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Case Report Open Access

Tracking EGFR Mutant Resistance in a Large Cell Neuroendocrine Tumor of the Lung with Activating and Resistance EGFR Mutations Treated with Erlotinib – A Case Report and Literature Review

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Abstract

In recent years, limited reports of epidermal growth factor receptor mutations in pulmonary large cell neuroendocrine tumors have implicated potential therapeutic targets in a tumor which has historically been treated with platinum based chemotherapy. We report partial response in metastatic large cell neuroendocrine tumor with an EGFR mutation. Moreover, targeted next generation sequencing analysis upon disease progression identified possible resistance pathways in EGFR and *PIK3CA* which parallels observations in adenocarcinoma of the lung. New therapeutic strategies may be need to be developed overcome resistance.

Keywords: Mutation; Neuroendocrine tumors; Carcinoma; Lung cancer

Abbreviations: PLNT: Pulmonary Neuroendocrine Tumor; Tkis: Tyrosine Kinase Inhibitors; EGFR: Epidermal Growth Factor Receptor

Introduction

Pulmonary large cell neuroendocrine tumors (PLNT) constitutes ~3% of lung malignancies [1]. Characteristically they are a high grade and form part of the spectrum of neuroendocrine tumors including small cell, typical and atypical carcinoid [2]. Prospective clinical trials in this cohort of patients have been hindered by the infrequent number of cases. Although there is no consensus on the optimal first line treatment for patients with metastatic disease, platinum based regimens have formed the mainstay treatment [1]. Response rates of 29% have been reported using carboplatin and etoposide [3].

In the last decade tyrosine kinase inhibitors (TKIs) have played a key role in reshaping the treatment of adenocarcinomas of the lung with increased response rates and improved progression free survival [4,5]. Reportedly 90% of activating mutations in EGFR (epidermal growth factor receptor) are present as two mutation hotspots, namely exon 21 L858R or deletions in exon 19 [6]. Despite the initial control exerted by the TKI, the effects are temporary. Multiple resistance pathways have emerged to overcome the inhibitory effect of the TKIs [7]. The primary resistance mechanism is the development of a T790M mutation in the gate keeper residue which reduces the affinity of the ATP-binding pocket [8].

The limited reports evaluating the frequency of EGFR mutations in PLNT suggest that they are uncommon in this subtype of tumors [9,10].

Case Report

An 81-year-old female, non-smoker commenced Erlotinib 150 mg OD as a second line treatment in the absence of genetic testing for EGFR, serial re-staging CT imaging demonstrated a partial response which was maintained. Despite this, treatment was discontinued after 7 cycles due to cumulative toxicity.

After an interval of 4 months the patient was subsequently enrolled on to the MK3475 clinical trial and randomized to receive docetaxel 75 mg/m2, though tolerated only one treatment cycle. A second EBUS guided mediastinal lymph node biopsy performed as a prerequisite for trial screening demonstrated a large cell neuroendocrine carcinoma with a pathogenic somatic EGFR exon 21 L858R mutation through sanger sequencing. In view of these findings the patient was re-challenged with erlotinib 150 mg OD, which was tolerated with a mixed radiological response after 6 cycles though was discontinued at this point due to cumulative toxicity.

A rapidly growing retro-auricular subcutaneous nodule was biopsied and was in keeping with a large cell neuroendocrine carcinoma (Figure 1). Targeted next generation sequencing of the subcutaneous nodule identified the original pathogenic EGFR mutation (L858R) with a variant allele frequency (VAF) of 38%. However, an additional non-synonymous mutation in EGFR (D761Y) and *PIK3CA* E542K were detected with VAFs of 41 and 50% respectively confirming that they were not sub clonal in nature. The patient died before further treatment decisions could take account of these findings.

Discussion

Histological transformations in adenocarcinoma of the lung have in patients treated with TKI is well documented. This transformation is considered to be a mechanism of resistance to TKI (Table 1) [11].

