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Case Report

EGFR-mutant lung adenocarcinoma transformed into small cell Lung cancer: A case report and literatures review

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ABSTRACT

Advances in molecular biology have positioned epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) as highly effective therapies for patients with EGFR-mutant carcinomas. However, the inevitable emergence of acquired resistance significantly limits their long-term efficacy. Among resistance mechanisms, the transformation of lung adenocarcinoma to small cell lung cancer (SCLC) following EGFR-TKIs therapy is an uncommon but clinically important phenomenon contributing to treatment failure.

We present a case of SCLC transformation in a patient with EGFR-mutant lung adenocarcinoma after 8 months of first-line osimertinib therapy. Following 4 cycles of etoposide combined with lobaplatin chemotherapy, adenocarcinoma cells regained predominance, illustrating a dynamic histological shift between adenocarcinoma and SCLC phenotypes. Subsequent treatment with 2 cycles of chemotherapy plus osimertinib resulted in disease stabilization. However, multiple brain metastases were identified 3 months after completing 6 cycles of chemotherapy.

This case underscores the bidirectional histological plasticity between lung adenocarcinoma and SCLC during treatment and highlights the critical importance of repeated biopsies for guiding management strategies in the context of resistance. We also provide a comprehensive review of the clinical manifestations, underlying mechanisms, predictive biomarkers, and therapeutic approaches for SCLC transformation.

1. Introduction

Lung cancer remains a leading cause of cancer-related morbidity and mortality globally, accounting for over 2.2 million new cases and nearly 1.8 million deaths annually [1]. Non-small cell lung cancer (NSCLC) constitutes approximately 80 %–85 % of all lung

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cancer diagnoses [2]. Despite significant advancements in diagnostic and therapeutic modalities, a large proportion of patients are diagnosed at advanced stages, resulting in a 5-year survival rate of only around 16 % [3].

The development of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) has revolutionized the treatment paradigm for advanced EGFR-mutant NSCLC, providing substantial clinical benefits [4]. However, disease progression remains inevitable, with a median progression-free survival (mPFS) of 12–18 months [5]. Among the diverse resistance mechanisms identified, histological transformation to small cell lung cancer (SCLC) has been reported in approximately 5 % of cases [6], representing a critical challenge in the management of these patients.

In this report, we describe a case of EGFR-TKIs resistance attributed to SCLC transformation. Following 4 cycles of etoposide and lobaplatin chemotherapy, adenocarcinoma cells re-emerged as the predominant subtype, demonstrating a dynamic interplay between adenocarcinoma and SCLC histologies. Additionally, we review the current literature to elucidate the clinical features, underlying mechanisms, predictive biomarkers, and therapeutic strategies associated with SCLC transformation.

1.1. Case presentation

A 38-year-old Chinese woman with no smoking history presented to the First Affiliated Hospital of Nanchang University (Jiangxi, China) in February 2021, complaining of cough and dyspnea. Contrast-enhanced computed tomography (CT) scans of the chest with contrast revealed a 2.6*2.0 cm mass in the dorsal lower lobe of the right lung, accompanied by right hilar and mediastinal lymphadenopathies (Fig. 1A). Single photon emission computed tomography(SPECT)of the whole skeleton indicated osseous metastasis involving 12th thoracic vertebra, left iliac bone, hip, and pubic bones. Magnetic resonance imaging (MRI) of the brain showed no abnormalities. Based on the 9th edition TNM classification of lung cancer, the clinical stage was determined to be T3N2M1c stage IVB. Laboratory findings were normal except for an elevated carcinoembryonic antigen (CEA) level of 8.89 ng/mL (normal range, 0–6.5ng/mL). To confirm the diagnosis, a CT-guided lung aspiration biopsy was performed in February 2021, which revealed lung adenocarcinoma (Fig. 2A). Immunohistochemistry (IHC) staining was positive for Napsin A, TTF-1, and CK7. Next generation sequencing (NGS) identified an EGFR exon 21 L858R mutation and a TP53 co-mutation. Due to the inoperable nature of the disease, the patient began a treatment regimen of Osimertinib (80mg, daily) on February 10, 2021. Within 8 months of Osimertinib (80mg daily) on February 10, 2021. Within 8 months, the disease decreased and remained stable according to the Response Evaluation Criteria in Solid

