Response to Icotinib Plus Chemotherapy in Pulmonary Atypical Carcinoid Harboring the *EGFR* L858R Mutation: A Brief Report

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ABSTRACT

Introduction: Pulmonary atypical carcinoid (PAC) is a rare subtype of pulmonary neuroendocrine neoplasm. Although *EML4-ALK* fusion has been detected in PAC, *EGFR* mutations have not been reported before.

Methods: We performed hematoxylin and eosin staining, immunohistochemistry, and next-generation sequencing on tissues at baseline and after surgery.

Results: The patient was diagnosed with having advanced PAC harboring the *EGFR* L858R mutation and then received a combination of icotinib and irinotecan plus cisplatin chemotherapy, achieving a partial response before the operation. Postoperative histology results revealed SCLC harboring the *EGFR* L858R mutation. Surprisingly, both the *KRAS* amplification and the *RB1* deletion disappeared.

Conclusions: EGFR tyrosine inhibitors plus irinotecan plus cisplatin chemotherapy might be a potential treatment option for advanced pulmonary neuroendocrine neoplasms harboring *EGFR* mutations.

Keywords: Pulmonary atypical carcinoid; Neuroendocrine tumor; *EGFR L858R*; Icotinib; Chemotherapy

Introduction

The 2021 WHO tumor classification (fifth edition) classified pulmonary neuroendocrine neoplasms (NENs) into four subtypes, typical carcinoid, atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNEC), and SCLC, according to some morphologic and protein expression immunohistochemistry (IHC) features.[1] Among NENs, AC accounts for only approximately 2.5% and 0.2% of lung carcinomas, making them rare lesions.[2,3] In addition, cancer-related gene mutations are rare.[4] Nevertheless, as reported by Rickman et al.,[5] *ErbB3* and *ErbB4* receptors can be expressed in AC tumors, and there were no activating mutations in the *EGFR* kinase domain from AC tumor tissue in the Mayo Clinic Lung Cancer Specimen Registry from 2001 to 2006. The *EML4-ALK* fusion gene was detected in patients with AC.[6] Nevertheless, no patients with pulmonary AC harboring *EGFR* mutations have been reported.

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Materials and Methods

Patient Information

A patient with advanced pulmonary AC also with the *EGFR* L858R mutation was treated and evaluated at Guangdong Provincial People's Hospital. The patient signed the informed consent form and gave permission for the use of their tumor tissues.

Pathological Characteristics and IHC Imaging

Pathology was confirmed by hematoxylin and eosin staining and tissue-specific markers according to the 2021 WHO tumor classification (fifth edition). Tissues were fixed in 4% formaldehyde, and 5-μm sections were stained with hematoxylin and eosin reagent after embedding in paraffin ($\times$100 and $\times$200 magnification). Immunohistochemical staining markers included Ki67, Syn, CgA, TTF1, and CD56. Each section was examined under a $\times$200 power field. Positive cells were scored as expressing less than 10% (−), 10% to 25% (+), 25% to 75% (++), and more than 75% (+++).

Next-Generation Sequencing

Next-generation sequencing (NGS) of baseline and postsurgical tissues was conducted using baseline and postsurgical tissues, respectively, without plasma at Guangdong Provincial People's Hospital using 196-gene panel (MiSeqDx, Illumina).

Results

The patient, a 72-year-old man who was a heavy smoker, presented with a physical examination of the chest and abdominal computed tomography revealing a 21-mm lesion in the right upper lung with multiple mediastinal lymph node (LN) metastases and bone destruction of the tenth thoracic vertebral body and left vertebral arch. He had no fever, cough, chest pain, or any other symptoms. Results of the endobronchial ultrasound-guided transbronchial needle aspiration of the right lower paratracheal (R4) LN revealed pulmonary AC with IHC staining results as Ki-67 (25%+), Syn (++), CgA (++), TTF-1 (+), and CD56 (+++) (Fig. 1*A*). NGS results revealed *EGFR* L858R mutation, *TP53* mutation, *KRAS* amplification, and *RB1* deletion (Fig. 2). He received icotinib (125 mg thrice a d) combined with four cycles of irinotecan plus cisplatin (IP) chemotherapy (irinotecan 60 mg/m^2 on d1, d8, and d15, cisplatin 60 mg/m^2 on d1), achieving partial response according to the Response Evaluation Criteria in Solid Tumors version 1.1 at 2 months and confirmed partial response at 4 months after the initiation of treatment (Fig. 3). The level of serum carcinoembryonic antigen was considerable decreased (Fig. 2).

