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Case Report

Successful Treatment of Combined Large Cell Neuroendocrine Carcinoma Harboring an EGFR Mutation with *EGFR*-TKIs plus Bevacizumab: A Case Report

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Keywords
Large cell neuroendocrine carcinoma · Epidermal growth factor receptor mutation · Tyrosine kinase inhibitors · Bevacizumab

Abstract
Large cell neuroendocrine carcinoma (LCNEC) of the lung with epidermal growth factor receptor (*EGFR*) mutation is rare, and few cases have been treated with EGFR tyrosine kinase inhibitors (TKIs). We report the treatment of combined LCNEC with adenocarcinoma harboring an *EGFR* mutation with EGFR-TKIs and bevacizumab. Our patient was a 70-year-old asymptomatic woman who underwent surgical resection of the lung for combined LCNEC with adenocarcinoma harboring an activating *EGFR* mutation 11 months previously. Magnetic resonance imaging (MRI) and positron emission tomography revealed metastatic lesions in the brain and lung. The patient was diagnosed with recurrence of combined LCNEC with adenocarcinoma. The brain lesion was irradiated, followed by administration of afatinib. Eight months after irradiation, brain MRI revealed ringed enhancement and perilesional edema after radiotherapy without new metastatic lesions. We switched treatment to erlotinib and bevacizumab, resulting in maintenance of stable disease for 10 months. Overall, the disease was controlled for 18 months with EGFR-TKIs and bevacizumab. Combination treatment with EGFR-TKIs and bevacizumab could be a treatment option for LCNEC of the lung harboring *EGFR* mutations, especially with brain metastasis.

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Introduction

Tyrosine kinase inhibitors (TKIs) are now the first choice for treatment of non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (*EGFR*) gene mutations. Recently, the efficacy of combination treatment of erlotinib with bevacizumab for NSCLC harboring *EGFR* mutations has been reported. Erlotinib and bevacizumab combination therapy improves progression-free survival to a greater extent than erlotinib monotherapy in patients with NSCLC harboring *EGFR* mutations [1, 2].

However, *EGFR* mutations have also been identified in large cell neuroendocrine carcinoma (LCNEC) of the lung [3–5]. LCNEC is a rare tumor of the lung, accounting for 3% of lung cancer cases, and is a type of neuroendocrine tumor. LCNEC resembles small cell lung cancer (SCLC) with features such as high-grade malignancy, poor prognosis, and high incidence in males and smokers. Both LCNEC and SCLC show neuroendocrine markers in immunohistochemistry. LCNEC is distinguished from SCLC by several morphological criteria including large cell size and abundant cytoplasm. Etoposide and platinum-based regimens are often selected for advanced LCNEC. LCNEC harboring *EGFR* mutations is extremely rare, and to our knowledge, only 2 cases of LCNEC treated with an EGFR-TKI have been reported to date, both of which were treated with gefitinib and showed a good response. Here we report a case of combined LCNEC with adenocarcinoma harboring an *EGFR* mutation treated with EGFR-TKIs and bevacizumab.

Case Presentation

A 70-year-old woman with no history of neoplastic disease presented with an abnormality identified by chest X-ray. Chest computed tomography (CT) scanning revealed a lung tumor in the left lower lobe. Tumor tissue obtained by transbronchial lung biopsy was diagnosed as LCNEC. Chromogranin A was positive in more than 50% of the tumor, and CD56 was weakly positive (Fig. 1). Thyroid transcription factor 1 and cytokeratin 7 were positively expressed and cytokeratin 20 was partially positive. An activating *EGFR* mutation (exon 19, E746–A750 deletion) was detected by the PCR-INVADER method. Positron emission tomography scanning and brain magnetic resonance imaging (MRI) did not show distant metastasis. Surgical resection was performed. The patient's lung cancer had various histological

