Official Case Reports Journal of the Asian Pacific Society of Respirology
Respirology Case Reports
OPEN ACCESS

Pulmonary micropapillary-type adenosquamous carcinoma sharing epidermal growth factor receptor mutation in adenocarcinoma and squamous cell carcinoma

Yusuke Takanashi[1], Shogo Tajima[2], Takamitsu Hayakawa[1], Tsuyoshi Takahashi[1], Hiroshi Neyatani[1] & Kazuhito Funai[3]

[1]Department of Thoracic Surgery, Fujieda Municipal General Hospital, Fujieda, Japan.
[2]Department of Pathology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan.
[3]Department of Surgery 1, Hamamatsu University School of Medicine, Hamamatsu, Japan.

Keywords
Epidermal growth factor receptor, lung adenosquamous carcinoma, micropapillary adenocarcinoma.

Correspondence
Shogo Tajima, Department of Pathology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. E-mail: stajima-tky@umin.ac.jp

Received: 26 May 2016; Revised: 10 July 2016; Accepted: 16 July 2016.

***Respirology Case Reports*, 4 (5), 2016, e00179**

doi: 10.1002/rcr2.179

Abstract

Adenosquamous lung carcinoma (AdSqLC) has a worse prognosis than adenocarcinoma (ADC) or squamous cell carcinoma (SQCC). Micropapillary pattern in lung ADC is an additional poor prognostic factor. We describe a rare case of AdSqLC with epidermal growth factor receptor (EGFR) mutation in both the micropapillary-ADC and SQCC components, showing long-term response to gefitinib. A 60-year-old woman underwent right lower lobectomy for primary lung cancer. Histopathological examination demonstrated adenosquamous carcinoma comprising micropapillary-ADC and moderately differentiated SQCC. EGFR exon 19 deletions mutation was detected in both the ADC and SQCC components. Gefitinib was administered for multiple metastatic recurrences on bilateral lung, resulting in remarkable shrinkage of visible lesions. The efficacy of gefitinib lasted for 31 months after the induction. AdSqLCs harbouring the EGFR mutation in both the ADC and SQCC components may well benefit from EGFR tyrosine kinase inhibitors, especially when they contain micropapillary-ADC component that correlates with frequent EGFR mutations.

Introduction

Adenosquamous lung carcinoma (AdSqLC) shows components of both adenocarcinoma (ADC) and squamous cell carcinoma (SQCC), with each component comprising at least 10% of the tumour; it has worse prognosis than ADC or SQCC [1–3]. A micropapillary pattern in lung ADC is an additional poor prognostic factor frequently associated with lymphatic invasion [4]. Cases of AdSqLC showing micropapillary pattern as an ADC component (a combination of both poor prognostic factors) have not been described previously. Here we describe a case of AdSqLC with shared identical epidermal growth factor receptor (EGFR) mutation in both the micropapillary-ADC and SQCC components showing a long-term marked response to gefitinib.

Case Report

A 60-year-old woman, non-smoker, was referred to us because of an abnormal chest X-ray finding. Chest computed tomography (CT) revealed a mass lesion 35 × 35 mm in the lower lobe of the right lung (Fig. 1A). The well-enhanced mass had lobulated margins, and no significant lymph node swelling was observed (Fig. 1B). Laboratory studies revealed elevated carcinoembryonic antigen (CEA: 5.9 ng/mL; normal value < 5.0 ng/mL) and carbohydrate antigen 19-9 (CA19-9: 105.5 U/mL; normal value < 37.0 U/mL). Transbronchial biopsy of the mass strongly suggested primary lung cancer; investigations for distant metastasis including systemic CT and brain magnetic resonance imaging showed negative results. The patient underwent right lower lobectomy and lymph node

