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Case Report

CASE REPORT

Epidermal growth factor receptor mutated oligometastatic adeno-squamous lung cancer transformation to small cell lung cancer

Connor G. O'Leary*, Lynda Corrigan, Petra Martin, Anne Horgan, Miriam O'Connor and Paula Calvert

Department of Medical Oncology, University Hospital Waterford, Waterford, Ireland

*Correspondence address. Medical Oncology Department, University Hospital Waterford, Dunmore Road, Waterford, Ireland. Tel: +353-51-84-8000; Fax: +353-51-84-8598; E-mail: connorgoleary@gmail.com

Abstract

A 66-year-old non-smoker was diagnosed with stage IIIB, epidermal growth factor receptor (EGFR) mutated, squamous cell lung carcinoma. Treatment included chemotherapy, 35 fractions of radiotherapy and later Gefitinib for 3.5 years. On progression he developed a solitary brain and liver lesion. The brain lesion was excised and histology revealed adenocarcinoma of a lung primary. Afatanib was commenced for 1 further year. At the second time of progression re-biopsy identified small cell carcinoma. He completed four cycles of Carboplatin and Etoposide however deteriorated on completion of chemotherapy. EGFR directed treatment is associated with improved patient outcomes. It has been suggested that EGFR mutated squamous cell carcinoma more likely represent mixed morphology or poorly differentiated adenocarcinoma. Patients with oligometastatic progression can be treated beyond progression however the addition of a local therapy may be required. Small cell transformation is described as a rare mechanism of resistance to EGFR treatment as in our case.

INTRODUCTION

Lung cancer is the second most common form of malignancy in both males and females in western populations. Significant advances in understanding the nature and variability of this disease has led to increased systemic treatment options for these patients. Non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations are typically identified in association with the adenocarcinoma sub-type and is reported to occur in 10–20% of patents in western populations. EGFR directed treatments has been shown to prolong progression free survival when used in the first line setting for patients with metastatic EGFR mutated NSCLC compared to chemotherapy.

CASE REPORT

A previously well 66-year-old male presented with one episode of haemoptysis and intermittent chest discomfort. He was a lifelong non-smoker and worked as a professional cycling tour guide. Eastern cooperative oncology group (ECOG) performance status at presentation was zero. He was diagnosed with a stage IIIb, pT4b N2 M0 moderately differentiated squamous cell carcinoma of the right upper lobe (Fig. 1). Immunohistochemistry (IHC) was positive for CK7, CK5/6 and P63. He initially was treated with Cisplatin and Vinorelbine chemotherapy but discontinued after cycle 2 due to grade 3 toxicity. On recovery, he completed 70 gray in 35 fractions with a good partial response seen on a restating scan (Fig. 2).

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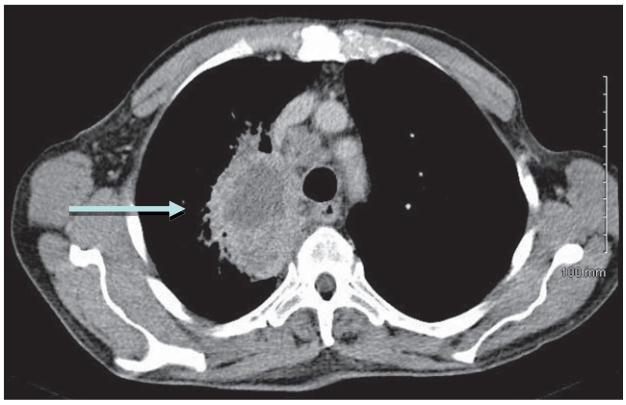

Figure 1: Left: CT thorax showing 9 cm right.

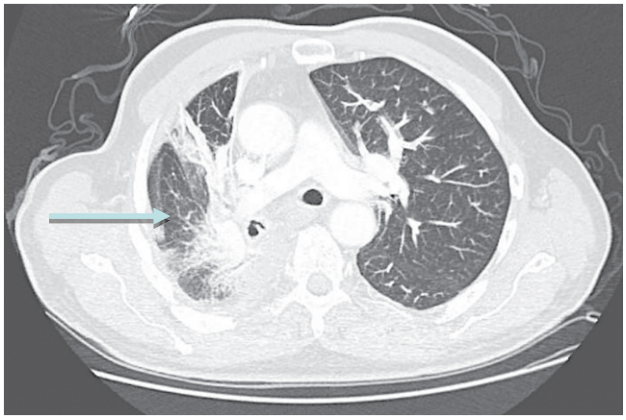

Figure 2: Right: CT thorax showing partial response to treatment (arrow).