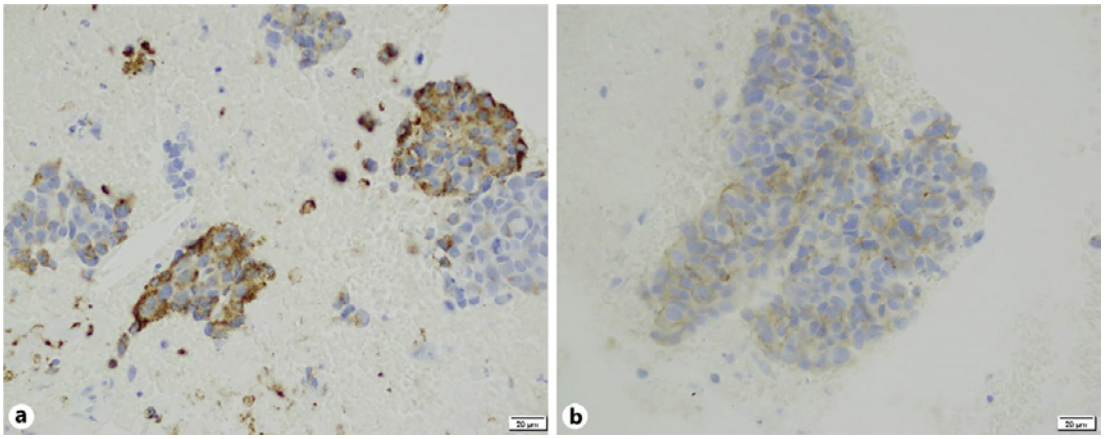

Fig. 1. Histological features. Chromogranin A was positive (**a**) and CD56 was weakly positive (**b**) in the tumor tissue obtained by transbronchial biopsy.

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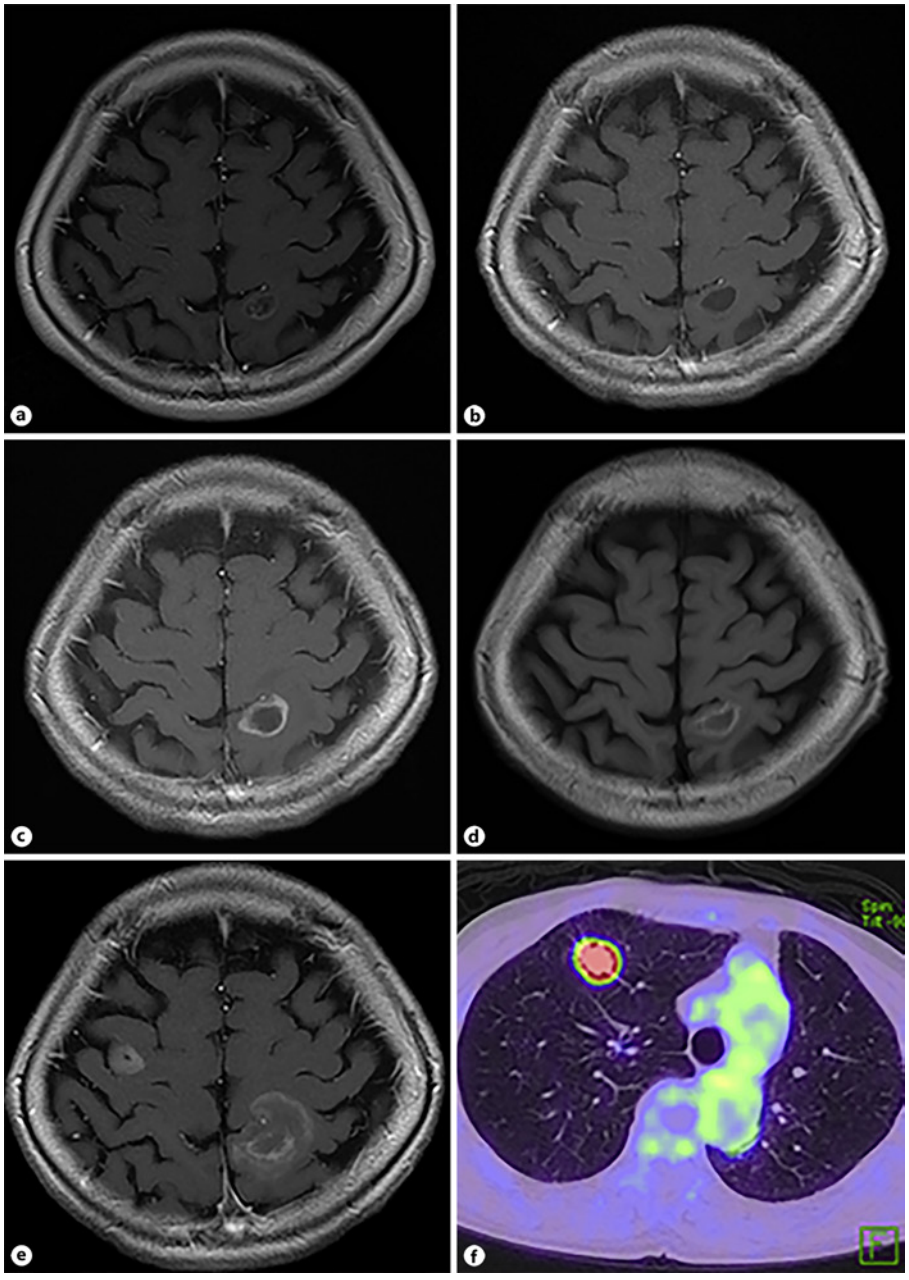

