

CASE REPORT

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Small-cell lung cancer with a rare epidermal growth factor receptor gene mutation showing “wax-and-wane” transformation

Yusuke Takagi^{1*}, Yoshiro Nakahara¹, Yukio Hosomi¹ and Tsunekazu Hishima²**Abstract**

Background: Small-cell lung cancer with epidermal growth factor receptor (EGFR) gene mutation typically manifests as a transformation occurring after EGFR tyrosine kinase inhibitor therapy for adenocarcinoma with *EGFR* mutation, whereas primary small-cell lung cancer showing *EGFR* mutation is extremely rare. Second biopsy of *EGFR*-mutated tumor has been broadly recognized as necessary, but is not always performed in daily practice, mainly due to the imbalance between the potential risk of the diagnostic procedure and the therapeutic impact of the biopsy result.

Case presentation: A 70-year-old woman who had never smoked was referred to our hospital with chief complaints of cough and back pain. Transbronchial lung biopsy from the primary tumor of the left upper lobe revealed combined small-cell lung cancer and adenocarcinoma, a subtype of small-cell lung cancer. *EGFR* L861Q mutation was detected in both small-cell lung cancer and adenocarcinoma components. Given the staging of cT2aN3M1b (Stage IV) and histological diagnosis, first-line chemotherapy with cisplatin plus irinotecan was initiated, and partial response was achieved. Seven months after initial diagnosis, the primary tumor enlarged again, and a second biopsy from the enlarged lesion detected only adenocarcinoma with the L861Q mutation. Erlotinib was started, but multiple brain metastases and enlarged mediastinal lymph nodes subsequently appeared. Whole-brain radiation therapy was performed, and endobronchial ultrasonography-guided transbronchial biopsy from the lymph node revealed reverse transformation to small-cell lung cancer with the L861Q mutation. Amrubicin therapy achieved partial response after two cycles, with the shrinkage lasting for eight months. Serum sialyl Lewis X antigen level increased when the adenocarcinoma component was dominant, whereas plasma pro-gastrin-releasing peptide level increased when the small-cell lung cancer component became dominant.

Conclusions: Transformation of the tumor correlates with the difference between small-cell lung cancer and adenocarcinoma in sensitivity to therapies, so repeated biopsies are beneficial for choosing appropriate treatments. Noninvasively obtainable parameters such as tumor markers can support the need for biopsy.

Keywords: Adenocarcinoma, Biopsy, Epidermal growth factor receptor, Erlotinib, Mutation, Pro-gastrin releasing peptide, Sialyl Lewis X antigen, Small-cell lung cancer, Transformation, Tumor marker

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Background

Epidermal growth factor receptor (EGFR) gene mutation is one of the most pervasive driver mutations in non-small cell lung cancer (NSCLC), particularly in adenocarcinoma [1]. Activating mutations in *EGFR* occur in exons 18 to 21, and most of the mutations in exons 18, 19 and 21 are regarded as sensitizing mutations for EGFR tyrosine kinase inhibitors (TKIs) [2]. Of these, exon 19 deletions and the exon 21 L858R point mutation account for more than 80% of mutations detected in tumors with *EGFR* mutations [2,3]. EGFR-TKI therapy for NSCLC with an *EGFR* mutation shows a significantly higher response rate, longer progression-free survival, and better quality of life when compared with platinum-doublet chemotherapy [4,5]. First-line treatment with EGFR-TKI is thus recommended for *EGFR* mutation-bearing NSCLC in recent clinical practice guidelines [6,7]. In contrast, *EGFR* mutation is rarely detected in small-cell lung cancer (SCLC). *EGFR* mutations in SCLC mostly manifest as a “transformation” after EGFR-TKI therapy in *EGFR*-mutated adenocarcinoma [8], whereas primary SCLC with *EGFR* mutation is extremely rare. Some case reports have described *EGFR*-mutated SCLC treated using EGFR-TKI, but responses to EGFR-TKI differ [9,10]. To date, whether EGFR-TKIs or cytotoxic chemotherapy should be administered for

SCLC with an *EGFR* mutation remains unclear. A case of SCLC with a rare *EGFR* mutation that showed “wax-and-wane” transformation is presented, and *EGFR* mutations in SCLC are comprehensively reviewed.

