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## CASE REPORT

# Heterogeneity of epidermal growth factor receptor mutations within a mixed adenocarcinoma lung nodule

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### KEYWORDS

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factor receptor  
mutations;  
Gefitinib

**Summary** It has been proposed that stepwise progression occurs from atypical adenomatous hyperplasia (AAH) through bronchioloalveolar carcinoma (BAC) to invasive lung adenocarcinoma. However, the underlying molecular mechanisms have not been identified. We report a patient with a mixed adenocarcinoma of the lung that had different *EGFR* mutations in the papillary subtype, the acinar subtype, and the surrounding AAH and BAC areas. *EGFR* mutations may accumulate during tumor progression and lead to heterogeneity of *EGFR* mutations within the tumor.

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## 1. Introduction

Lung adenocarcinoma with bronchioloalveolar carcinoma (BAC) features is frequently seen on thin-section chest computed tomography (CT) [1]. This type of adenocarcinoma is thought to develop from atypical adenomatous hyper-

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plasia (AAH) through BAC [1,2]. However, the molecular mechanism by which AAH and BAC evolve into invasive adenocarcinoma has not yet been determined. In BAC, mutations of the epidermal growth factor receptor (*EGFR*) gene are often observed [3–5]. Recently, two study groups have reported that transgenic mice bearing *EGFR* mutations develop BAC and lung adenocarcinoma [6,7]. Since *EGFR* mutations may be involved in the evolution of adenocarcinoma, it is important to know the *EGFR* mutation status in the various parts of a lung adenocarcinoma. We report a patient with different *EGFR* mutation patterns in the invasive adenocarcinoma and in the surrounding AAH and BAC areas.

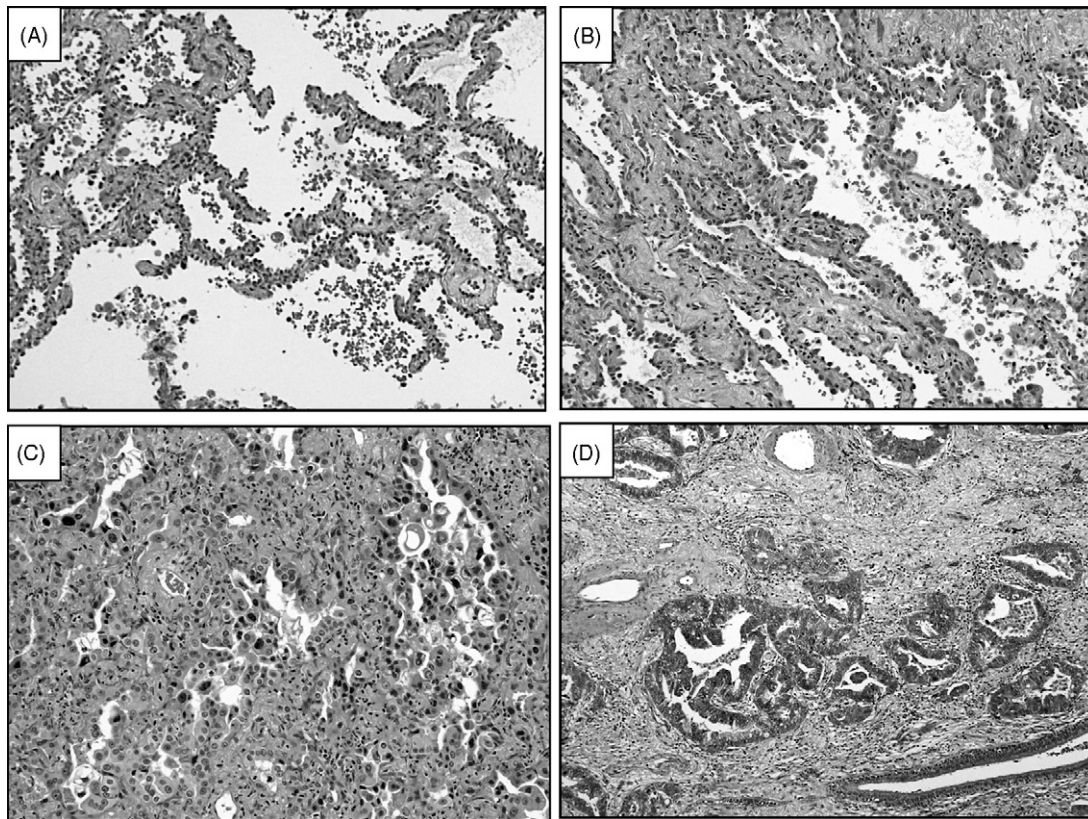
## 2. Case report

A 61-year-old, Japanese, female non-smoker was admitted for investigation of a nodule that was seen on chest radiography. A chest CT scan showed a 4-cm, solid nodule surrounded by ground-glass opacity (GGO) in the right upper lobe, along with enlargement of mediastinal lymph nodes (Fig. 1). A diagnosis of stage IIIA lung adenocarcinoma was made; the patient received combination chemotherapy followed by right upper lobectomy. Histological examination showed mixed adenocarcinoma with papillary and acinar subtypes and surrounding AAH and BAC areas (Fig. 2). On the CT scan, the AAH and BAC areas showed GGO, while the papillary and acinar subtypes formed the solid part of the nodule. Four months later, the patient developed mul-



**Fig. 1** Transverse, thin-section, computed tomography scan shows a 4-cm, lobulated nodule consisting of a solid portion and ground-glass opacity with coarse spiculations in the right upper lung lobe.

tle bilateral lung metastases. The patient was treated with several anti-cancer drugs. Two years after the recurrence was noted, the patient began taking gefitinib, an *EGFR* tyrosine kinase inhibitor. For 1 year, the pulmonary lesions improved remarkably, but then progressed. Gefitinib treatment was interrupted for 2 months, and then re-started. Though the lesions regressed for 1 month,



**Fig. 2** Histological findings of the different areas of a resected lung nodule. (A) Atypical adenomatous hyperplasia, (B) bronchioalveolar carcinoma, (C) papillary adenocarcinoma, and (D) acinar adenocarcinoma.

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