CASE REPORT

Long-Term Efficacy of Immune Checkpoint Inhibitor for Squamous Cell Carcinoma Lesion Transformed From *EGFR*-Mutated Adenocarcinoma After Osimertinib Treatment: A Case Report

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Received 16 September 2023; revised 5 January 2024; accepted 14 January 2024
Available online - 20 January 2024

ABSTRACT

Histologic transformation is one of the mechanisms of resistance to EGFR tyrosine kinase inhibitor in patients with NSCLC with *EGFR* mutation. The transformation from adenocarcinoma to squamous cell carcinoma (SCC) has been recently recognized as a mechanism of resistance to osimertinib. The prognosis after transformation to SCC is considered to be poor, and the therapeutic strategy for these patients is unclear. Herein, we report a case of long-term response to pembrolizumab monotherapy for an SCC-transformed lesion in a patient with *EGFR*-mutated adenocarcinoma after osimertinib treatment. A 68-year-old man underwent right upper lobectomy and was diagnosed with lung adenocarcinoma, pathologic stage IIA, with *EGFR L858R*. Five years after the surgery, he was diagnosed with recurrence and administered osimertinib. Ten months after, biopsy for an enlarged subpleural lesion revealed SCC with *EGFR L858R*, leading to a diagnosis of histologic transformation. Notably, the programmed death-ligand 1 expression level of the transformed lesion was higher than that of the adenocarcinoma (90% versus <1%). The size of the SCC lesion had reduced with pembrolizumab monotherapy, and the reduction was maintained for over 47 months since transformation. Nevertheless, the original adenocarcinoma lesion progressed after pembrolizumab therapy and was controlled by other cytotoxic drugs and readministration of osimertinib. Immune checkpoint inhibitor therapy is generally ineffective against *EGFR*-mutated adenocarcinoma. Nevertheless, it may be promising for achieving a good prognosis when *EGFR*-mutated adenocarcinoma transforms to SCC after developing EGFR tyrosine kinase inhibitor resistance—particularly if the transformed lesion has high programmed death-ligand 1 expression.

Keywords: Acquired resistance; Histologic transformation; Osimertinib; Immune checkpoint inhibitor; Case report

Introduction

EGFR is a mutation frequently found in Asian patients with NSCLC. EGFR tyrosine kinase inhibitors (TKIs) have higher antitumor efficacy than cytotoxic chemotherapy. Nevertheless, most patients develop drug resistance to EGFR TKI in 1 to 2 years.

Histologic transformation is one of the mechanisms of resistance to EGFR TKIs. Transformation to squamous

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Cite this article as: Takahashi S, Sato Y, Sato Y, et al. Long-term efficacy of immune checkpoint inhibitor for squamous cell carcinoma lesion transformed from *EGFR*-mutated adenocarcinoma after osimertinib treatment: a case report. *JTO Clin Res Rep*. 2024;5:100639.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2024.100639