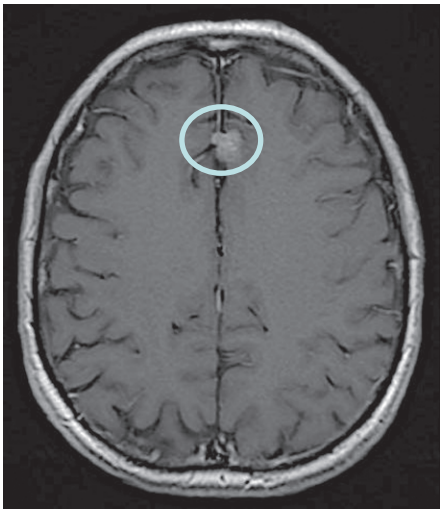

Figure 3: Above: MRI brain showing solitary brain metastasis (circle).

Tumour molecular profiling identified an activating EGFR mutation in exon 21, L858R, and at that stage he commenced Gefitinib. He achieved a 3.5-year period of disease stability on this therapy. On progression he was found to have a solitary brain lesion and a single liver lesion (Figs 3 and 4).

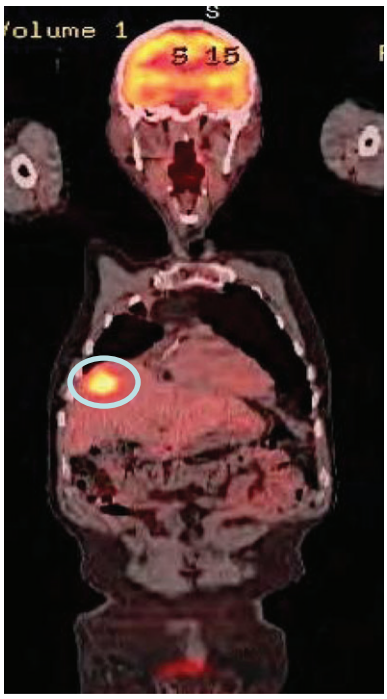

Figure 4: Right: PET/CT showing single liver metastasis (circle).

The brain metastasis was excised and he received 10 fractions of whole brain radiotherapy. Surprisingly, the pathology results from his brain lesion returned as metastatic adenocarcinoma likely of a lung origin. IHC was positive for CK7 and TTF-1. This suggested that his primary lung tumour was likely a mixed adeno-squamous lung cancer. The regional hepatobiliary tumour board recommended against local therapy to the liver metastasis. It was decided to continue EGFR directed therapy beyond progression in the form of Afatinib given his low disease burden. With this approach his liver disease remained stable for a further 1 year. At the time of his second progression of disease he presented with fatigue, weight loss, right wall chest swelling, pain and prominent chest wall vasculature. Imaging revealed a new lesion involving the right chest wall with an increase in size of the liver metastasis (Figs 5 and 6).

A right chest wall biopsy was performed to evaluate for the presence of a T790M mutation. On this occasion the histological features were consistent with small cell carcinoma. IHC was positive for synaptophysin and TTF-1. T790M testing was negative. It was concluded his cancer had dedifferentiated into small cell carcinoma post prolonged EGFR inhibition. He commenced Carboplatin and Etoposide combination chemotherapy for treatment of extensive stage small cell carcinoma. He achieved an initial partial response clinically to chemotherapy with evidence of shrinkage of the chest wall lesion. Within a month of completing four cycles of Carboplatin and Etoposide he deteriorated rapidly and passed away due to rapidly progressive disease.

DISCUSSION

EGFR mutations are typically identified in association with adenocarcinoma lung cancers however have also been described in mixed adeno-squamous histology with responses to EGFR directed therapy reported in this group [1]. EGFR mutations are

