Squamous Cell Carcinoma "Transformation" Concurrent with Secondary T790M Mutation in Resistant *EGFR*-Mutated Adenocarcinomas

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Received 10 October 2015; revised 29 November 2015; accepted 7 December 2015

ABSTRACT

The authors report two cases of epidermal growth factor receptor gene (EGFR)-mutant stage IV lung adenocarcinomas developing immunohistochemically proven squamous cell carcinoma (SCC) "transformation" concurrently with T790M EGFR mutation, leading to acquired resistance to EGFR inhibitors. Moreover, the histologic change of EGFR-mutant lung adenocarcinoma into SCC has been recently reported in literature. The histological transformation to SCC appears as a novel mechanism of acquired EGFR TKI resistance in EGFR-mutated adenocarcinomas and it may be challenging for treatment.

Keywords: Lung; Adenocarcinoma; Squamous cell carcinoma; EGFR; T790M

Case Report

Case 1

A 74-year-old women, a former smoker, presented with persistent cough. Chest radiography, whole-body computed tomography (CT), and positron emission tomography revealed two nodules in the left lung, enlarged mediastinal lymph nodes, and a mass of the left adrenal gland. The findings of brain imaging were negative. Bronchial biopsy showed a lung adenocarcinoma (thyroid transcription factor 1 [TTF-1] positive, p40 negative). The mutational analysis by matrix-assisted laser desorption/ionization time-of-flight revealed an exon 21 epidermal growth factor receptor gene (*EGFR*) L858R mutation, excluding additional alterations (LungCarta Panel v1.0, Agena Bioscience, San Diego, CA). Sanger sequencing confirmed the molecular data. In January 2014, the patient began taking gefitinib. Her symptoms improved rapidly, and a CT scan (in May 2014) revealed a partial response. In October 2014, the patient complained of dry cough and a CT scan showed enlargement of her lung lesions. A bronchial rebiopsy surprisingly provided evidence of a squamous cell carcinoma (SCC) (p40 positive, TTF-1 negative). In molecular investigations, tumor cells harbored the original exon 21 *EGFR* mutation and also carried an exon 20 T790M mutation. Second-line chemotherapy (carboplatin and vinorelbine) achieved stabilization of the disease, and radiosurgery successfully controlled the occurrence of brain metastasis. As of September 2015, the patient is still alive with stable disease.

Case 2

A 79-year-old woman, a never-smoker, was admitted to the hospital for thoracic trauma and hemoptysis. Chest CT and positron emission tomography scans revealed a

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Disclosure: The authors declare no conflict of interest.

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ISSN: 1556-0864

http://dx.doi.org/10.1016/j.jtho.2015.12.096

Table 1. Summary of the Main ClinicoPathologic and Molecular Characteristics of Change/Transformation of *EGFR*-Mutated Adenocarcinoma into Squamous Cell Carcinoma

Sex/age	Smoker	Stage	*EGFR* mutation	EGFR TKI (mo)[a]	Acquired gene alterations	Second-/third-line therapy	Status (mo)	Reference
F/63	Never	IV	L858R	Erlotinib (5)	PIK3CA ex 20 (H1047R)	Cis/pem Gefitinib Carbo/gem	DOD (14)	1
F/66	Never	IV	ex19	Erlotinib (8)	None	None	DOD (9)	2
F/79	Never	IV	delE746-A750	Gefitinib (15)	T790M	RT Gefitinib	AWD (24)	Current article
F/74	Former	IV	L858R	Gefitinib (10)	T790M	RT	AWD (20)	Current article

[a]Months to progression to EGFR TKI.

EGFR, epidermal growth factor receptor gene; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; F, female; mo, months; RT, radiotherapy; cis, cisplatin; carbo, carboplatin; pem, pemetrexed; gem, gemcitabine; DOD, died of disease; AWD, alive with disease.

right lower lobe mass and pleural nodules. Cell blocks prepared from pleural effusion and bronchial biopsies showed a lung adenocarcinoma (TTF-1 positive, p40 negative). Molecular analysis revealed an exon 19 delE746-A750 *EGFR* mutation. Gefitinib was started in July 2013 and resulted in partial remission of the lung and pleural lesions. In October 2014, a right brain metastasis was treated with stereotactic radiotherapy. In February 2015, pleural effusion and brain metastasis reappeared. A bronchial rebiopsy revealed a SCC (p40 positive, TTF-1 negative) harboring naive delE746-A750 and exon 20 T790M missense mutations. Gefitinib was continued; the thoracic disease remained stable for 7 months, but soft-tissue metastases from SCC occurred at the left leg.

