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Epidermal growth factor receptor (*EGFR*) mutations in small cell lung cancers: Two cases and a review of the literature

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ABSTRACT

Activating mutations in the epidermal growth factor receptor (*EGFR*) gene are exceedingly rare in small cell lung cancer (SCLC). We present two cases of SCLC harboring *EGFR* mutations, one in an 82 year-old male smoker with a combined SCLC and adenocarcinoma with a novel D855H point mutation in exon 21, and the second in a 68 year-old female never smoker with the L858R point mutation in exon 21. The cases, accompanied by a review of the literature, highlight the importance of integration of clinicopathologic considerations and adherence to recently promulgated Guideline recommendations for molecular testing in lung cancer.

1. Introduction

Activating mutations in the gene that encodes the epidermal growth factor receptor (*EGFR*) have been identified in 10–15% of non-small cell lung cancers (NSCLCs) [1–3], most notably lung adenocarcinomas. Rare, however, are reports of *EGFR* mutations occurring in small cell lung cancer (SCLC). Cases of resistance to *EGFR* tyrosine kinase inhibitor (TKI) therapy have been associated with transformation from adenocarcinoma to SCLC. Exceedingly scarce are cases of *EGFR* mutations occurring *de novo* in SCLCs. While improvements in progression free survival with tyrosine kinase inhibitor therapy have been shown in NSCLCs with *EGFR* gene mutations compared to those with the wild type gene [4], the medical literature remains very limited with regard to the clinical impact of TKI therapy in the setting of SCLCs. Here we report two separate cases of SCLC harboring *EGFR* mutations and review the current literature on the prevalence and clinical implications of *EGFR* mutations in SCLC.

2. Case series

2.1. Case 1

An 82 year-old male, 35-pack year smoker with a past medical history significant for locally advanced head and neck squamous cell carcinoma previously treated with radiation therapy presented for evaluation for recurrent disease. A positron emission tomography/computed tomography (PET/CT) scan revealed an unanticipated fluorodeoxyglucose (FDG)-avid nodule in the right upper lobe of the lung. A right upper lobe sublobar resection with thoracic lymphadenectomy yielded a 1.8 cm lung tumor.

Microscopic evaluation of hematoxylin and eosin (H&E) stained slides of the lung nodule demonstrated a mixed population of hyperchromatic cells with a “salt-and-pepper” chromatin pattern in a sheet-like architecture, as well as a smaller population of gland-forming cells (Fig. 1a). A preliminary pathologic diagnosis was given of combined small cell lung cancer (small cell lung cancer [90%] and adenocarcinoma [10%]). Immunochemical studies revealed tumor cells to be positive for staining by cytokeratin AE1/3 monoclonal antibody clone AE1/AE3 (Dako, Carpinteria, CA), synaptophysin monoclonal antibody clone 27G12 (Leica Biosystems, Buffalo Grove, IL), chromogranin monoclonal antibody (Cell Marque, Rocklin, CA), CD56 monoclonal antibody clone CD564 (Leica Biosystems, Buffalo Grove, IL), and TTF-1 monoclonal anti-

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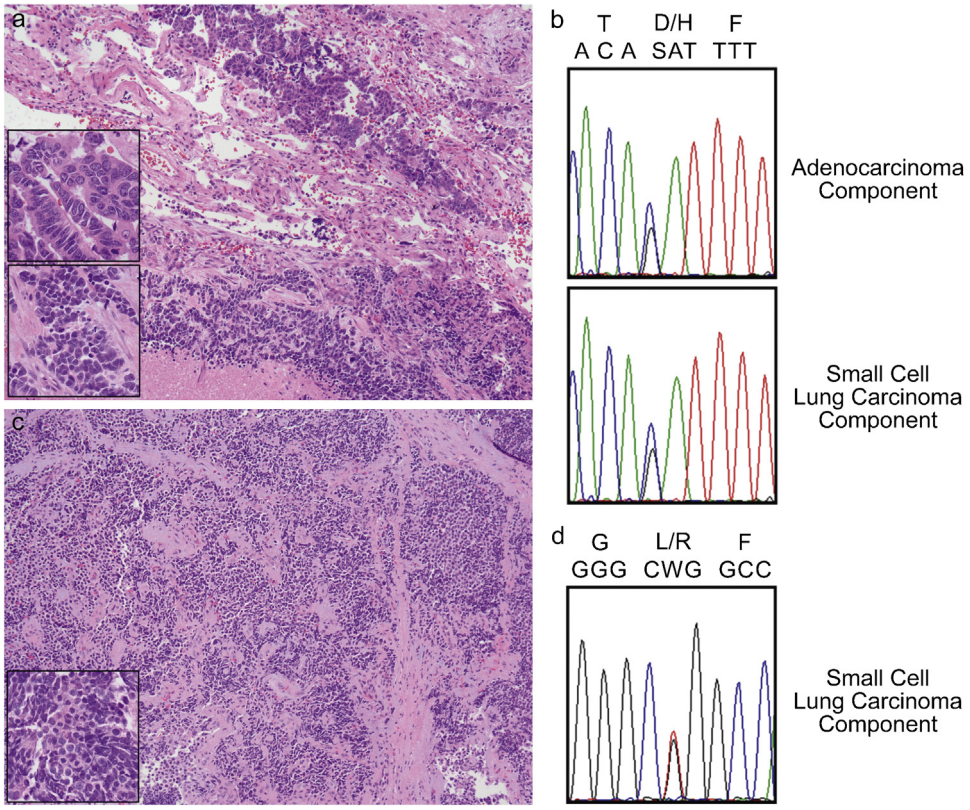