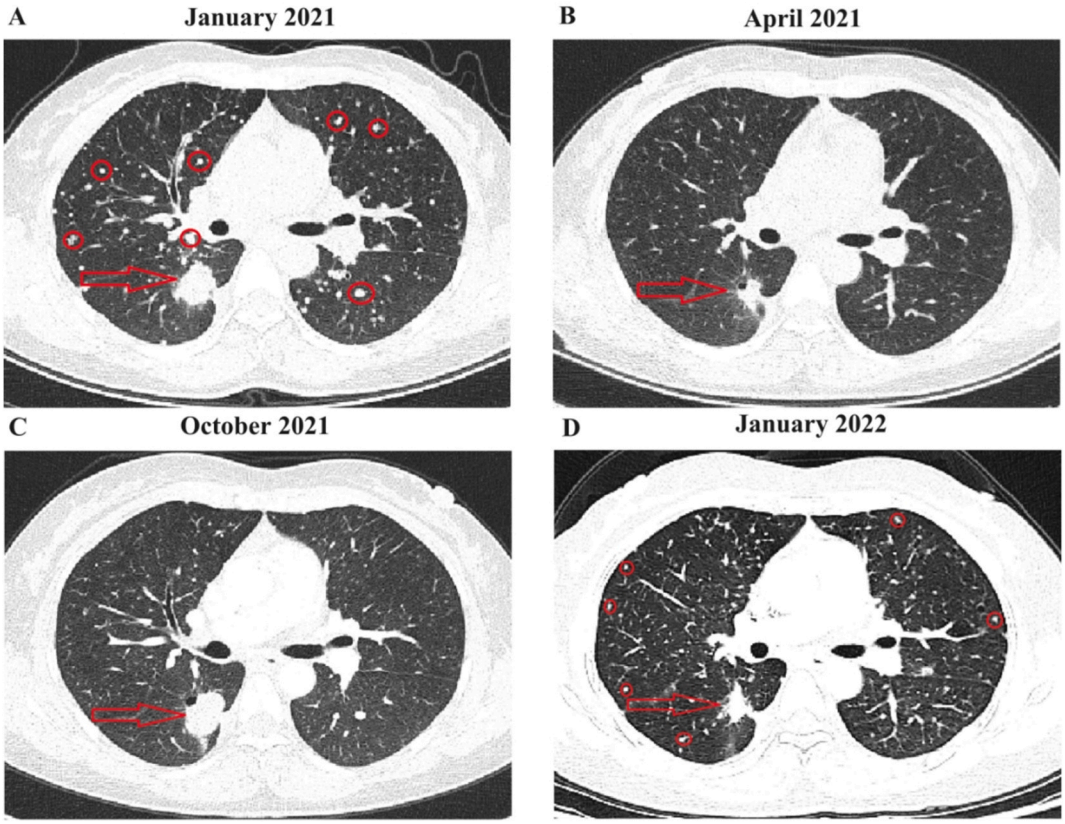

Fig. 1. CT revealed a 2.6*2.0 cm mass in the dorsal lower lobe of the right lung and diffuse nodules in both lungs.(A) Partial remission upon osimertinib treatment.(B) 8 months later after osimertinib treatment, disease increased.(C) After 4 cycles of etoposide plus lobaplatin,The primary lesion was narrowed, and the primary lesion was narrowed,diffuse nodules in both lungs became numerous and enlarged.(D).

