Journal of Cancer Research and Practice

journal homepage: www.ejcrp.org

Case Report

A Case of Small-Cell Lung Cancer Harboring an Epidermal Growth Factor Receptor Mutation that Responded to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Treatment

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Abstract

Epidermal growth factor receptor (EGFR) mutations are extremely rare in small-cell lung cancer (SCLC), and the efficacy of EGFR tyrosine kinase inhibitors (TKIs) in SCLC is unclear. Herein, we present a case with SCLC harboring an EGFR mutation who also responded to a second-generation EGFR TKI (afatinib).

Keywords: Epidermal growth factor receptor mutation, epidermal growth factor receptor tyrosine kinase inhibitor, small-cell lung cancer

Introduction

Lung cancer is the leading cause of cancer death both in Taiwan and worldwide.[1] It can be classified into the following two different categories: small-cell lung cancer (SCLC) and nonsmall-cell lung cancer (NSCLC). SCLC accounts for approximately 13%–15% of all lung cancers and has distinct disease features and treatment strategies from NSCLC.[2] In NSCLC, the reported frequency of epidermal growth factor receptor (EGFR) mutations ranges from 7% to 53% across different countries,[3] and the correlation between EGFR mutations and clinical response to EGFR tyrosine kinase inhibitors (TKIs) has been well studied.[4] However, the frequency of EGFR mutations in SCLC is low, and the efficacy of EGFR TKIs in the treatment of EGFR-mutated SCLC has not been well studied. Herein, we present a case with SCLC harboring an EGFR mutation with a good respond to EGFR TKI treatment.

Case Report

A 54-year-old male smoker with no significant systemic diseases presented with intermittent headaches for 2 months.

Received: 28-Jul-2019 **Revised:** 26-Sep-2019
Accepted: 12-Dec-2019 **Published:** 02-Jun-2020

Access this article online

Quick Response Code:

Website: www.ejcrp.org

DOI: 10.4103/JCRP.JCRP_31_19

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How to cite this article: Chang CF, Wang CW, Hsu CL. A case of small-cell lung cancer harboring an epidermal growth factor receptor mutation that responded to epidermal growth factor receptor tyrosine kinase inhibitor treatment. J Cancer Res Pract 2020;7:78-81.

A computed tomography (CT) scan of his brain showed a right parieto-occipital tumor with perifocal edema [Figure 1]. The tumor was removed by right occipital craniotomy, and the pathology disclosed a malignant tumor. Immunohistochemical staining of tumor cells was positive for CDX2, CD56, synaptophysin, TTF-1, chromogranin A, and napsin A and negative for CK7, CK20, and p40 [Figure 2a]. The patient was enrolled in a study of patient-derived xenografts (PDX) at that time, and the removed tumor was sent to a laboratory for culture. The following CT scan of his chest showed confluent enlarged lymph nodes at the mediastinum and clustered small lung nodules (<1 cm) in the left upper lobe (LUL) [Figure 3]. A positron emission tomography scan showed the distribution of ^{18}F-fluorodeoxyglucose over the LUL nodules (standardized uptake value [SUV] 3.24) and mass (SUV 10.41), pancreatic nodular lesions (SUV 9.57), and mesenteric mode (SUV 5.02). Taken together, extensive SCLC was impressed. The tentative staging was cT1aN3M1c, according to the 8th edition of the American Joint Committee on Cancer staging system.

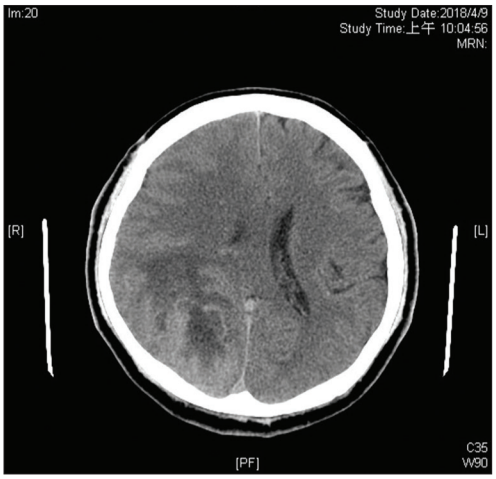

Figure 1: Brain computed tomography showed a tumor over the right parieto-occipital area with perifocal edema

The patient received palliative radiotherapy (RT) with 3.66 Gray/12 fractions to the metastatic brain lesions over the tumor bed, followed by standard systemic chemotherapy with the EP regimen (etoposide 100 mg/m^2 on day 1 and cisplatin 25 mg/m^2 on day 1–3 every 28 days). The initial evaluation revealed stable disease; however, the disease eventually progressed 9 months later [Figure 4].