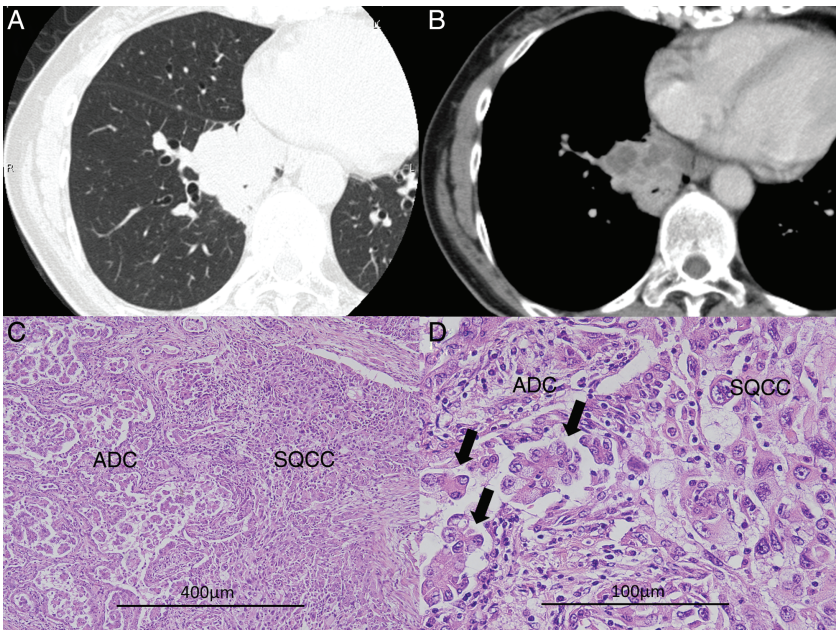

Figure 1. Chest computed tomography revealed a mass lesion measuring 35 × 35 mm in the right lower lobe (A). A well-enhanced mass with lobulated margins was seen, and no significant lymph node swelling was observed (B). Haematoxylin and eosin staining (original magnification ×100) of the mass demonstrated adenosquamous carcinoma composed of pure micropapillary-adenocarcinoma (ADC) and moderately differentiated squamous cell carcinoma (SQCC) (C). On higher magnification (original magnification ×400), small papillary tufts with no fibrovascular core floating in alveolar spaces (arrows) well represented the ADC component, which was clearly separated from the SQCC component showing eosinophilic foci of intracellular keratinization and intercellular bridges around the tumour cells (D).

dissection with a diagnosis of clinical stage T2aN0M0 lung cancer in the right lower lobe. Histopathological examination of the specimen revealed adenosquamous carcinoma predominantly comprising pure micropapillary-ADC accounting for approximately 60% of the tumour and moderately differentiated SQCC (Fig. 1C). On higher magnification, small papillary tufts with no fibrovascular core floating in alveolar spaces represented the micropapillary-ADC component, which was clearly separated from the SQCC component showing eosinophilic foci of intracellular keratinization and intercellular bridges around the tumour cells (Fig. 1D). Identical EGFR exon 19 deletion mutations from both the ADC and SQCC components were detected using polymerase chain reaction. Although mediastinal lymph node metastasis indicating pathological stage T2aN2M0 was confirmed on histopathological examination, the patient refused adjuvant chemotherapy. Multiple metastatic recurrences were observed on bilateral lungs 12 months post-operatively (Fig. 2A). She accepted gefitinib (250 mg/day), resulting in a marked response of drastically decreased visible lesions 12 months post-induction (Fig. 2B). The efficacy of gefitinib lasted favourably for 24 months, but decreased 31 months post-induction with disease progression (Fig. 2C). Further treatment with cytotoxic chemotherapy was not initiated due to decreased performance status, and she received supportive care.

Discussion

The present case is valuable as it presents a relatively rare histopathology of AdSqLC containing micropapillary pattern as the ADC component. AdSqLC with shared identical EGFR mutation in both the ADC and SQCC components showed a remarkable response to gefitinib.

AdSqLCs are more aggressive and associated with a worse prognosis than ADC or SQCC [1–3]. However, it is unknown whether the subtype of the ADC component in AdSqLC affects the prognostic outcome. A micropapillary pattern in lung ADCs is an additional poor prognostic factor correlated with significantly poor prognosis due to frequent lymphatic invasion, even in early stage cancers [4]. Although AdSqLC with a micropapillary-ADC component is relatively rare, it may result in a poor prognosis because of the combination of both poor prognostic factors. Contrary to our estimation, the present case achieved long-term survival showing remarkable response to gefitinib despite not receiving initial adjuvant chemotherapy.

EGFR mutations are a well-described oncogenic driver gene mutations identified in approximately 24–31.6% of lung ADCs in the East-Asian population [1,2]. Although AdSqLCs harbouring the EGFR mutation are treated with EGFR-tyrosine kinase inhibitors (TKIs) in the same manner as ADCs and tend to have a more positive prognosis than EGFR mutation-negative AdSqLCs with this treatment [1], ordinary response to EGFR-TKIs in AdSqLCs with the EGFR mutation is poor compared with ADCs harbouring this mutation. However, Iwanaga et al. reported a case of AdSqLC harbouring the EGFR mutation in both the ADC and SQCC components, which presented a marked response to gefitinib, lasting for 36 months [3]. Furthermore, our present case demonstrated identical EGFR mutations in both the ADC and SQCC components and showed a remarkable response to gefitinib, lasting for 31 months, similar to Iwanaga's case. Previous studies found that two components of AdSqLCs carry identical EGFR mutations as they are