Tumors (RECIST) 1.1 (Fig. 1B). However, on October 28, 2021, reimaging with chest and abdominal CT revealed the nodules of the dorsal lower lobe of the right lung were significantly larger than the former (about 2.7*2.1cm in size), and several new liver metastases, and new adrenal metastases were added (Fig. 1C). And neuron specific enolase (NSE) increased to 119.70 ng/mL (normal range, 0–16.3 ng/mL) (Fig. 3). A repeat biopsy of the nodule of dorsal lower lobe of the right lung was performed, and histologic analysis showed SCLC (Fig. 2B) and IHC staining was confirmed as positive for CD56, TTF-1 and Syn (Fig. 4). The patient was treated with etoposide plus lobaplatin for 4 cycles. At this duration, the nodule decreased. Before the fifth cycle of chemotherapy, the patient had some lesion enlargement and partial shrinkage (Fig. 1D). Multiple pathological subtypes were considered, so a repeat biopsy of the nodule of dorsal lower lobe of the right lung was performed, and histologic analysis showed lung adenocarcinoma (Fig. 2C), the results of IHC staining were positive for Napsin A, TTF-1 and CK7. EGFR exon 21 L858R mutation and TP53 co-mutation were identified using NGS method. Two cycles of etoposide plus lobaplatin and osimitinib were administered. Reimaging after 2 months, CT indicated the lesion stopped growing. In May 2022, brain MRI suggested cerebral metastases (Fig. 5), leading to the initiation of the whole brain radiotherapy. Follow-up brain MRI 1 month after completing radiotherapy showed significant reduction in intracranial metastases. However, 2 months later, chest CT revealed enlarged intrapulmonary lesions, and brain MRI indicated significant enlargement of multiple metastases with increased edema around the left frontal lobe lesion. The patient subsequently did not return to our hospital for further treatment, and the effect is unknown.

2. Discussion

2.1. Clinical features

SCLC transformation is more frequently observed in lung adenocarcinomas harboring EGFR-activating mutations compared to those with EGFR wild-type tumors [7]. Previous studies have reported a median time of 19 months (range: 1–61 months) from the initial diagnosis of lung adenocarcinoma to SCLC transformation [8,9]. The clinical characteristics and therapeutic options after transformation resemble those of primary SCLC. However, the prognosis remains poor, with a reported mPFS of 2.4–5.4 months and a median overall survival (mOS) of 8.0–13.7 months. Additionally, the risk of central nervous system (CNS) metastasis significantly increases following transformation, further complicating disease management.

In our case, the PFS from the initiation of osimertinib to SCLC transformation was approximately 8.6 months, and multiple brain metastases were detected 7 months after the transformation. These findings align with previously reported characteristics of SCLC transformation, underscoring its aggressive clinical course and poor prognosis.

2.2. Mechanisms

Several mechanisms of resistance to EGFR-TKIs have been described, including secondary mutation (T790M, C797S), the activation of alternative signalling pathways (Met, HGF, AXL, Hh, IGF-1R), aberrations in downstream pathways (AKT mutations, loss of PTEN), the impairment of the EGFR-TKIs-mediated apoptosis pathway (BCL2-like 11/BIM deletion polymorphism) and histological transformation [10]. However, the potential mechanism underlying the phenotypic conversion to SCLC after EGFR-TKIs therapy remains unclear. We propose three potential mechanisms that could explain the switch between NSCLC and SCLC.

First, many scholars believe that Lung adenocarcinoma and SCLC originate from common precursor cells—alveolar type II cells. These cells proliferate into lung adenocarcinoma cells under the influence of EGFR mutation gene. EGFR-TKIs hinder this proliferation, and when combined with TP53 and retinoblastoma gene 1 (RB1) mutations, this process promotes SCLC transformation. Consequently, lung adenocarcinoma cells produced by these alveolar type II cells and carrying EGFR mutation into SCLC [7]. LEE et al. [11]described the process in more detail from the molecular level: SCLC precursor cells under the selection pressure of EGFR-TKIs through the epigenetic changes, including insulin-like growth factor-1 receptor (IGF-1R) mediated signaling pathway, nuclear factor-κB (NF-κB) signal transduction pathway, converted into a "persisiter" cell [12] in a low or non-proliferative state, thereby surviving by EGFR-TKIs,