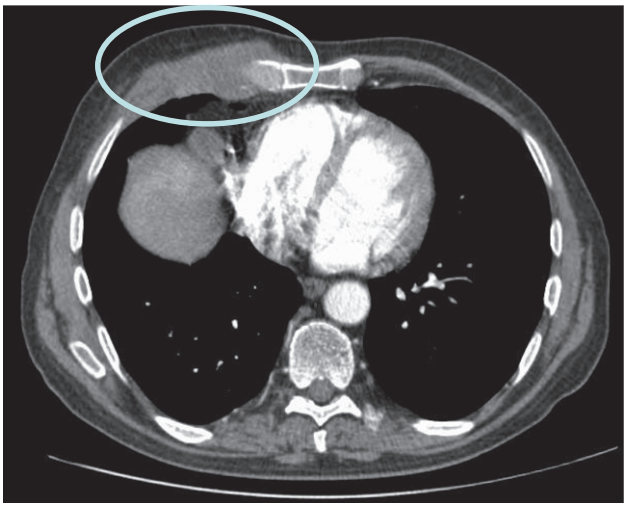

Figure 5: CT thorax showing right chest wall soft tissue lesion (circle).

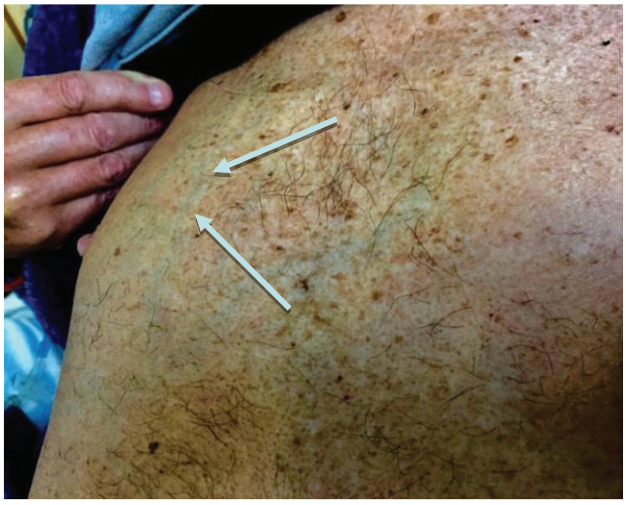

Figure 6: Above: right chest wall swelling and prominent chest wall vessels (arrows).

not felt to occur in pure squamous cell histology with very low rates reported in some studies, 0–4.9% [2]. A review of EGFR mutated non small cell lung cancer initially classified as squamous cell lung cancer was able to reclassify most cases as mixed adeno-squamous or poorly differentiated adenocarcinoma with squamoid morphology suggesting true EGFR mutated squamous cell lung cancer is exceptionally rare [3]. Treatment of patients beyond progression with ongoing EGFR therapy is an accepted practice in asymptomatic slowly progressive disease and in particular for those with oligometastatic progression [4, 5]. The addition of a local therapy may be required for disease control, in particular in the oligometastatic setting, followed by reintroduction of anti-EGFR therapy. Median overall survival of 41 months has been described with this approach [6].

It is inevitable that EGFR mutated lung cancer will develop resistance requiring a change of treatment. A range of mechanisms have been described including T790M mutation, MET amplification, HER2 amplification and small cell transformation [7]. In the majority of cases resistance develops due to an acquired EGFR T790M point mutation in exon 20 post exposure to EGFR targeting drugs. Up to two-thirds of cases develop resistance by this mechanism [7]. Resistance by means of transformation to small cell carcinoma occurs less frequently (3%) [7, 8]. In the case we describe, transformation to small cell carcinoma was an unexpected finding. It therefore highlights the importance of tumour re-biopsy on progression to guide the next treatment strategy. Data in the literature is lacking on how best to approach patients who develop small cell carcinoma post exposure to EGFR therapy. Our approach was to adopt a therapeutic plan similar to the standard of care for de novo extensive stage small cell lung cancer. We observed a response during chemotherapy but it was of short duration. On completing four cycles of Carboplatin and Etoposide the patient experienced a rapid deterioration suggesting aggressive underlying disease biology. Our experience is similar to other reported cases describing aggressive small cell carcinoma variants post-transformation with limited response to standard chemotherapy regimens [9, 10]. Research is required to further characterize the nature of these tumours as they may represent a more chemotherapy refractory sub-type and to define the intervention to be offered in this patient cohort.

ACKNOWLEDGEMENTS

Nil.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

FUNDING

No funding was received when compiling this case report.

ETHICAL APPROVAL

Ethical approval was not sought in this case.

CONSENT

As the patient had passed away at the time of writing this case report consent was not obtained. We felt it would be ethically inappropriate to contact his next of kin at this point. Every effort has been made to protect the anonymity of the patient.

GUARANTOR

Dr Connor O'Leary, Medical Oncology Department, University Hospital Waterford, Waterford, Ireland

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