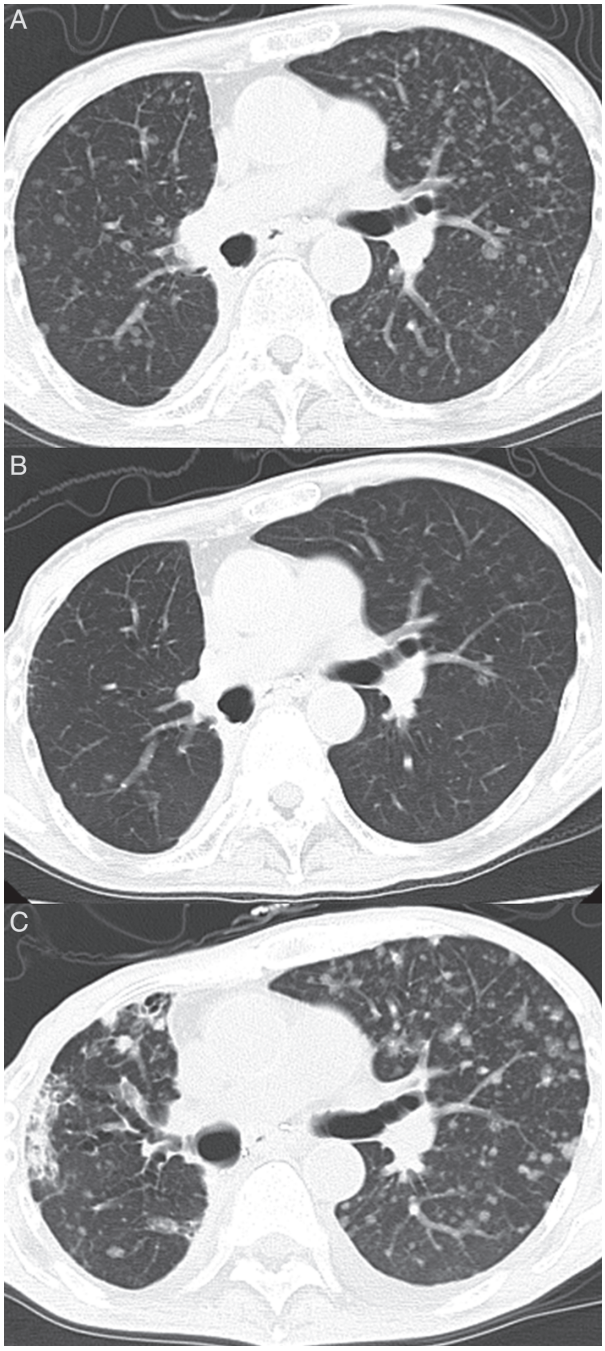

Figure 2. Multiple metastatic recurrences emerged on bilateral lungs 12 months after the surgery (A). Gefitinib administration resulted in a marked response that drastically decreased the visible lesions 12 months after the induction (B). The efficacy of gefitinib decreased 31 months post-induction with disease progression (C).

considered to originate from pluri-potential cancer stem cells [2]. These facts suggest that AdSqLCs harbouring EGFR mutations in both the ADC and SQCC components may have good response to EGFR-TKIs.

The frequency of the EGFR mutation in micropapillary-ADCs may be relatively high (though it varies from 25% to 84.6% according to several studies) compared with that in conventional ADCs [5]. The ADC component of Iwanaga's case was bronchioloalveolar carcinoma (BAC), which also has a positive correlation with the EGFR mutation. Although respective frequencies of the EGFR mutation in AdSqLC with micropapillary-ADC or BAC components have not been confirmed, we propose that AdSqLCs, which contain an ADC component correlated with the EGFR mutation, such as micropapillary-ADC or BAC, are associated with higher frequencies of the EGFR mutation and have more opportunities to benefit from EGFR-TKI treatment compared with other subtypes of AdSqLCs with papillary, acinar or solid-ADC components.

In conclusion, AdSqLCs harbouring the EGFR mutation in both the ADC and SQCC components may well benefit from EGFR-TKIs. AdSqLCs with micropapillary-ADC component may be associated with high frequency of the EGFR mutation and opportunities of subsequent EGFR-TKI treatment.

Disclosure Statements

No conflict of interest declared.
Appropriate written informed consent was obtained for publication of this case report and accompanying images.

Acknowledgment

We appreciate the technical assistance provided by Ms. Toyoko Mizuno.

References

1. Shiozawa T, Ishii G, Goto K, et al. 2013. Clinicopathological characteristics of EGFR mutated adenosquamous carcinoma of the lung. Pathol. Int. 63:77–84.
2. Wang R, Pan Y, Li C, et al. 2014. Analysis of major known driver mutations and prognosis in resected adenosquamous lung carcinomas. J. Thorac. Oncol. 9:760–768.
3. Iwanaga K, Sueoka-Aragane N, Nakamura T, et al. 2012. The long-term survival of a patient with adenosquamous lung carcinoma harbouring EGFR-activating mutations who was treated with gefitinib. Intern. Med. 51:2771–2774.
4. Kamiya K, Hayashi Y, Douguchi J, et al. 2008. Histopathological features and prognostic significance of the micropapillary pattern in lung adenocarcinoma. Mod. Pathol. 21:992–1001.
5. Cao Y, Zhu LZ, Jiang MJ, et al. 2015. Clinical impacts of a micropapillary pattern in lung adenocarcinoma: a review. Onco Targets Ther. 9:149–158.