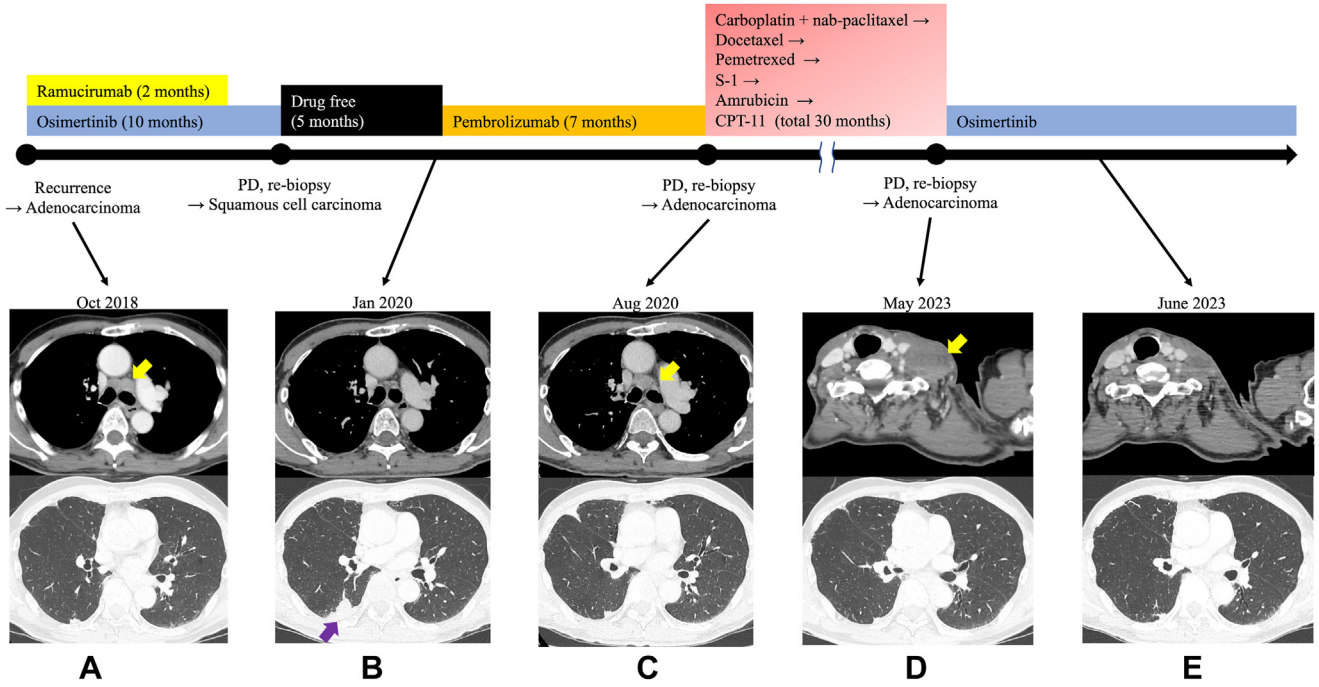

Figure 1. Case timeline. Clinical course of the patient. The black circle indicates the time points of disease progression and biopsies. Computed tomography scan revealing the following: (*A*) Enlargement of mediastinal lymph nodes 5 years after surgery. Biopsy revealed recurrence. (*B*) Appearance of subpleural lesion after osimertinib treatment. Rebiopsy revealed squamous cell carcinoma. (*C*) Reduction in the size of subpleural lesion. In contrast, mediastinal lymph nodes progressed. Rebiopsy revealed adenocarcinoma. (*D*) Maintenance of reduction in the size of subpleural lesion and appearance of new lesion in the cervical lymph node. Rebiopsy revealed adenocarcinoma. (*E*) Reduction in the size of cervical lymph node. Maintenance of reduction in subpleural lesion.

cell carcinoma (SCC) is a relatively rare mechanism of drug resistance to first- and second-generation EGFR TKIs. Osimertinib, a third-generation EGFR TKI, is widely administered as the standard of care. The frequency of SCC transformation is unclear. One study stated that SCC transformation was more frequent than SCLC transformation as a mechanism of drug resistance to osimertinib.[1]

The standard care after EGFR TKI resistance is unclear, and the efficacy of immune checkpoint inhibitor (ICI) monotherapy is highly controversial. After transformation to SCC, the prognosis is reported to be poor.[2] We report a case of long survival of a patient after EGFR-mutated adenocarcinoma transformed to SCC.

Case Presentation

A 68-year-old man with no significant medical history, no smoking history, and no symptoms presented to our hospital in May 2013 with an abnormal chest radiograph result. Further examinations revealed right upper lobe adenocarcinoma. He underwent right upper lobectomy in June 2013. The final diagnosis was stage IIA (p-T1bN1M0), with activating *EGFR L858R* (detected through the PNA-LNA PCR clamp method). Adjuvant chemotherapy with cisplatin and pemetrexed was started but discontinued after one course because of the occurrence of anorexia and hyponatremia; he was observed as an outpatient.

In August 2018, an enlarged mediastinal lymph node was observed (Fig. 1*A*); biopsy was performed with endobronchial ultrasound-guided transbronchial needle aspiration. The biopsy revealed adenocarcinoma with *EGFR L858R*, and the programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) was negative (<1%) (Fig. 2*A*). He was diagnosed with recurrence and administered osimertinib and ramucirumab as the first-line chemotherapy in December 2018. Ramucirumab was discontinued because of adverse events of bleeding and oral mucositis, and osimertinib alone was continued from February 2019; the patient achieved partial response, and he experienced no adverse events including pneumonitis.

