Case Report

Combined Large Cell Neuroendocrine Carcinoma and Adenocarcinoma with Epidermal Growth Factor Receptor Mutation in a Female Patient Who Never Smoked

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A female patient in her sixties, who had never smoked, was found to have a 5-mm nodule in a computed tomography (CT) scan. The follow-up CT scan after 19 months showed that the nodule had grown to 26 mm. We performed a left upper lobectomy. Pathological examination revealed a combined large cell neuroendocrine carcinoma (LCNEC) and adenocarcinoma with components of large cell carcinoma and bronchioloalveolar carcinoma (BAC). Tumor cells were separately collected from components of both the LCNEC and adenocarcinoma, and a mutational analysis of the epidermal growth factor receptor (EGFR) gene demonstrated that both components had the same L861Q mutation at exon 21. We assume that the LCNEC originated from the adenocarcinoma based on the fact that the patient was a non-smoking female, the tumor was located in the periphery, the tumor had a BAC component, and the same EGFR mutation was found in both the LCNEC and adenocarcinoma components.

Keywords: epidermal growth factor receptor, non-small-cell lung carcinoma, surgical pathology, smoking, x-ray computed tomography

Introduction

Pulmonary neuroendocrine tumors are classified into four major categories: typical carcinoid, atypical carcinoid, LCNEC and small cell carcinoma (SCLC).1) The origin and natural history of LCNEC are currently unknown.

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bronchioloalveolar carcinoma (BAC) (Figs. 2 and 3). A synaptophysin immunohistochemical study indicated positive staining in the areas of the LCNEC and BAC. The pathological stage was IA, and there was no evidence of recurrence 4 years and 6 months after surgery.

Written informed consent for the genomic analysis was obtained from the patient, and the study was approved by the institutional review board. Tumor cells were collected from components of LCNEC and invasive adenocarcinoma, separately, by manual dissection using a sterilized toothpick under a microscope on paraffin-embedded formalin-fixed sections. DNA was extracted by using a QIAamp DNA FFPE Tissue Kit (QIAGEN, Hilden, Germany), and the polymerase chain reaction (PCR)-Invader method was used for mutational analyses of the epidermal growth factor receptor (EGFR) gene. Both components had the same L861Q mutation in exon 21.

Discussion

LCNEC is defined as a subtype of large cell carcinoma and accounts for approximately 3% of lung cancers in surgical series.\textsuperscript{2} LCNEC and SCLC are characterized as high-grade neuroendocrine carcinoma because of the similarity of their clinical and prognostic features, in addition to the results of gene expression profiling.\textsuperscript{3,4} Ninety percent of LCNEC patients are male smokers, and the 5-year survival rate after surgical resection is only 40%.\textsuperscript{5} The origin, natural history, and genomic alterations of LCNEC are rarely unknown.

Our case is unique in that the patient was a female who had never smoked, radiological changes were documented and the tumor had an EGFR mutation.

Lung cancer sometimes has heterogeneous components in the tumor, as in our case. Among 141 LCNECs, 15 tumors (10.6%) were combined with other histologic types in which squamous cell carcinoma was the major counterpart, while among 113 SCLCs, 30 tumors (26.6%) were combined with other histologic types in which LCNEC was the major counterpart.\textsuperscript{3} One case report, which examined genomic alterations of combined LCNEC by using array comparative genomic hybridization, showed a genetic distinction among histologies in the tumor and possible carcinogenesis from different normal airway progenitor cells that might be pluripotent or lineage-defined.\textsuperscript{5} The patient in that report was an elderly man who had smoked heavily. We believe that LCNEC in our case originated from the adenocarcinoma based on
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the fact that the patient was a non-smoking female, the initial CT scan indicated that the tumor was located in the periphery, the tumor had a BAC component, and the same EGFR mutation was found in both the LCNEC and adenocarcinoma components.

EGFR mutations are predictive response markers for EGFR tyrosine kinase inhibitors (TKI), and gefitinib therapy in patients with non-small cell lung cancer harboring EGFR mutations improved progression-free survival compared to platinum-containing chemotherapy.6) De Pas, et al. reported a case of LCNEC harboring an EGFR mutation that had responded to gefitinib, and the patient was a female without a smoking history, suggesting that a small percentage of tumors with a non-adenocarcinoma histology have EGFR mutations, as in our case.7) Therefore, a mutational analysis might be encouraged for a non-adenocarcinoma histology including LCNEC if the patient is a female without a smoking history.

**Disclosure Statement**

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**References**