Fig. 2. Gadolinium-enhanced magnetic resonance imaging and positron emission tomography. Stereotactic irradiation followed by afatinib controlled brain metastasis (**a**) for 6 months (**b**). Ringed enhancement appeared 8 months later (**c**). Erlotinib and bevacizumab improved the perilesional edema, and stable disease was maintained for 6 months (**d**). Metastatic lesions in the brain (**e**) and lung (**f**) began to grow 10 months later.

features including rosette formation, necrotic tissue, and adenocarcinoma with an acinar and solid architecture. The pathological diagnosis was combined LCNEC with adenocarcinoma, and the pathological stage was T1cN1M0 stage IIB. Cisplatin and vinorelbine as adjuvant chemotherapy were administered only once after surgery because of several adverse events.

Eleven months later, the lung cancer recurred as a brain metastasis in her left parietal lobe (Fig. 2a) alongside a small lung metastasis. After stereotactic irradiation of this brain

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lesion, afatinib (20 mg/day) was administered as the first-line treatment, and stable disease was maintained for 6 months (Fig. 2b). The patient had grade 2 rash acneiform and paronychia during this period. Eight months later, paralysis of the right lower limb manifested. Brain MRI revealed ringed enhancement and perilesional edema after radiotherapy without new metastatic lesions (Fig. 2c). New lesions were not identified by positron emission tomography scan. The treatment was then switched to erlotinib (150 mg/day) and bevacizumab (15 mg/kg q3w). The paralysis rapidly improved, and stable disease was maintained for 6 months (Fig. 2d). During this time, she had grade 2 paronychia, rash acneiform, anorexia, and hypertension. Erlotinib was decreased to 100 mg/day at first, then 50 mg/day. The lung metastatic lesion remained stable during the afatinib, erlotinib, and bevacizumab treatment period. After 10 months of treatment with erlotinib and bevacizumab, metastatic lesions in the brain and lung began to grow (Fig. 2e, f). *EGFR*^{T790M} mutation was not found in serum biopsy.

Discussion

LCNEC of the lung is a rare tumor, and there are no established standard treatment strategies. Cases of advanced or recurrent LCNEC are often treated as SCLC [6]. It was reported that LCNECs have a similar genomic profile to SCLC, including *TP53* mutations and genetic alterations in the PI3K/AKT/mTOR pathway, and *EGFR* mutation was detected in only one of 78 LCNEC samples [7]. There are few reports that describe EGFR-TKI treatment of *EGFR*-mutated LCNECs [4, 8]. Gefitinib was selected in both of these previous reports and resulted in a good response. In our case, we first conducted radiotherapy because of brain metastasis and subsequently administered afatinib. After progression of the disease, we undertook treatment with erlotinib and bevacizumab because of brain edema around the metastatic lesions.

Vascular endothelial growth factor produced in the perinecrotic area is thought to be a major cause of both angiogenesis and perilesional edema after radiation therapy to metastatic lesions of the brain [9]. The efficacy and safety of bevacizumab treatment for brain metastasis of NSCLC are well known [10–12], while efficacy of bevacizumab combined with EGFR-TKIs for *EGFR*-mutated NSCLC with brain metastasis has also been reported [13, 14]. Furthermore, Mairinger et al. [15] reported that angiogenesis was also activated to some extent in LCNECs. Thus, the addition of bevacizumab to treatment regimens for LCNECs is thought be one of the reasons for the long-term effectiveness of this treatment strategy.

A limitation of our study is that we could not perform biopsies of the recurrent lesions. Because our patient had combined LCNEC with adenocarcinoma, recurrent lesions might have consisted of adenocarcinoma components. Despite this limitation, this is the first report showing the activity of EGFR-TKIs and bevacizumab in LCNEC harboring an *EGFR* mutation. EGFR-TKIs and bevacizumab could be a treatment option for LCNECs harboring *EGFR* mutations, especially with brain metastasis.

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Statement of Ethics

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization: Satoshi Muto and Hiroyuki Suzuki. Investigation: Satoshi Muto. Resources: Yuki Ozaki, Naoyuki Okabe, Yuki Matsumura, Takeo Hasegawa, and Yutaka Shio. Supervision: Hiroyuki Suzuki. Validation: Yuko Hashimoto. Writing – original draft: Satoshi Muto. Writing – review and editing: Satoshi Muto and Hiroyuki Suzuki.

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