Case presentation

A 70-year-old Japanese woman was referred to our hospital with chief complaints of cough and back pain. She had never smoked and had no history of malignancy. Computed tomography (CT) revealed a 4-cm-diameter mass in the left upper lobe, enlargement of mediastinal lymph nodes, and left pleural dissemination (Figure 1). Asymptomatic brain metastasis was also detected on magnetic resonance imaging. A transbronchial lung biopsy (TBLB) specimen from the left upper lobe showed combined SCLC and adenocarcinoma (Figure 2), and the TNM classification of the tumor was cT2aN3M1b (BR). The TBLB specimens were analyzed using a peptide nucleic acid-locked nucleic acid PCR clamp test, and *EGFR* exon 21 L861Q mutations were detected in both SCLC and adenocarcinoma components (Figure 3).

The patient underwent four cycles of chemotherapy comprising cisplatin (60 mg/m²) and irinotecan (60 mg/m²). The total effect of chemotherapy was partial response, and symptoms resolved. Serum sialyl Lewis X antigen (SLX) level decreased from 35 U/mL at the initiation of

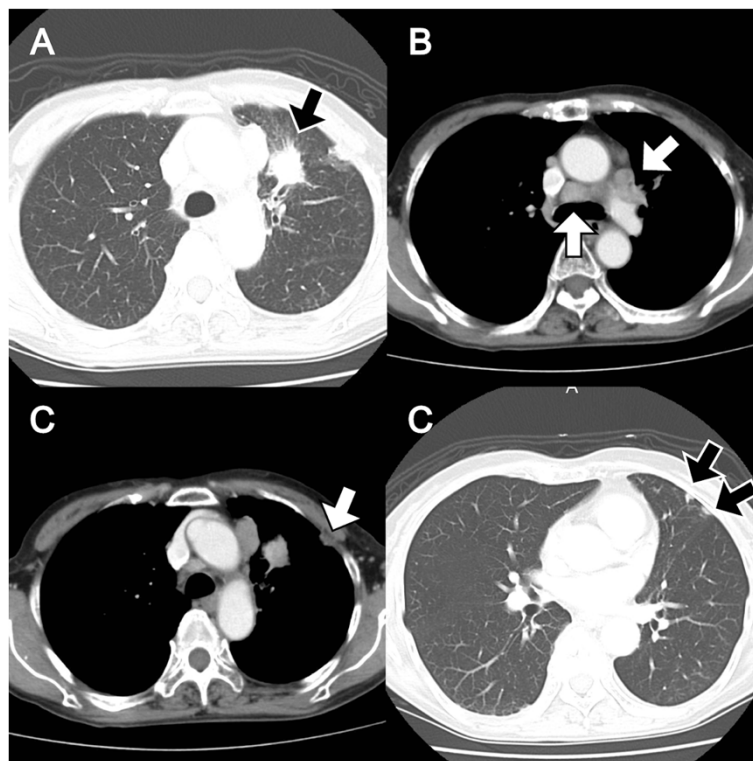


Figure 1 Computed tomography at the time of initial diagnosis. **A)** Primary lung cancer lesion in the upper lobe of the left lung. **B)** Enlargement of the mediastinal lymph nodes. **C)** Left pleural dissemination.

