kota Kinabalu, Sabah, Malaysia Email: redzwanrashid@gmail.com*

(1) LCNEC, (2) Large cell carcinoma with neuroendocrine differentiation (LCCND), (3) Large cell carcinoma with neuroendocrine morphology (LCCNM), and (4) Classic large cell carcinoma (CLCC)

*How do we differentiate LCNEC from the other subtypes?*
LCNEC is characterised by: (a) light microscopic Neuroendocrine (NE) appearance, (b) cells of large size, polygonal shape, low nuclear-cytoplasmic ratio (N: C), coarse nuclear chromatin, and frequent nucleoli; (c) high mitotic rate [greater than 10/10 high-power fields (HPF)] and frequent necrosis; and (d) NE features by immunohistochemistry (IHC) or electron microscopy (EM) [2]. The above features are present clearly in this patient Histopathological specimen.

*Large cell Neuroendocrine Carcinoma (LCNEC)*
The clinical and radiological presentations are as follows: two thirds of cases present as peripheral growing tumours or nodules, with a mean size of 3.4-4.0 cm; and are relatively asymptomatic. It is usually located in the upper lobes. The occurrence of paraneoplastic syndrome is very rare. Its radiological features are non-specific and similar to other types of Non-small cell lung carcinoma (NSCLC). It is usually diagnosed post operatively in resected cases. It afflicts more men compared to women, aged above 60 years old and 60% are smokers. In our case report, this patient was an ex-smoker and was relatively asymptomatic despite a huge lung mass noted which is slightly atypical compared to LCNEC cases described in the literature.

LCNEC has also been reported in various organs such as breast, uterine, cervix, gallbladder, urinary bladder, ovaries and colon. The most common site of metastasis is liver and bone. Rare cases of cutaneous metastases have also been reported. This could have been a differential in our case as initially it was presumed that the subcutaneous lumps were a manifestation of either subcutaneous or skin metastases of the primary LCNEC (which usually shows predilection to the back). Other differentials that were entertained were metastatic basal cell carcinoma to the lung (very rare), squamous cell carcinoma, amelanotic melanoma, metastatic carcinoid tumour and Merkel cell carcinoma. The other rare possibility would include conditions such as Lynch syndrome that is associated with multiple malignancies of different primaries with a genetic predisposition. Synchronous extrathoracic tumours in association with primary neuroendocrine lung carcinoma have also been rarely described in case reports, which may point towards a common gene carcinogenesis mutation [3].

However, histopathological features in this patient clearly showed evidence of basal cell carcinoma, which was a separate double pathology that occurred concurrently in this case. Separate double pathology of a primary lung carcinoma and coexistent basal cell carcinoma is very rare and has rarely been reported.

*Prognosis and Therapy*
Traditionally, LCNEC clinical aggressiveness was placed in between AC and SCLC [5]. The 5-year survival for Stage I LCNEC patients is only 18% and the 5-year survival for all stages is 13%. Thus it portends a poor prognosis even in very early stage disease with no survival improvement even on adjuvant therapy [4, 5].

Compared to other subtypes of large cell carcinoma, LCNEC has a poorer prognosis. Neuroendocrine features, older age, larger tumour size, increased tumour mitotic rate, and lymph node metastasis predicted poorer overall and disease-free survivals. Hence lies the importance of identifying neuroendocrine and histologic features in tumour tissue from patients diagnosed with large cell carcinoma of the lung [4, 5].

Treatment options available are based on case reports, as there is no standard therapy for LCNEC. Platinum based polychemotherapy are used in general such as Cisplatin + Etoposide with/without radiotherapy; that is a similar regime for cases of SCLC. For resectable cases or even metastatic disease, use of Octreotide with/without radiotherapy also has been reported in patients with positive pre-op OctreoScan.

In summary, early diagnosis and accurate histopathological classification of LCNEC is important as the prognosis is poorer and progression is more aggressive compared to other subtypes of lung carcinoma.

## REFERENCES


1. Arrigoni MG, Woolner LB, Bernatz PE. Atypical carcinoid tumors of the lung. J Thorac Cardiovasc Surg 1972; 64(3): 413-21.
2. Travis WD, Linnoila RI, Tsokos MG *et al.* Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma. An ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. Am J Surg Pathol 1991; 15(6): 529-53.
3. Jung-Legg Y, McGowan SE, Sweeney KG, Zitzman JL, Pugatch RD. Synchronous triple malignant tumors of the lung. A case report of bronchial carcinoid, small cell carcinoma and adenocarcinoma of the right lung. Am J Clin Pathol 1986; 85(1): 96-101.
4. Iyoda A, Hiroshima K, Toyozaki T, Haga Y, Fujisawa T, Ohwada H. Clinical characterization of pulmonary large cell neuroendocrine carcinoma and large cell carcinoma with neuroendocrine morphology. Cancer 2001; 91(11): 1992-2000.
5. Travis WD, Rush W, Flieder DB *et al.* Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. Am J Surg Pathol 1998; 22(8): 934-44.