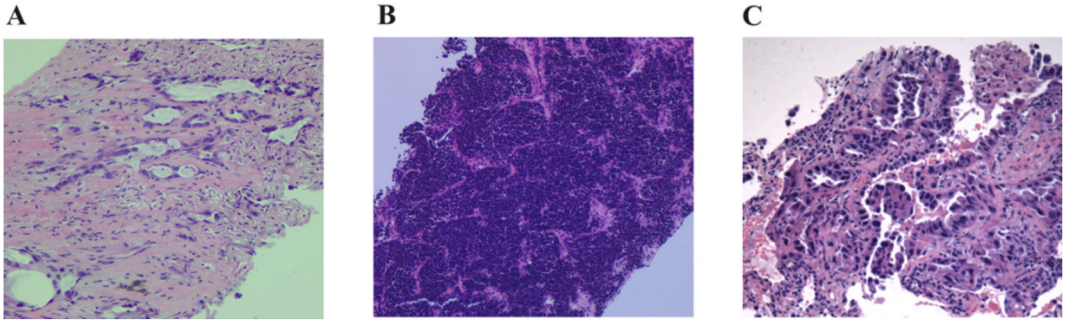

Fig. 2. The first biopsy pathological diagnosis was lung adenocarcinoma.(A) The pathological diagnosis of the second biopsy is small cell lung cancer.(B) The pathological diagnosis of the third biopsy is lung adenocarcinoma.(C) Images were obtained through hematoxylin and eosin (H&E) staining.

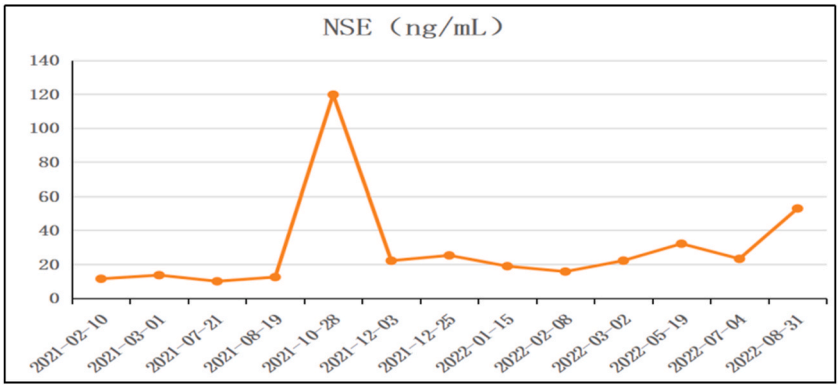

Fig. 3. The profile of NSE in serum.

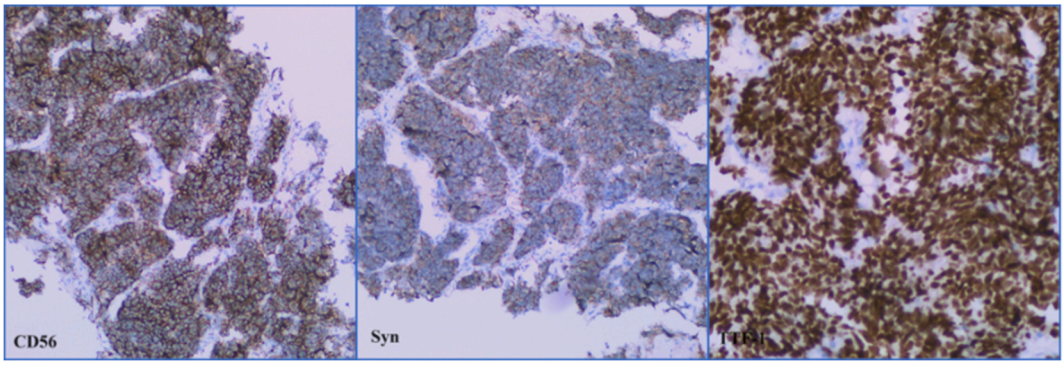

Fig. 4. Immunohistochemical staining confirmed CD56,Syn and TTF-1 as positive.