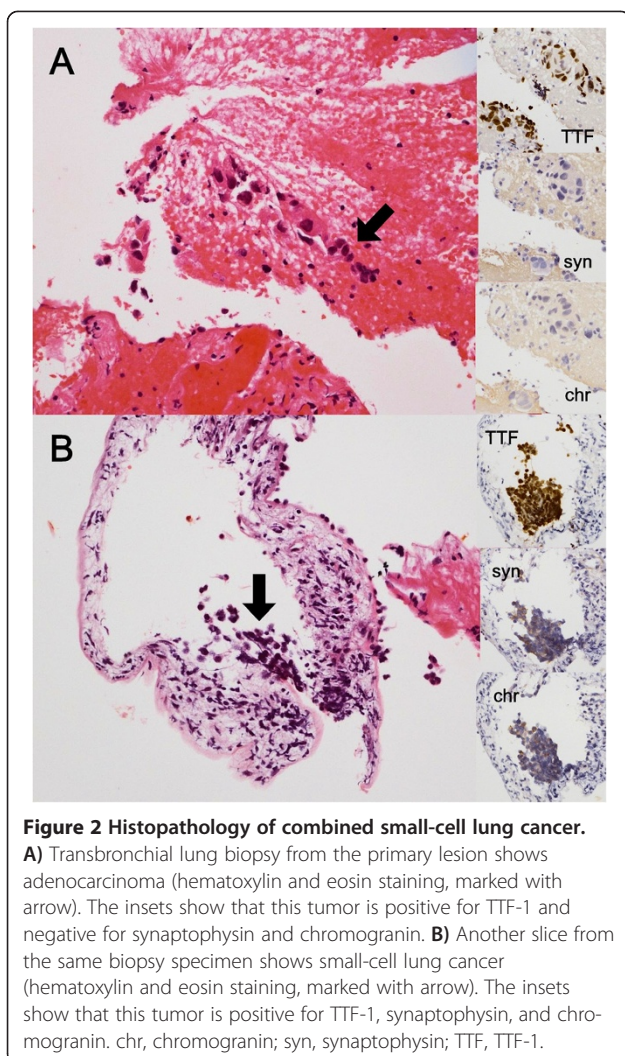


Figure 2 Histopathology of combined small-cell lung cancer.

A) Transbronchial lung biopsy from the primary lesion shows adenocarcinoma (hematoxylin and eosin staining, marked with arrow). The insets show that this tumor is positive for TTF-1 and negative for synaptophysin and chromogranin. **B)** Another slice from the same biopsy specimen shows small-cell lung cancer (hematoxylin and eosin staining, marked with arrow). The insets show that this tumor is positive for TTF-1, synaptophysin, and chromogranin. chr, chromogranin; syn, synaptophysin; TTF, TTF-1.

chemotherapy to 5.2 U/mL after four cycles of chemotherapy, and plasma levels of pro-gastrin releasing peptide (pro-GRP) also decreased from 695 pg/mL to 102 pg/mL. Complete remission of the brain metastasis was also achieved, and whole-brain radiation therapy (WBRT) was postponed at the request of the patient.

Seven months after initial diagnosis, disease progression with enlargement of the primary tumor and lymph nodes was observed. Serum SLX level was elevated to 14 U/mL, while plasma pro-GRP level remained stable (102 pg/mL). TBLB of the primary tumor was performed again, and only adenocarcinoma with the *EGFR* L861Q mutation was detected (Figure 3). Treatment with erlotinib (150 mg daily) was thus started.

After two months of disease stabilization, multiple brain metastases developed without any symptoms. The patient underwent WBRT of 30 Gy. Soon after the completion of WBRT, mediastinal lymph node enlargement occurred again. Serum SLX level was decreased (9.1 U/mL), but plasma pro-GRP level increased to 133 pg/mL.

Endobronchial ultrasonography-guided transbronchial biopsy was performed. At that time, only SCLC with the *EGFR* L861Q mutation was identified (Figure 3). *PIK3CA* mutation analysis of the second (adenocarcinoma) and third (SCLC) biopsy specimens was performed, but no mutation was detected from either sample. Erlotinib was stopped, and chemotherapy with amrubicin (35 mg/m²) achieved partial response after two cycles. This treatment was therefore continued for nine cycles without disease progression. SLX and pro-GRP levels both decreased, to <2.5 U/mL and 79.8 pg/mL, respectively. However, chemotherapy was terminated when performance status decreased after lumbar vertebral compression without bone metastasis. Chemotherapy was then terminated. The patient remains alive as of 21 months after diagnosis.