Although the mediastinal lymph node lesion had sustained reduction, a computed tomography conducted in August 2019 revealed an enlarged subpleural lesion in the right lung (Fig. 1*B*). Biopsy was performed with video-assisted thoracic surgery, and pathologic examination revealed SCC, with partly positive expression of cytokeratin 5/6. Notably, the PD-L1 TPS increased to 90% (Fig. 2*B*). *EGFR L858R* remained positive in SCC

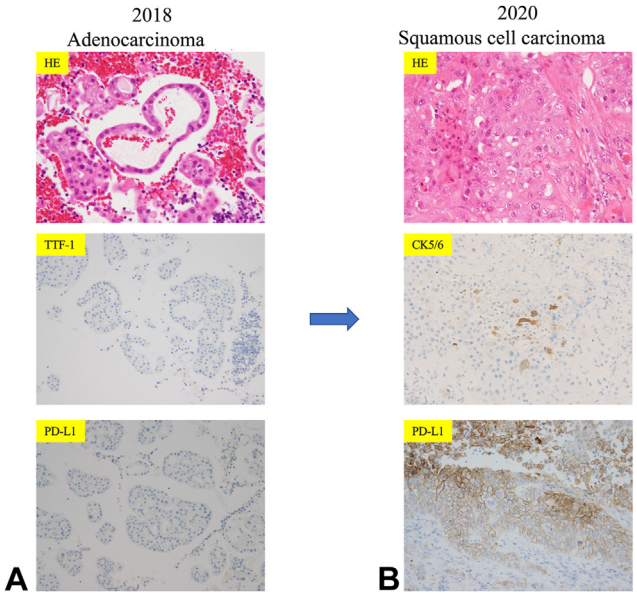

Figure 2. Pathologic examination at recurrence. (*A*) Pathologic examination at recurrence revealed adenocarcinoma. Magnification of the HE-stained images was ×400. Immunohistochemical staining results were negative for TTF-1. PD-L1 TPS was negative. (*B*) Pathologic examination of subpleural lesion revealed squamous cell carcinoma. Magnification of the HE-stained images was ×400. Immunohistochemical staining results were partly positive for cytokeratin 5/6. High PD-L1 TPS (90%). PD-L1 TPS, programmed cell death-ligand 1 tumor proportion score; HE, hematoxylin and eosin; TTF-1, thyroid transcription factor-1.

(detected through the PNA-LNA PCR clamp method), leading a diagnosis of histologic transformation. RNA sequencing performed using Novaseq 6000 (Supplementary Data 1), of pre- and post-histologic transformation specimens revealed several changes in gene expression (Supplementary Fig.), including the enrichment of PIK3-AKT-mTOR pathway (Table 1). Neither specimen had *EGFR T790M* or *C797S*, but both had the *EGFR L858R*. In January 2020, treatment with pembrolizumab was initiated; the transformed lesion responded well, and the patient achieved partial response, and no immune-mediated adverse events were observed. The SCC lesion had sustained reduction, but in September 2020, an enlargement was observed in the mediastinal lymph (Fig. 1*C*). Biopsy with endobronchial ultrasound-guided transbronchial needle aspiration revealed adenocarcinoma with *EGFR L858R* mutation (detected through the PNA-LNA PCR clamp method). The chemotherapy regimen was changed to carboplatin and nab-paclitaxel. Subsequently, the patient was treated with some cytotoxic drugs (Fig. 1). He experienced adverse events of neutropenia with docetaxel and symptomatic drug-induced lung injury with pemetrexed, which required dose reduction and oral corticosteroids therapy for one month, respectively. In February 2023, the reduction of subpleural SCC-transformed lesion was maintained (Fig. 1*D*). Biopsy of a new enlarged cervical lymph node lesion revealed the presence of an adenocarcinoma (Fig. 1*D*). In May 2023, we readministered osimertinib, and the adenocarcinoma lesion reduced in size (Fig. 1*E*).

Discussion

We experienced a case of *EGFR*-mutated lung adenocarcinoma that transformed into SCC as a mechanism of resistance to EGFR TKI, and ICI therapy exhibited long-term efficacy against the transformed lesion. Indeed, it is occasionally difficult to prove whether an SCC has transformed from an adenocarcinoma or whether it is a combined tissue (e.g., adenosquamous carcinoma) at the time of diagnosis because of the small tissue specimens obtained for biopsy. Nevertheless, because the specimen excised at the first surgery was a pure adenocarcinoma and the subpleural lesion was diagnosed as SCC through video-assisted thoracic surgery, it was determined to have transformed to SCC through drug resistance.