Discussion

The histologic change of *EGFR*-mutant lung adenocarcinoma into SCC has been recently reported in two never-smoking women who underwent rebiopsy when resistance to erlotinib occurred.[1,2] Here we report two additional cases of *EGFR*-mutant stage IV adenocarcinomas developing concurrently with immunohistochemically proven SCC "transformation" and T790M *EGFR* mutation leading

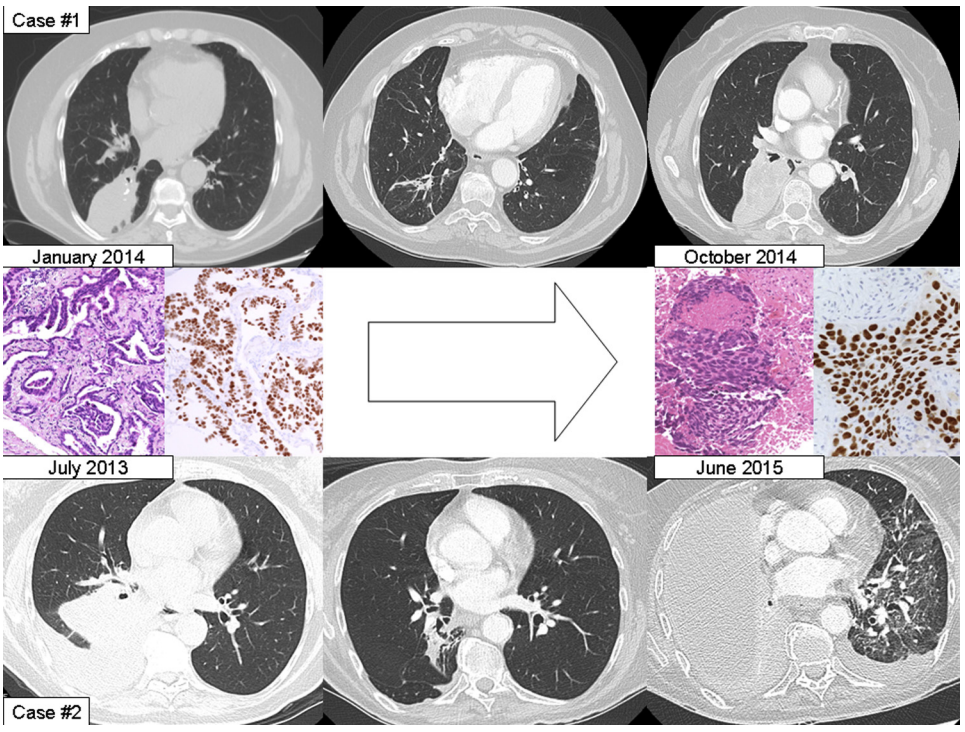

Figure 1. Computed tomography scans showing the clinical course during administration of gefitinib therapy in case 1 (*top*) and case 2 (*bottom*). Histologic change from adenocarcinoma (hematoxylin and eosin stain with thyroid transcription factor 1 immunoreactivity [*left*]) to squamous cell carcinoma (hematoxylin and eosin stain with p40 immunoreactivity [*right*]).

to acquired resistance to gefitinib after 15 and 10 months (Table 1). SCC harbored the original *EGFR* mutation together with T790M (Fig. 1). In *EGFR*-mutated adenocarcinoma, so-called transformation could be secondary to metaplastic plasticity of tumor cells,[3] but the possibility of unsampled combined (i.e., adenosquamous)[4] neoplasms selecting a different tumor component under the pressure of an EGFR tyrosine kinase inhibitor (TKI) cannot be excluded. In their case, Kuiper et al.[1] reported an additional mutation concomitant to the naive L858R, namely, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene (*PIK3CA*) exon 20 (H1047R).

Transformation to SCC appears as a novel mechanism of acquired EGFR TKI resistance in *EGFR*-mutated adenocarcinomas. The therapeutic strategies to adopt in these cases may be challenging and are still unclear because subsequent management could be based on the new histologic findings (SCC-based chemotherapy) rather than on novel molecular characteristics (third-generation pyrimidine-based EGFR TKIs).

References

1. Kuiper JL, Ronden MI, Becker A, et al. Transformation to a squamous cell carcinoma phenotype of an EGFR-mutated NSCLC patient after treatment with an EGFR tyrosine kinase inhibitor. *J Clin Pathol*. 2015;68:320–321.
2. Levin PA, Mayer M, Hoskin S, Sailors J, Oliver DH, Gerber DE. Histologic transformation from adenocarcinoma to squamous cell carcinoma as a mechanism of resistance to EGFR inhibition. *J Thorac Oncol*. 2015;10:e86–e88.
3. Oser MG, Niederst MJ, Sequist LV, Engelman JA. Transformation from non-small-cell lung cancer to small-cell lung cancer: molecular drivers and cells of origin. *Lancet Oncol*. 2015;16:e165–e172.
4. Rekhtman N, Paik PK, Arcila ME, et al. Clarifying the spectrum of driver oncogene mutations in biomarker-verified squamous carcinoma of lung: lack of EGFR/KRAS and presence of PIK3CA/AKT1 mutations. *Clin Cancer Res*. 2012;18:1167–1176.