After 5 months of treatment, repeated positron emission tomography-computed tomography results revealed no increase in fludeoxyglucose (F-18) in the primary lesion of the right upper lung, whereas the R4 LN and the tenth thoracic vertebral body, including the left vertebral arch, were still F-18 positive. To further confirm the pathologic diagnosis and to achieve better disease control, we conducted wedge resection of the anterior segment of the right upper lung lobe and the mediastinal LNs followed by the intended palliative radiation of the tenth thoracic vertebrae. Intraoperative frozen results revealed poorly differentiated cancer. Interestingly, the postoperative pathology and IHC results of the LNs and the lung primary lesion were Ki-67 (60%+), Syn (+), Cg A (+), TTF-1 (++), and CD56 (+++) and Ki-67 (60%+), Syn (+), CgA (+), TTF-1 (+), and CD56 (+), respectively. (Fig. 1B and 1C) Furthermore, the NGS results still revealed the *EGFR* L858R mutation, whereas both the *KRAS* amplification and the *RB1* deletion had disappeared (Fig. 2).

Discussion

Pulmonary AC has a low frequency of cancer-related mutations, and patients with AC harboring *EGFR* mutations have not been reported.[5] The low mutation frequency was related to the low detected frequency to some extent among patients with AC. Thus, performing NGS to detect any targetable mutations, particularly in patients with rare diagnosis, is of vital importance that may give more patients opportunity to receive tyrosine kinase inhibitors (TKIs) that may be a better choice for them. Among NENs, the malignant degree of AC is between typical carcinoid and LCNEC, and LN metastasis is common.[3,7] Approximately 20% of patients with pulmonary AC were first diagnosed with distant metastases; therefore, we tend to administer the chemotherapy recommended for SCLC.[2] A Japanese study revealed both a longer median overall survival time and a higher two-year survival rate in the IP group than in the etoposide plus cisplatin group ($p < 0.005$) among patients with advanced-stage SCLC.[8] A meta-analysis suggested that icotinib achieved better efficacy in patients with *EGFR* 21 exon L858R mutation than in those with *EGFR* wild type (progression-free survival [PFS] = 8.7 versus 2.6 mo).[9] In our previous study, published in the 2020 World Conference on Lung Cancer, the median PFS of patients with transformed SCLC with *EGFR* mutations receiving EGFR TKI plus chemotherapy was significantly longer than the PFS times of those treated with chemotherapy alone.[10] Thus, this patient was treated with a combination of icotinib and IP chemotherapy. To the best of our knowledge, this was the first patient with advanced pulmonary AC with *EGFR* mutation who responded to EGFR TKI plus chemotherapy.