This case is unique in terms of long-term survival (47 mo as of September 2023) after the adenocarcinoma transformed to SCC. The prognosis after transformation to SCC is usually poor, with a reported median overall survival of 3.5 months in a pooled analysis.[2] A previous retrospective large-scale study revealed the limited efficacy of ICI for patients with histologic transformations (including some with transformation to SCC) after EGFR TKI resistance.[3] Nevertheless, two previous case reports revealed the potential long-term efficacy of ICI for the *EGFR*-mutated lung adenocarcinoma that transformed

Table 1. List of the Pathways Enriched by Differentially Expressed Genes Between Pre- and Post-Specimens

Pathway	Genes Found in Pathways (n)	Differentially Expressed Genes in the Pathway	Enrichment *p* Value
PI3K-Akt signaling pathway	340	86	0
Focal adhesion-PI3K-Akt-mTOR-signaling pathway	302	84	0
PI3K-AKT-mTOR signaling pathway	22		

into SCC.[4,5] The similarity between these two cases and ours is that the SCC lesion had high expression levels of PD-L1. In some cases, severe adverse events (including immune-mediated adverse events) can lead to poor prognoses in patients with NSCLC. Fortunately, immune-mediated adverse events with pembrolizumab and drug-induced pneumonitis with osimertinib did not occur in this case. A favorable prognosis was, therefore, feasible from the perspective of adverse events.

This case is unique in the concurrence of PD-L1 TPS up-regulation and SCC transformation after the patient developed osimertinib resistance; the PD-L1 TPS was high in the SCC lesion after transformation, whereas that in the adenocarcinoma lesion was negative before transformation. It was reported that the number of patients with *EGFR*-mutated lung cancer expressing high level of PD-L1 increased after EGFR TKI resistance, and the sequence ICI treatment was more effective in the high PD-L1 group than that in the low and negative.[6] In this case, PD-L1 change could lead to clinical durable responses of SCC lesion to pembrolizumab monotherapy. Nevertheless, it is unclear whether PD-L1 TPS up-regulation is involved in histologic transformation. To the best of our knowledge, there is no large-scale clinical research on the association between PD-L1 TPS up-regulation and histologic transformation.

One of the strong points of this case report is that we conducted RNA sequencing using pre- and post-specimens. Surprisingly, the gene expression was highly altered, and the enrichment of PIK3/AKT/mTOR pathway was found in the RNA sequence of post-transformation specimens compared with that of the pre-transformation specimens. This finding is consistent with that of a previous report where genetic alterations related to the PI3K/AKT/mTOR pathway were involved in the transformation from adenocarcinoma to SCC.[7]

Conclusions

ICI might be a promising treatment for transformation of *EGFR*-mutated adenocarcinoma to SCC with high PD-L1 expression. Rebiopsy should be performed to determine the therapeutic strategy for patients who develop EGFR TKI resistance.

CRediT Authorship Contribution Statement

Shota Takahashi: Conceptualization, Writing—Original Draft and Visualization.

Yuki Sato: Project Administration and Writing—Review and Editing.

Yoshiharu Sato: Resource and Writing—Review and Editing.

Ryosuke Hirabayashi: Data Curation, Resource, and Writing—Review and Editing.

Shigeo Hara: Visualization and Writing—Review and Editing.

Yutaka Takahashi: Resource and Writing—Review and Editing.

Keisuke Tomii: Supervision and Writing—Review and Editing.

Informed Consent

The patient provided consent to publish the details of his case, and his identity has been protected.

Disclosure

Dr. Yuki Sato received a fee from the speakers' bureau of AstraZeneca, Chugai Pharmaceutical, Merck Sharp & Dohme, Ono Pharmaceutical, Novartis, Pfizer, Taiho Pharmaceutical, Nippon Kayaku, Bristol-Myers Squibb, Eli Lilly, Takeda, and Kyowa Kirin in addition to the role in the submitted work. Dr. Tomii received benefits from the speakers' bureau of Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai Pharma, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Kyorin, Kyowa Kirin, Merck Sharp & Dohme, Nippon Kayaku, Novartis Pharma, Pfizer, Sanofi, Shionogi, Taiho Pharmaceutical, and Teijin Pharma and had an advisory role at Eli Lilly in addition to the role in the submitted work. All remaining authors declare no conflict of interest.

Acknowledgments

The authors thank Editage (www.editage.com) for English language editing. The authors received internal funding from Kobe City Medical Center General Hospital.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100639.

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