During treatment, the PDX tumor, which survived and had been passaged to the third generation, was sent for the next-general sequencing. Surprisingly, the report revealed

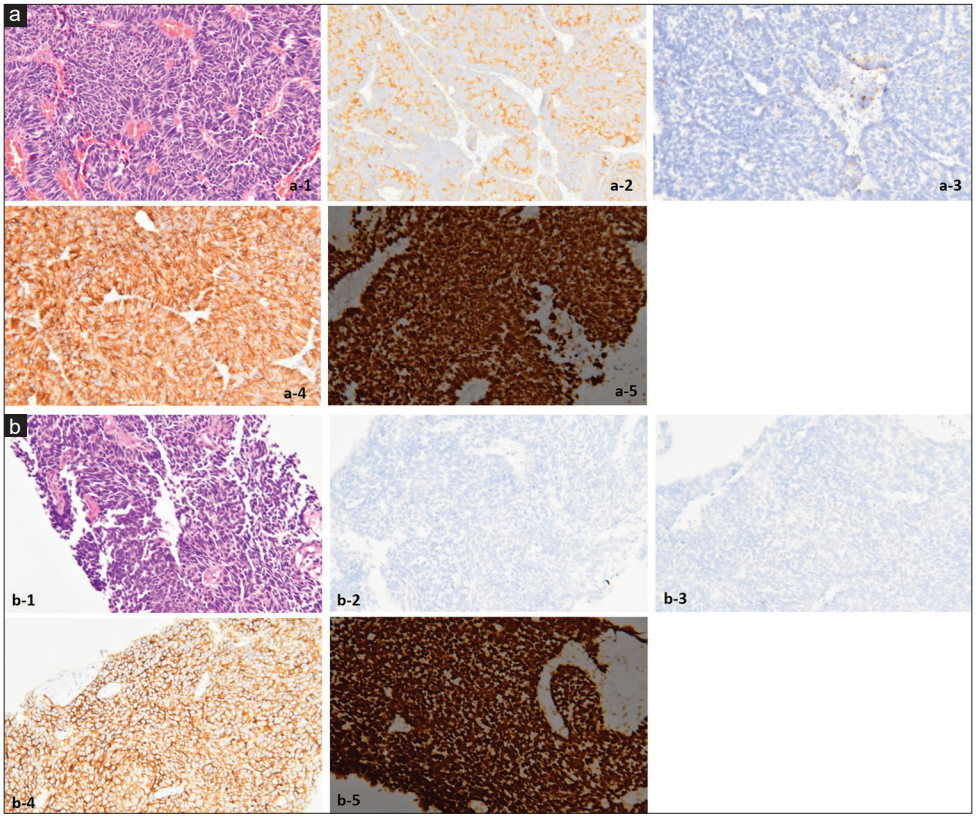

Figure 2: (a) H and E stain and immunohistochemical of the brain tumor under 200 high-power field: The section shows metastatic carcinoma with small hyperchromatic nuclei, no nucleoli, scant cytoplasm, and a cordlike pattern (a-1); The tumor was positive for synaptophysin (a-2), scattered expression of chromograninA (a-3), and strongly positive for CD56 (a-4) and TTF-1(a-5). (b) H and E stain and immunohistochemical of the lung tumor under 200 high-power field: The tumor cells were hyperchromatic with scant cytoplasm and no nucleoli (b-1); they were negative for synaptophysin (b-2) and chromogranin-A (b-3) but still strongly positive for CD56 (b-4) and TTF-1 (b-5)

an EGFR mutation (L858R). The point mutation of L858R was also subsequently confirmed by analyzing the original brain tumor using the polymerase chain reaction and direct sequencing. After the failure of standard first-line therapy, we discussed with the patient about receiving chemotherapy or an EGFR TKI. He agreed to receive afatinib (40 mg/day) as the second-line treatment. After 1 month of treatment, the tumor responded well [Figure 5]. However, progressive oral mucositis and general erythematous maculopapular eruptions with some scattered purpuric macules developed, and afatinib-related adverse effects were highly suspected. The medication was thus discontinued because of intolerance.

After the failure of the treatment, we rebiopsied the lung tumor, and pure SCLC was confirmed. The tumor cells were still positive for CD56 and TTF-1 but negative for chromogranin A and synaptophysin [Figure 2b].

Discussion

SCLC may be identified at the time of diagnosis (*de novo*) or be discovered secondary to EGFR TKI-treated NSCLC (acquired),[5] with or without (pure) other histological components. Both conditions are rare. Our case had "pure" and "*de novo*" SCLC harboring an EGFR mutation and responded to an EGFR TKI.