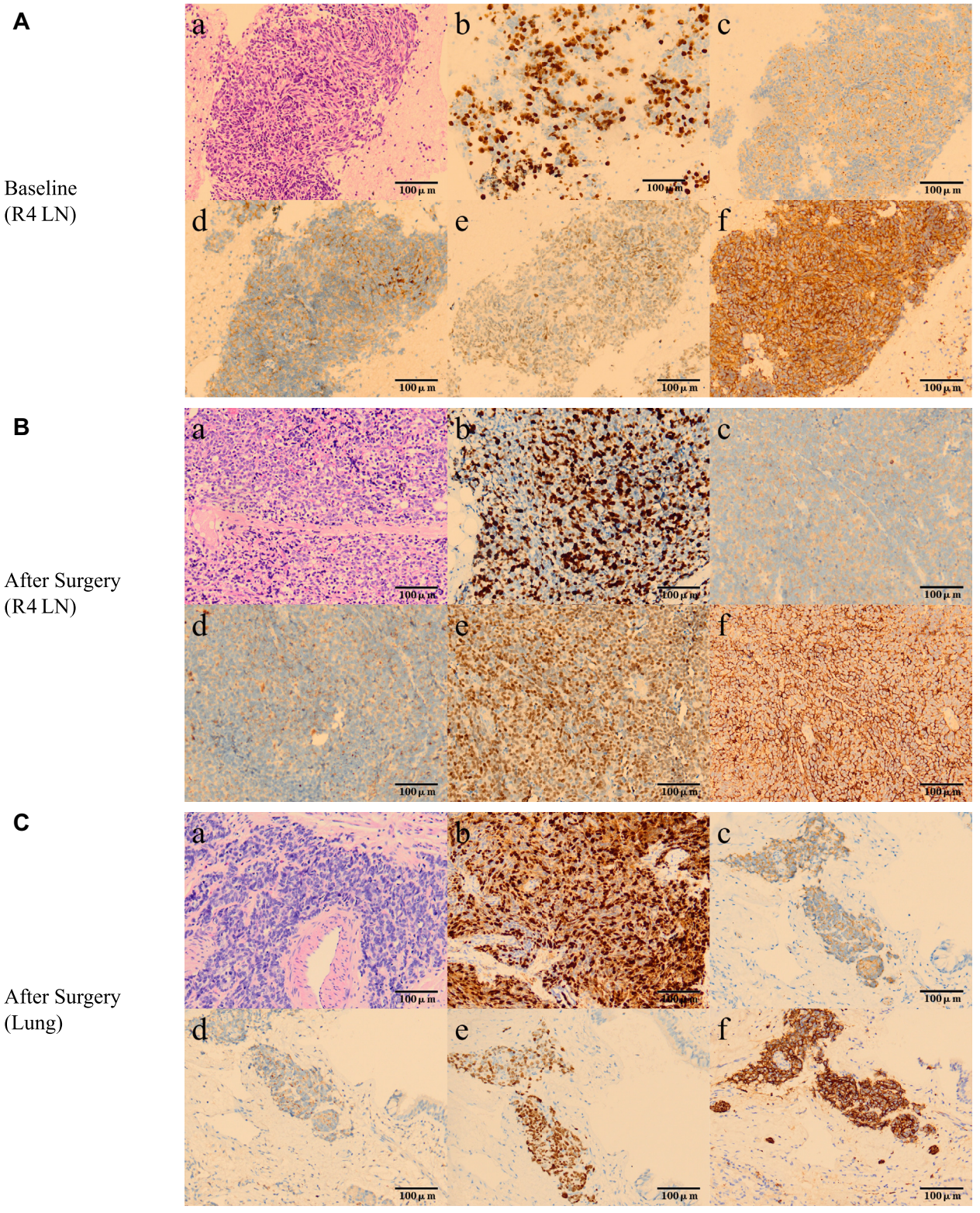

Figure 1. Pathology images of HE staining and IHC (×200). *A*: (*a*): HE staining result of LN as AC at baseline. (*b-g*): IHC staining revealed Ki-67 (25%+), Syn (++), CgA (++), TTF-1 (+), and CD56 (+++). *B*: (*a*): HE staining result of LNs after surgery for SCLC. (*b-g*): IHC staining revealed Ki-67 (60%+), Syn (+), Cg A (+), TTF-1 (++), and CD56 (+++). *C*: (*a*): HE staining result of the lung lesion after surgery, which was diagnosed with SCLC. (*b-g*): IHC staining revealed Ki-67 (60%+), Syn (+), CgA (+), TTF-1 (+), and CD56 (+). Scale bar = 100 μm. AC, atypical carcinoid; HE, hematoxylin and eosin; IHC, immunohistochemistry; LN, lymph node; R4, right lower paratracheal.