Fig. 1. Histology and Sanger Sequencing Results. Case 1. (a) Histologic features of combined SCLC. Hematoxylin & eosin stain with low power image (10×) of adenocarcinoma (40× [inset above]) and SCLC components (40× [inset below]). (b) Sanger sequencing chromatograms demonstrating a guanine to cytosine point mutation in Exon 21 of the *EGFR* gene at position 2563 (c.2563G > C) resulting in an aspartate to histidine missense mutation in amino acid 855 (p.D855H) shared by the adenocarcinoma tissue component (above) and small cell tissue component (below). Case 2. (c) Histologic features of pure SCLC. Hematoxylin & eosin stain with low power (10×) and high power (40× [inset]) image of SCLC. (d) Sanger sequencing chromatogram demonstrating a tyrosine to guanine point mutation in Exon 21 of the tyrosine kinase domain of the *EGFR* gene at position 2573 (c.2573T > G) resulting in a leucine to arginine missense mutation in amino acid 858 (p.L858R).

body clone 8G7G3/1 (Dako, Carpinteria, CA), with a Mib-1/Ki-67 proliferative index of up to 90% in the small cell lung cancer component by monoclonal antibody clone MIB-1 (Dako, Carpinteria, CA). Lymph nodes were negative for malignant involvement.

Formalin-fixed paraffin-embedded tissue sections were manually microdissected as previously described [5], with targeted malignant cells isolated from surrounding tissue with the aid of a dissecting microscope. The SCLC and adenocarcinoma components were separately microdissected, isolated malignant cells were digested, and DNA was subsequently extracted and purified. Sanger sequencing was performed, demonstrating a guanine to cytosine point mutation in Exon 21 of the *EGFR* gene (c.2563G > C) resulting in an aspartate to histidine missense mutation in amino acid 855 (p.D855H) in both the small cell lung carcinoma and the adenocarcinoma cell populations (Fig. 1b). Non-tumor tissue from the patient was separately analyzed, without identification of the p.D855H mutation (data not shown).

The final pathologic diagnosis of combined small cell lung cancer (small cell lung cancer and adenocarcinoma) with a p.D855H mutation in the *EGFR* gene was rendered.

The patient transferred his oncologic care to a local facility for convenience and received adjuvant cisplatin and etoposide chemotherapy. The patient was subsequently lost to clinical follow up.

2.2. Case 2

A 68 year-old Caucasian female never-smoker with no significant past medical history was incidentally discovered to have liver masses on a diagnostic ultrasound of the kidneys. A CT of the chest and abdomen demonstrated a right upper lobe lung mass with a right pleural effusion, as well as extensive mediastinal lymphadenopathy. A fine needle aspirate of the liver demonstrated cells consistent with a diagnosis of small cell lung cancer. Immunochemical studies revealed tumor cells to be positive for staining by CD56 monoclonal antibody clone CD564 (Leica Biosystems, Buffalo Grove, IL) and TTF-1 monoconal antibody clone SPT24 (Leica Biosystems, Buffalo Grove, IL).

Additional tumor tissue was retrieved by mediastinoscopic biopsy of the 4R lymph node. The diagnosis of small cell lung cancer was confirmed (Fig. 1c), and, given the patient's never-smoking history, tissue was submitted for testing for an *EGFR* gene mutation.

Formalin-fixed paraffin-embedded tissue sections were microdissected, with isolated malignant cells digested and DNA extracted and purified, as described above for Case 1. Sanger sequencing demonstrated the presence of a tyrosine to guanine point mutation in Exon 21 of the tyrosine kinase domain of the *EGFR* gene (c.2573T > G) resulting in a leucine to arginine missense mutation in amino acid 858 (p.L858R) (Fig. 1d).

The final pathologic diagnosis of small cell lung cancer with a p.L858R mutation in the *EGFR* gene was rendered.

The patient was treated with several chemotherapy regimens prior to molecular analysis, experiencing an initial response followed by progressive spread of the tumor locally within the chest and distantly to the brain. Whole brain radiotherapy and, subsequently, topotecan were initiated concurrent with submission of material for molecular analysis. Unfortunately the patient experienced rapid deterioration and died prior to the final results of molecular testing.