Only case reports and case series but no large clinical trials have studied SCLC with EGFR mutations to date. According to two reviews of the literature and retrospective studies, the prevalence of EGFR mutations in SCLC is about 2.6% in Taiwan,[6] whereas the prevalence of EGFR mutations in NSCLC is around 55%.[7] In another study, 59 cases of SCLC with EGFR mutations were collected, and 46% (27 of 59) of the cases were *de novo* SCLC. Among these 27 cases, 63% (17 of 27) were SCLC without other histological components ("pure" SCLC).[8]

The efficacy of EGFR TKIs in the treatment of EGFR-mutated SCLC is controversial. Compared with NSCLC, SCLC expresses less EGFR and has different pathogenesis such as loss of *Tp53* and *Rb1* genes.[9] However, gefitinib, a first-generation EGFR TKI which was developed much earlier than afatinib, has been shown to inhibit the phosphorylation of ERK 1/2 despite different EGFR expression levels *in vitro*.[10] Clinically, Shiao *et al*. concluded that both *de novo* and acquired SCLC with EGFR mutations may not respond to gefitinib.[6] In other studies, gefitinib was effective in the treatment of SCLC harboring an exon 19 deletion as the first-line treatment,[11] and a partial response was also observed in the case of SCLC with an exon 19 deletion treated with afatinib as second-line therapy.[12] Due to the low prevalence and the uncertainty of efficacy, routine studies of mutations in SCLC without an adenocarcinoma component are not recommended.[13]

Four to six cycles of platinum-based chemotherapy with or without RT have remained the standard treatment for SCLC in the past few decades, however, whether SCLC with driver

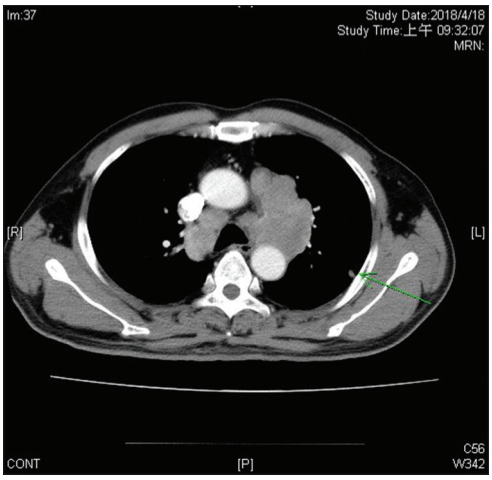

Figure 3: Chest computed tomography showed confluent enlarged lymph nodes at the mediastinum and clustered small lung nodules (green arrow) in the left upper lobe

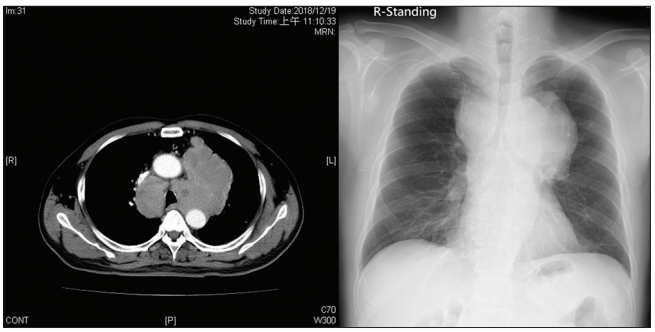

Figure 4: Chest computed tomography showed an enlarged mediastinal confluent mass. The size of the tumor increased from 7.8 cm to 8.7 cm in diameter. The change in tumor size was also observed on a chest X-ray

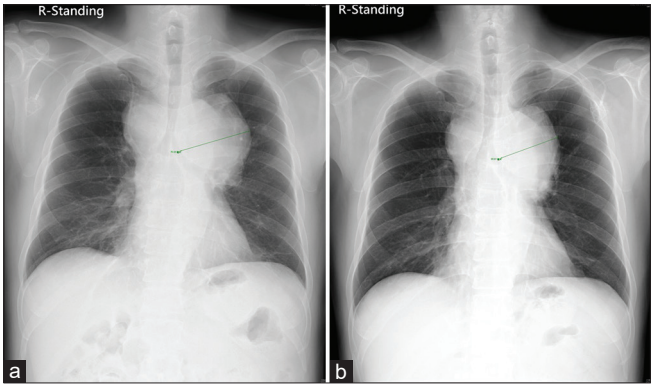

Figure 5: (a) Chest X-ray before receiving afatinib; the mass was bulging and compressed the left bronchus. (b) The mass was more flattened and had significantly decreased in size (from 75 mm to 60 mm)

mutations would benefit from targeted therapy is unclear.[9] In small-cell-transformed adenocarcinoma, re-challenging with an effective front-line TKI after the failure of chemotherapy as salvage therapy may be considered, although the median progression-free survival with gefitinib and erlotinib has been reported to be only 2.8 and 6.5 months, respectively.[14]

In conclusion, our case report demonstrated the efficacy of afatinib in EGFR-mutated SCLC, although the medication was discontinued due to intolerance. SCLC with EGFR mutations is rare, and the optimal treatment strategy has not yet reached a consensus. Further studies are required to elucidate this issue.

Ethics approval and consent for publication

Local institutional review board approval was obtained (No. 201801033B0). The patient has provided informed consent for the publication of the case.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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