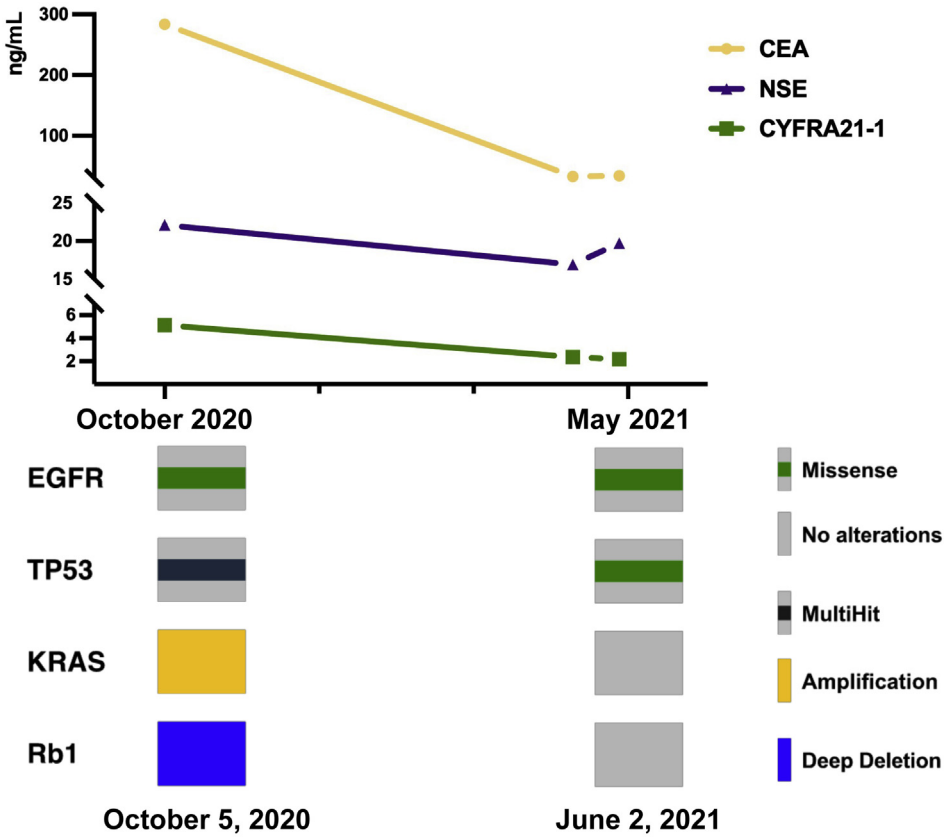

Figure 2. Dynamic changes in serum tumor markers and cancer-related gene variant changes of tumor tissues by NGS. The levels of CEA, CYFRA21-1, and NSE at baseline were 283.53 ng/mL, 5.14 ng/mL, and 22.11 ng/mL, respectively. After 6 months, the levels of CEA, CYFRA21-1, and NSE were 33.13 ng/mL, 2.36 ng/mL, and 16.91 ng/mL, respectively. The preoperative levels of CEA, CYFRA21-1, and NSE were 34.19 ng/mL, 2.17 ng/mL, and 19.71 ng/mL, respectively. NGS results revealed that the variant allele frequencies of the EGFR L858R missense mutation were 31.37% and 13.30% at baseline and after surgery, respectively. Both the KRAS amplification and the Rb1 deletion had disappeared. NGS, next-generation sequencing.

Regarding histology, this patient was first diagnosed with having pulmonary AC, and according to a survival analysis of patients with AC, receiving surgery could reduce the risk of death (hazard ratio = 0.19, 95% confidence interval: 0.137–0.264, $p < 0.001$).[2] To our surprise, this patient was diagnosed with having SCLC after surgery. For this changed pathology, we have two hypotheses. First, this might be due to the spatial heterogeneity of the tumor tissue, as we observed that the postoperative pathology indicated a large spatial heterogeneity, whereas the baseline sample was too small to reveal heterogeneity. Meanwhile, it also suggested that more tissue or multispot biopsy would do more help for diagnosis and may reveal the spatial heterogeneity of tumors to a certain extent, thus providing more information for the precise treatment decision made at the time of diagnosis. Second, a two-way clustering analysis of NGS data of patients with NENs suggested an innovative view, as low- and middle-grade NENs have the potential to evolve into high-grade tumors, indicating most high-grade pulmonary NENs are likely to develop from pre-existing carcinoids.[11] Radiotherapy of the tenth thoracic vertebrae is currently conducted, with close follow-up.

Rubino et al.[12] proposed the concept of lung carcinoids with high proliferative activity, defined as mitotic count greater than 10/2 mm^2 and Ki-67 index greater than 20%. They indicated that the recurrence-free survival times of patients with carcinoids on the basis of pathological characteristics who underwent primary tumor surgery by AC and lung carcinoids with high proliferative activity were 178 and 24 months, respectively ($p < 0.01$). In addition, patients harboring the *EGFR* L858R mutation achieved a lower efficacy with EGFR TKIs than those with the *EGFR* 19del mutation.[13] The INCREASE study revealed that icotinib had a significantly longer median PFS in the L858R high-dose group (250 mg, thrice a d) than in the L858R routine-dose group (125 mg, thrice a d) (12.9 versus 9.2 mo, hazard ratio = 0.75, 95% confidence interval: 0.53–1.05, $p < 0.05$) and was comparable to that in the 19del group at 12.5 months.[14] Thus, how to individualize the postoperative follow-up and when to