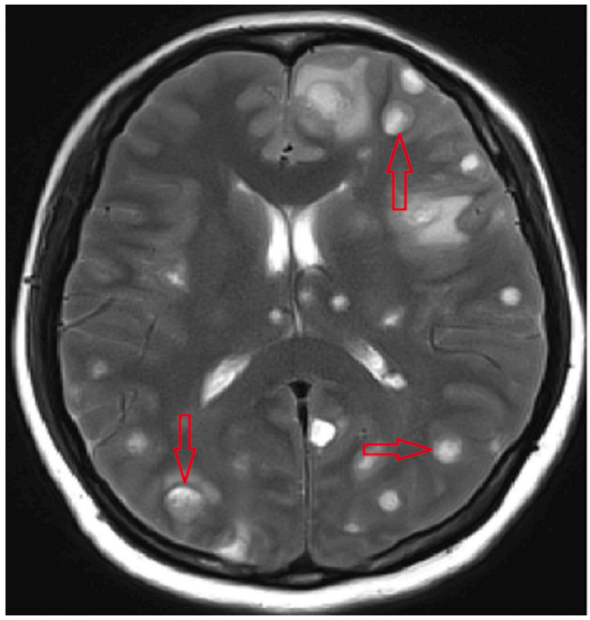

Fig. 5. Brain MRI suggested cerebral metastases (May 2022).

subsequently producing inactivation of TP53 or RB 1 tumor suppressor genes or altered Notch signaling pathway, which is finally converted to the SCLC phenotype [11–13]. Therefore, SCLC and adenocarcinoma cells could originate from the same cancer stem cells or progenitor cells.

Second, SCLC can result from the dedifferentiation of a previously well-defined cancer, a mechanism similar to that observed in prostate cancer [14,15]. Most transformed SCLC cases retain the original EGFR-activating mutation, supporting this theory. Sequist LV et al. reported that 5 (14 %) of the 37 patients experienced a fundamental histology transformation from NSCLC to SCLC at the time of EGFR-TKI resistance [16]. The original EGFR mutation was maintained in all five patients, further validating this mechanism.

Third, it is possible that the initial tumor consisted of a combination of NSCLC and SCLC homologies. As the number of NSCLC cells decreased due to treatment, the SCLC component of the initial tumor became dominant [7]. Consequently, both components may be present at the initial diagnosis. In our case, after the transformation of lung adenocarcinoma into SCLC, the disease continued to progress during chemotherapy with etoposide combined with lobaplatin, and the pathological biopsy of the same site showed lung adenocarcinoma, and the patient has high-risk factors for SCLC such as TP53 mutation [17] and environmental tobacco smoke [18], further confirming the presence of both pathological types at the initial diagnosis. As the treatment progresses, these two components exhibit a phenomenon of mutual growth and decline. Given the general condition of the patient, she agreed to continue the treatment regimen of etoposide combined with lobaplatin and oral EGFR-TKIs. After 2 cycles, imaging showed stable disease, suggesting that the coexistence of the two pathological subtypes may coexist, and the combination of chemotherapy regimen for SCLC with EGFR-TKIs may improve the survival benefits of patients during this period. This phenomenon emphasizes the importance of repeat biopsies in the clinical design of treatment regimens.

2.3. Predictors of SCLC transformation

Therapeutic strategies for SCLC and NSCLC differ substantially, making the identification of a non-invasive method to detect potential disease transformation before re-biopsy crucial. A rapid increase in the serum NSE and a poor response to EGFR-TKIs typically indicate a transformation from adenocarcinoma to SCLC [19,20].In our case, after eight months of EGFR-TKIs treatment, disease progression occurred alongside a significant increase in NSE levels. The mPFS was notably lower than the expected 18.9 months [21], suggesting a poor prognosis, potentially due to the simultaneous presence of both adenocarcinoma and SCLC at the time of initial diagnosis. In this case, the significant increase in serum NSE levels highlights the necessity of repeat biopsy. This case demonstrates that patients can benefit from routine testing of serum NSE levels to monitor SCLC transformation. NSE is an important biomarker of SCLC and may play a potential role in the diagnosis of SCLC transformation in EGFR positive lung cancer patients receiving EGFR-TKI treatment.