Conclusions

Few case reports have described primary *EGFR*-mutated adenocarcinoma transforming to SCLC and then reverse-transforming to adenocarcinoma [8,11]. As far as we can determine, this represents the first report of initially diagnosed SCLC with an *EGFR* mutation that showed transformations in both directions. *EGFR* L861Q mutation was detected from all specimens obtained on each occasion. Taking the rarity of L861Q mutation among *EGFR* activating mutations [2] into account, it appears very likely that both the SCLC and adenocarcinoma components shared a common origin. Relatively good response to cytotoxic chemotherapy was observed throughout the course of treatment. Tumor markers such as SLX and pro-GRP reflected the pathological changes in the tumor.

Although the objective response to erlotinib therapy was modest, the dominant component of the tumor in the present case changed from adenocarcinoma to SCLC after *EGFR*-TKI therapy. Generally, histological examination of TBLB specimens can provide the histology of only a part of the disease, but all biopsies were performed from enlarging lesions, reflecting the dominant component of the progressing disease. We suggest that responsiveness to *EGFR*-TKI varies between SCLC and adenocarcinoma, and the SCLC component that did not respond to erlotinib progressed selectively. In a similar manner, most cases of SCLC with *EGFR* mutations have been reported as developing acquired resistance to *EGFR*-TKI, and were initially diagnosed as NSCLC [8,11-15]. In general, lung adenocarcinoma and SCLC show different genetic characteristics [15,16]. In mouse models, concomitant knockout of *Rb* and *p53* causes a high incidence of SCLC, whereas mice with somatic inactivation of *p53* alone develop adenocarcinomas [17]. A previous study showed an acquired *PIK3CA* mutation in SCLC transformed from *EGFR*-mutated adenocarcinoma after *EGFR*-TKI therapy [8]. Unfortunately, it was not possible to detect concomitant molecular alterations in the present

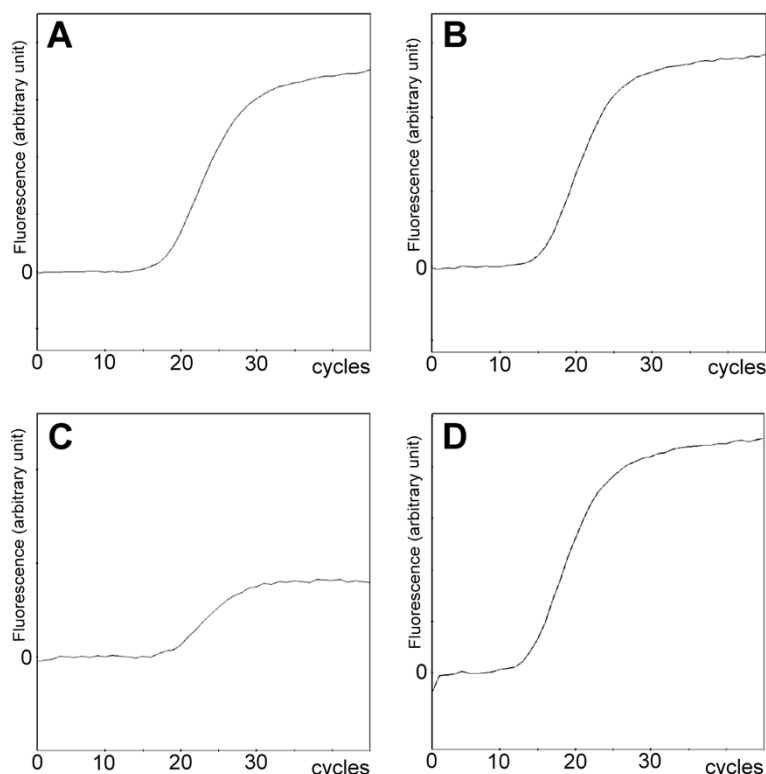


Figure 3 *EGFR* L861Q amplification curve for each specimen by the peptide nucleic acid-locked nucleic acid PCR clamp test. **A)** Small-cell lung cancer component of the specimen at the time of initial diagnosis. **B)** Adenocarcinoma component of the specimen at the time of initial diagnosis. **C)** Adenocarcinoma at the time of disease progression after cisplatin-irinotecan therapy. **D)** Small-cell lung cancer at the time of disease progression after erlotinib therapy.