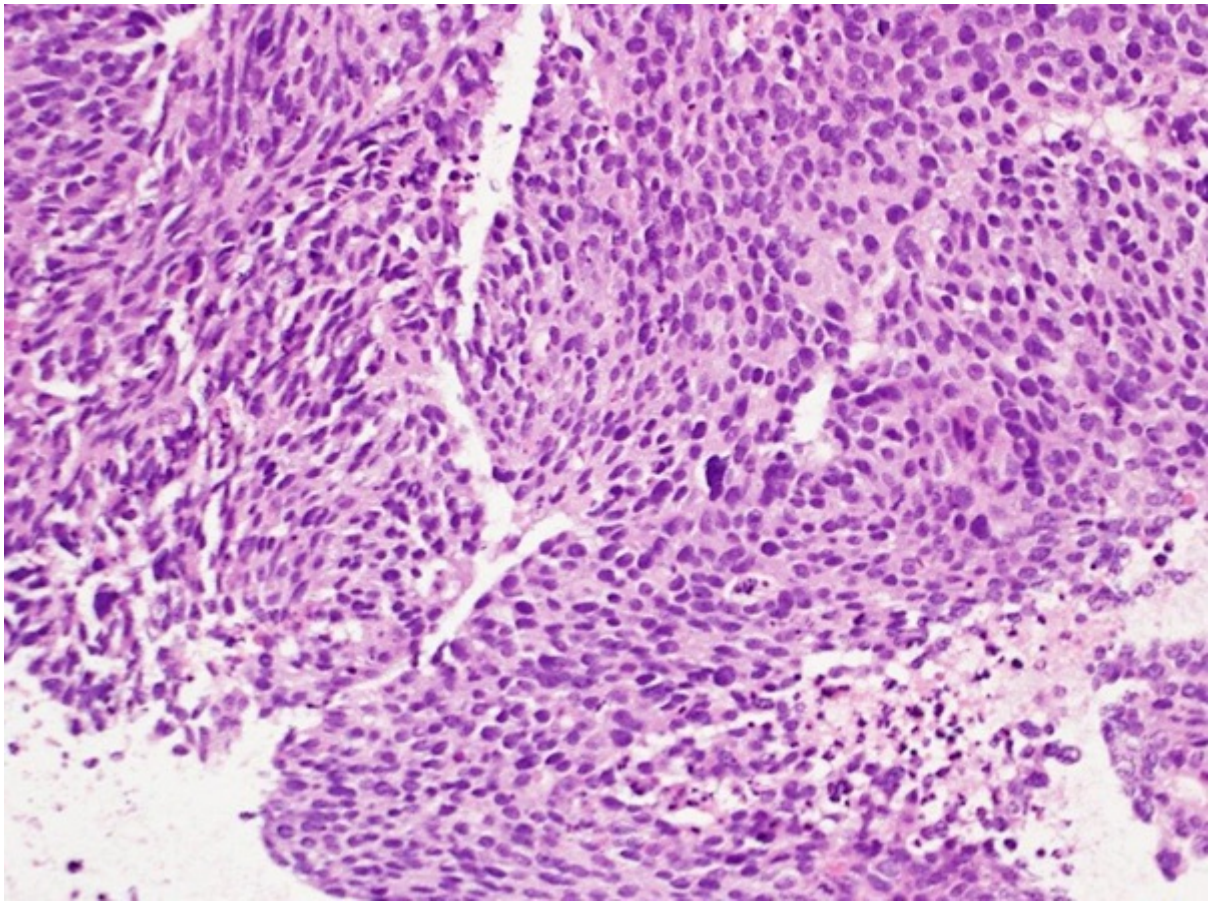

Figure 1: H and E stain 200x. The tumor was composed of pleomorphic cells with eosinophilic cytoplasm. The morphological picture consistent with a high grade neuroendocrine carcinoma.

Study	Age (Years)	Sex	Ethnicity	Smoking status	Mutation	TKI	PFS months
De Pas et al. in 2011	66	F	unknown	Nonsmoker	exon19, p.L747_A755>AT	gefitinib	>6
Aroldi et al. in 2014	47	F	Caucasian	Nonsmoker	exon 19	gefitinib	>5
Le et al. in 2015	73	M	Asian	Smoker	exon19, p.L747_P753insQ	erlotinib	Progression at first imaging at 3 months
Our Study in 2017	81	F	Caucasian	Nonsmoker	L858R activating mutation D761Y acquired resistance mutation	erlotinib	6 months

Table 1: Summary of cases reporting a radiological response to TKI in PLNT.

In our case the patient demonstrated a radiological response to erlotinib in the presence of an L858R EGFR mutation. Interestingly, targeted sequencing utilising a custom panel identified a nonsynonymous mutation in exon 19 (D761Y) known to confer resistance to TKI therapy [12]. Although the T790M mutation has been predominantly associated with primary resistance to TKI, other acquired resistance mutations in EGFR are present at lower frequencies: D761Y, T854A, and L747S (7). Balak et al. conducted *in vitro* studies introducing concurrent mutations L858R and D761Y in EGFR cDNAs in transfected cells. Evaluation of surrogate kinase

activity exhibited a modest reduction in sensitivity to gefitinib in these transfected cell lines [12].

A nonsynonymous mutation in the *PIK3CA* gene, (E542K) which encodes the p110α catalytic subunit of phosphatidylinisitol-3-kinase, was detected in our case. This mutation is located in the conserved helical binding domain of exon 9 and hinders p85 binding, resulting in constitutive activation of *PIK3CA*. It has been postulated that *PIK3CA* mutations can confer acquired EGFR mutant resistance through activation of parallel signaling pathways acting on downstream targets of EGFR. *In vitro* studies demonstrated that pathogenic mutations in *PIK3CA* can lead to downstream activation of AKT abrogating gefitinib induced apoptosis [13]. Alternative pathways conferring acquired resistance include amplification of MET, HER2, MAPK and mutations in BRAF and AXL [7].

Conclusion

The incidence of actionable EGFR mutants in PLNT may be underreported They have either analyzed mixed neuroendocrine tumor populations or retrospectively analyzed known EGFR mutant lung samples where the proportion of PLNET is likely to be low [10,14]. Larger–scale sequencing studies are required to validate the true frequency of EGFR mutant disease in this population and determine if outcomes in patient population parallel that observed in EGFR mutant lung cancer. We recommend all PLNT should be tested for EGFR mutational status.

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