Moreover, pro-gastrin releasing peptide (pro-GRP) levels during EGFR-TKIs treatment also indicate a transformation from NSCLC to SCLC [22]. However, NSE and pro-GRP levels are often overlooked, as routine clinical tests for these markers are not commonly performed in NSCLC patients.

Therefore, routine, and dynamic testing serum NSE and pro-GRP levels in the serum may help screen for SCLC transformation before invasive biopsies.

2.4. Treatment after transformation

Most cases of SCLC transformation demonstrate neuroendocrine differentiation, which is associated with increased chemosensitivity. Current evidence suggests that patients with SCLC transformation should be treated with platinum-based chemotherapy, typically combined with etoposide or irinotecan [23]. However, in this case, standard chemotherapy did not provide sustained survival benefits, although unexpected positive outcomes were observed with the addition of targeted therapy.

Lai et al. [24] reported that continuing the original EGFR-TKI regimen after SCLC transformation, in combination with etoposide and cisplatin, resulted in an extended mPFS of 8.0 months. These findings suggest that combining standard SCLC chemotherapy with EGFR-TKIs may represent a promising therapeutic strategy for managing SCLC transformation. However, this hypothesis remains speculative due to the lack of robust evidence. Large-scale randomized controlled trials (RCT) are urgently needed to validate this approach and establish definitive treatment guidelines.

3. Conclusion

In summary, we present a case of EGFR-mutant NSCLC that underwent transformation to SCLC during EGFR-TKIs therapy and subsequently reverted to NSCLC following four cycles of etoposide plus lobaplatin chemotherapy. This transformation from adenocarcinoma to SCLC likely originates from a preexisting minor population of SCLC cells, which are selected under the pressure of EGFR-TKIs treatment. Re-biopsy plays a critical role in detecting genetic and histological changes, enabling the selection of optimal therapeutic strategies following EGFR-TKIs resistance. Additionally, monitoring serum NSE levels may facilitate the early detection of SCLC transformation, improving clinical outcomes through timely intervention.

CRediT authorship contribution statement

Jinhong Chen: Writing – original draft, Conceptualization. **Hongxiang Huang:** Writing – original draft, Resources. **Peiyuan Zhong:** Resources. **Sujuan Peng:** Resources. **Xie Zhu:** Resources. **Xinjing Ding:** Resources. **Fen Wang:** Resources. **Ping Kong:**

Resources. **Tiantian Song:** Resources. **Zhihui Lu:** Resources. **Li Chen:** Methodology, Conceptualization.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this paper and any accompanying images.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki. Ethical review and approval were waived due to the type of the study. Written informed consent was obtained from the patient.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

List of abbreviations

Abbreviations	Full name
EGFR-TKIs	Epidermal growth factor receptor-tyrosine kinase inhibitors
SCLC	Small cell lung cancer
NSCLC	Non small cell lung cancer
CT	Computed tomography
SPECT	Single photon emission computed tomography
IHC	Immunohistochemistry
H&E	Hematoxylin and eosin
MRI	Magnetic resonance imaging
CEA	Carcinoembryonic antigen
mPFS	Median progression free survival
mOS	Median overall survival
CNS	Central nervous system
NSE	Neuron specific enolase
pro-GRP	Pro-gastrin releasing peptide
RECIST 1.1	Response evaluation criteria in solid tumors 1.1
NGS	Next generation sequencing
IGF-1R	Insulin like growth factor-1 receptor
NF-κB	Nuclear factor-κB
RB1	Retinoblastoma gene 1
RCT	Large randomized controlled trials

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