A Rare Case of Pleomorphic Carcinoma of the Lung Harboring an Anaplastic Lymphoma Kinase (ALK) Rearrangement

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Abstract

Molecular testing for anomalies, such as epidermal growth factor receptor mutations and anaplastic lymphoma kinase (ALK) rearrangement, is part of the current standard of care for non-small cell lung cancer, particularly adenocarcinoma. ALK rearrangement occurs most frequently in adenocarcinoma cells and rarely in non-adenocarcinoma cells. We herein report a rare case of pleomorphic lung carcinoma with ALK rearrangement in both its adenocarcinoma and spindle cell components. This case suggests the possibility of ALK rearrangement in pleomorphic carcinoma.

Key words: ALK rearrangement, pleomorphic carcinoma, spindle cell carcinoma

(Intern Med 54: 2741-2743, 2015)

(DOI: 10.2169/internalmedicine.54.4474)

Introduction

The EML4- anaplastic lymphoma kinase (ALK) fusion gene is a key oncogenic driver in a subset of patients with advanced non-small-cell lung cancer (NSCLC). ALK rearrangement is uncommon, occurring in from 2 to 7% of all NSCLC cases, and it is more frequently found in never-smokers or light ex-smokers, younger patients, and in those with adenocarcinomas (1-5). Patients with ALK rearrangement often manifest dramatic responses to ALK inhibitors, such as crizotinib, alectinib and ceritinib (6, 7). ALK rearrangement occurs most frequently in adenocarcinoma cells and rarely in non-adenocarcinoma cells (8), however, the targeted inhibition of ALK in patients with ALK rearrangement may lead to an improved survival and quality of life, in comparison to conventional cytotoxic chemotherapy. Therefore, physicians may consider performing ALK testing

in patients with not only adenocarcinomas, but also in those with non-adenocarcinomas, especially in cases where there is any possibility of ALK rearrangement based on the clinical background and no other effective treatments can be identified. We herein report a rare case of a pleomorphic lung carcinoma with ALK rearrangement in both its adenocarcinoma and spindle cell components.

Case Report

A 69-year-old woman who had never smoked presented with pain in the left side of her chest. Computed tomography revealed a 24-mm solitary tumor in the left lower lobe (Fig. 1) and single left hilar lymph node enlargement. Adenocarcinoma was diagnosed based on a pathological examination of a bronchoscopic biopsy specimen, and the clinical stage was determined to be IIIA (cT3N1M0). Surgical resection was performed, and the histological findings showed

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Received for publication November 7, 2014; Accepted for publication March 9, 2015

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the tumor to consist of an adenocarcinoma component (approximately 30%) (Fig. 2A) and malignant spindle cells (70%) (Fig. 2B). Ultimately, the tumor was diagnosed to be pleomorphic carcinoma, stage IIIA (T3N1M0). The tumor expressed wild-type epidermal growth factor receptors

(EGFRs), as revealed in molecular studies using peptide nucleic acid-locked nucleic acid polymerase chain reaction clamping. Immunohistochemistry showed a strongly positive expression of rearranged ALK (5A4; Nichirei Biosciences, Tokyo, Japan) not only in the adenocarcinoma component (Fig. 3A), but also in the spindle cell component (Fig. 3B). ALK rearrangement at 2p23 was confirmed in both components by fluorescence *in situ* hybridization using break-apart probes (LSI Medience, Tokyo, Japan). Thereafter, the patient received cisplatin plus vinorelbine as adjuvant chemotherapy.

Figure 1. Computed tomography on admission showing a 24-mm lung tumor in the left lower lobe.

Discussion

We herein report a rare case of pleomorphic carcinoma harboring an ALK rearrangement in both its adenocarcinoma and spindle cell components. Molecular testing for anomalies, such as EGFR mutations and ALK rearrangement, is part of the current standard of care for NSCLC, particularly adenocarcinoma. ALK rearrangement occurs most frequently in adenocarcinoma cells and rarely in non-adenocarcinoma cells (8). The ALK inhibitor crizotinib and next generation

Figure 2. Histopathological findings of resected lung specimens. (A) Hematoxylin and Eosin (H&E) staining showing a moderately differentiated adenocarcinoma; (B) H&E staining showing the spindle cell component of the tumor (magnification: $\times 200$).

Figure 3. Testing for ALK rearrangement by immunohistochemistry (IHC). (A) IHC showing strong positivity for ALK in the adenocarcinoma component of the tumor; (B) IHC showing the expression of ALK in the spindle cell component of the tumor (magnification: $\times 400$).

ALK inhibitors, such as alectinib and ceritinib, have shown promising activity in NSCLC patients with ALK rearrangements (6, 7). Although the benefit of administering ALK inhibitors to patients with non-adenocarcinoma harboring ALK rearrangements is unclear, the opportunity to provide a potentially life-extending treatment could be lost by overlooking the presence of such ALK rearrangement. Molecular testing guidelines recommend ALK testing in all patients with lung adenocarcinomas or mixed lung cancers with an adenocarcinoma component, irrespective of the patient characteristics, such as sex, race, and smoking status (8). The present case indicates that ALK rearrangement can also be present in pleomorphic lung carcinomas (both adenocarcinoma and spindle cell components). Pleomorphic carcinoma is generally characterized by frequent postoperative recurrence, a poor response to conventional chemotherapies and a disappointing clinical prognosis. Therefore, in those situations, molecular testing should thus be performed before the onset of recurrence. The decision to perform EGFR and ALK testing should be finally made based on an evaluation of the costs versus benefits for each patient. Because the specimens obtained in these patients tend to be small, such as a transbronchial biopsy specimens, these specimens may not represent the entire histology of the tumor, and therefore an adenocarcinoma component cannot always be excluded, and ALK testing should thus be performed even in cases with squamous or small cell histology if there is any possibility of ALK rearrangement based on the clinical background. Several reports have described ALK-positive squamous, small cell, and large-cell neuroendocrine carcinomas (9-11). The clinical background of the patient (e.g., female sex, young age, never smoker) may be useful in selecting the appropriate samples for testing (8). If recurrence occurs in the patient described in this report, then the administration of ALK inhibitors is planned. As for other rare driver mutations, such as RET and ROS1, a nationwide genomic screening system in Japan (LC-SCRUM-Japan) for the development of targeted therapies against advanced non-small lung cancers has recently been established (12).

The authors state that they have no Conflict of Interest (COI).

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