Table 1 Small-cell lung cancer with *EGFR* mutations and treatment outcomes

Prior TKI	Mutation	Chemotherapy	PFS	Hist after Tx	Ref.
None	L861Q	CDDP + CPT-11	7 mo	Adenocarcinoma	*
E	L861Q	AMR	8 mo	N/A	*
None	G719A	G	N/A (PR)	N/A	[9]
None	Ex19del	CRT	7 mo	N/A	[10]
None	Ex19del	CDDP + VP-16	6 mo	N/A	[10]
G	Ex19del	G	5 mo	N/A	[18]
G, E	Ex19del	G + VP-16	N/A (PD)	N/A	[12]
G	Ex19del	CDDP + CPT-11	6 mo	Adenocarcinoma	[11]
G, E	L858R	TOP	>4 mo (CR)	N/A	[13]
E	L858R	CRT	6 mo	Adenocarcinoma	[8]
E	L858R	CDDP + VP-16	N/A (PR)	N/A	[8]
G	L858R	CDDP + VP-16	N/A (PR)	N/A	[14]

Reports without sufficient information about treatment are not included on this table.

*, present case; *AMR*, Amrubicin; *CDDP*, Cisplatin; *CPT-11*, Irinotecan; *CR*, Complete response; *CRT*, Combined chemoradiotherapy; *E*, Erlotinib; *Ex19del*, Exon 19 deletions; *G*, Gefitinib; *Hist after Tx*, Histology after treatment; *mo*, Months; *N/A*, Not assessed; *PFS*, Progression-free survival; *PR*, Partial response; *Ref.*, Reference; *TKI*, Epidermal growth factor receptor tyrosine kinase inhibitor; *TOP*, Topotecan; *VP-16*, Etoposide.

case, but oncogenic drivers out of *EGFR* may explain the resistance to EGFR-TKI in *EGFR*-mutated SCLC.

SCLC with an *EGFR* mutation is often resistant to EGFR-TKI, as mentioned above, whereas most cytotoxic chemotherapies achieve good response (Table 1). Second biopsy after cytotoxic chemotherapy for SCLC with an *EGFR* mutation revealed transformation to adenocarcinoma in various reports [8,11], indicating that the SCLC component is more sensitive to cytotoxic chemotherapy than the adenocarcinoma component. The differences in effectiveness of therapeutic regimens between histological types strongly support the indication of repeated biopsies at the time of each treatment change.

In this case, transitions in tumor markers (SLX and pro-GRP) appeared to occur in parallel with histological transformation. Second biopsy has been broadly recognized as necessary [8], but has not always been carried out in daily practice. This is mainly attributable to the imbalance between the potential risk of the diagnostic procedure and the therapeutic impact of the biopsy result. Given the sensitivity of EGFR-mutated SCLC to cytotoxic chemotherapies, re-biopsy for detecting tumor transformation can prove highly beneficial for patients. Noninvasive methods, including tumor markers, circulating tumor cells [19], and highly sensitive mutation detection using plasma samples [20] may play an important role in guiding the decisions of physicians and patients for the next diagnostic step, particularly when an invasive procedure is needed for obtaining tumor samples.

In conclusion, the optimal regimen for SCLC with an *EGFR* mutation cannot be uniformly defined, and should be decided according to the dominant histology at each point in the treatment course. Repeated biopsies are sometimes difficult in daily practice, but noninvasively obtainable parameters such as tumor markers can support the need for diagnostic procedures. Detailed examination of combined SCLC and adenocarcinoma, including comprehensive genome analysis, may reveal the factors that determine the histological and clinical characteristics of these tumors.

Ethics statement

This case study was approved by the ethics committee of Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital (Tokyo, Japan), and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YT was responsible for clinical management of the patient, acquisition of data, and drafting the manuscript; YN, YH and TH were responsible for interpretation of data and critical revision of the manuscript. All authors read and approved the final manuscript.

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