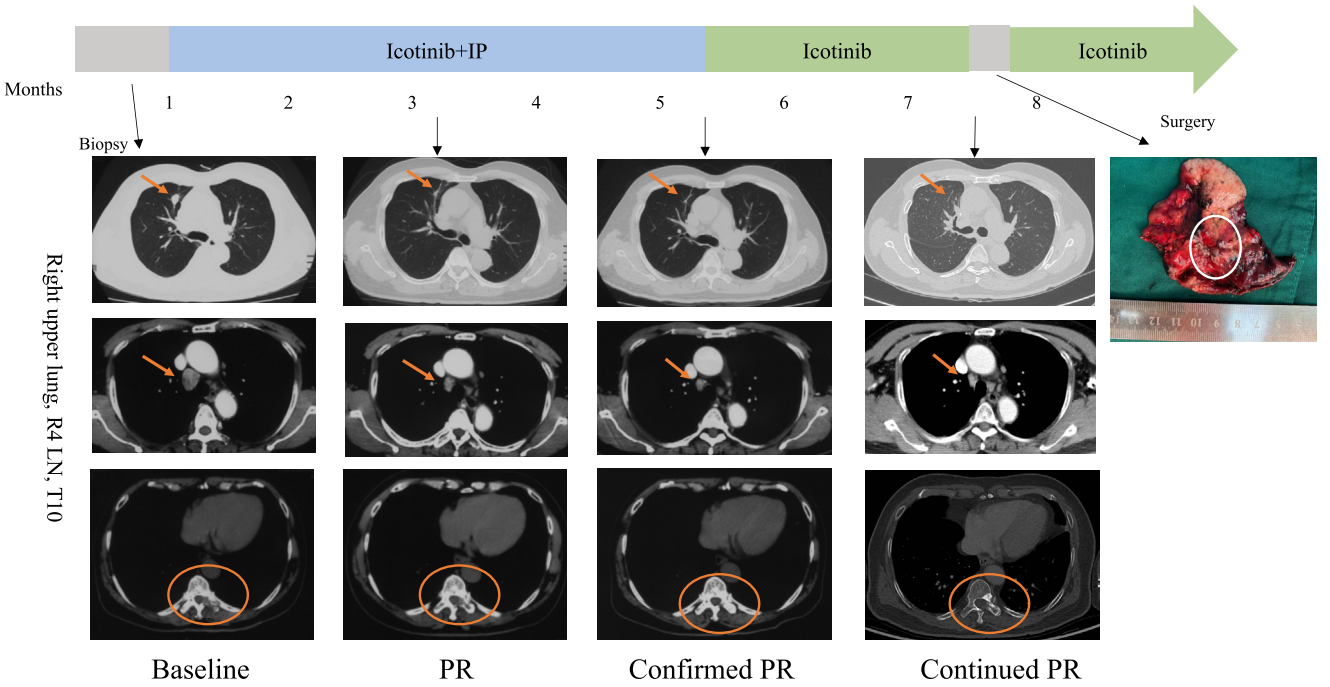

Figure 3. Timeline of treatment with clinical responses to a combination of icotinib and IP chemotherapy. The patient achieved a PR after 2 months of treatment with a combination of icotinib and chemotherapy (IP). PR was confirmed 2 months after. After 6 months of treatment, he continued to achieve PR, and the T10 vertebral body had an osteogenesis change, and we performed a wedge resection. The arrows and circles indicate lesions. IP, irinotecan plus cisplatin; PR, partial response; LN, lymph node; R4, right lower paratracheal.

double the dose of icotinib for maintenance treatment are questions that need to be further investigated.

EGFR TKI plus IP chemotherapy administered successfully in the first patient with pulmonary AC with *EGFR* mutation may provide a potential treatment mode for advanced NENs harboring *EGFR* mutations. Nevertheless, further investigations of treatment regimens and genomic specificity of patients with AC are warranted.

CRediT Authorship Contribution Statement

Yu-Qing Chen: Investigation, Data curation, Writing - original draft, Visualization.

Yu-Fa Li: Investigation, Data curation.

Chan-Yuan Zhang: Investigation.

Shi-Ling Zhang: Visualization.

Zhi-Yi Lv, Xu-Chao Zhang: Resources.

Song Dong, Hua-Jun Chen: Validation.

Yi-Long Wu: Supervision.

Jin-Ji Yang: Conceptualization, Methodology, Writing - review & editing.

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