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Case Report

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Transformation to small-cell lung cancer as a mechanism of acquired resistance to crizotinib and alectinib

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Abstract

A 56-year-old woman, a never-smoker, had postoperative recurrence of anaplastic lymphoma kinase rearranged lung cancer. She achieved a partial response to treatment with an anaplastic lymphoma kinase tyrosine kinase inhibitor, crizotinib. After the tumor regrowth, crizotinib was switched to alectinib; once again a partial response was observed. At the second recurrence, transbronchial needle aspiration of the right paratracheal node was performed, which revealed cytological findings of small-cell carcinoma. While treatment with cisplatin–irinotecan chemotherapy made reduction of some tumor shadows, including the biopsied mediastinal lymph nodes, new, small, nodular shadows, highly suggestive of pulmonary metastases, were detected in both lung fields. This case may show proof of the transformation to small-cell lung cancer as a mechanism of resistance to anaplastic lymphoma kinase tyrosine kinase inhibitors in anaplastic lymphoma kinase rearranged tumor. However, this transformation may also be only one part of the resistance mechanism of the heterogeneous tumor.

Key words: small-cell lung cancer, ALK-positive lung cancer, transformation, acquired resistance

Introduction

Anaplastic lymphoma kinase (ALK) is a strong lung cancer oncogene identified in 2007 accounting for ~5% of causal genes in cases of non-small cell lung cancer (NSCLC). ALK is considered to be mutually exclusive to other driver mutations. Although ALK tyrosine kinase inhibitors (ALK-TKIs), including crizotinib and alectinib, are usually effective against ALK-positive lung cancer, resistance to them occurs. Studies are currently being conducted to clarify the mechanisms underlying acquired resistance and how to overcome them. Here we report a rare case, in which transformation to small-cell lung cancer (SCLC) was cytologically documented, probably upon acquired resistance to therapy with ALK-TKIs.

Case report

A 56-year-old woman, a never-smoker, had postoperative recurrence of ALK-positive lung cancer. Following left lower lobectomy with hilar and mediastinal lymph node dissection performed 4 years ago, she had been diagnosed as having pT3N2M0 adenocarcinoma with mixed subtypes (mucinous and papillary) (Fig. 1). She received adjuvant chemotherapy with cisplatin and vinorelbine. Her disease

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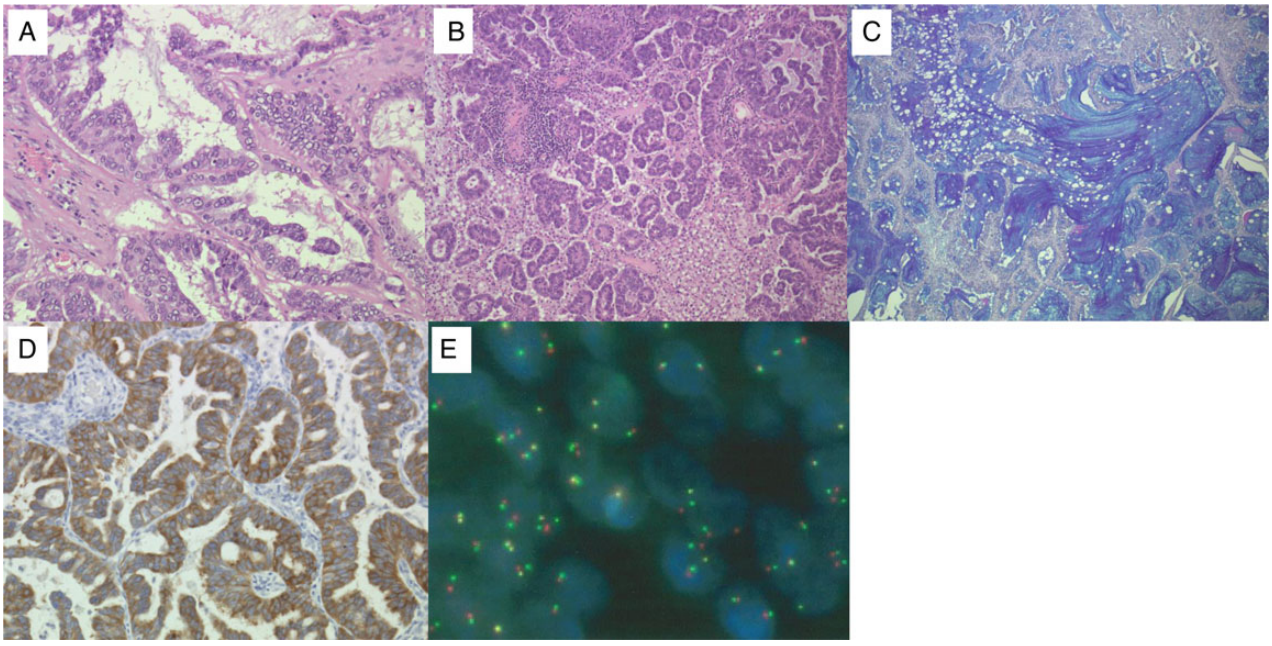

Figure 1. Surgical lung specimen. (A) and (B) are a hematoxylin- and eosin-stained section, respectively, and (C), an Alcian Blue-PAS stained section, showing papillotubular proliferation with dendritic stroma around the center of the tumor and accumulation of mucus in the alveolar space in the peripheral region. (D) Immunohistochemical analysis showing strong diffuse ALK positivity. (E) Break-apart fluorescent in situ hybridization showed ALK translocation.

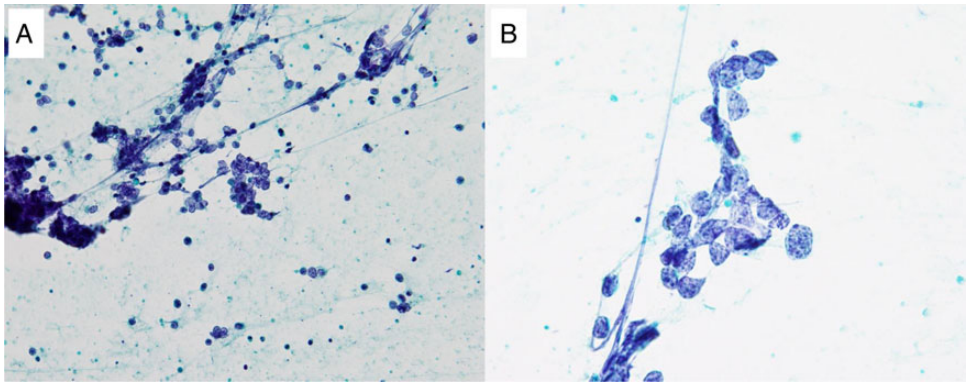

Figure 2. Transbronchial needle aspiration specimen. In cytology with Giemsa stain, small atypical cells characterized by a high nuclear/cytoplasm ratio and the absence of cytoplasm accompanied by salt-and-pepper chromatins are findings of small-cell carcinoma. (A) Low magnification. (B) High magnification.

relapsed 1 year after surgery with swollen mediastinal lymph nodes and multiple lung metastases. Six cycles of carboplatin–pemetrexed chemotherapy were performed, with a partial response (PR) as the best response. Three months later, computed tomography (CT) revealed progression of the recurrent tumors. Tumor samples of the surgical specimen were then tested for ALK, which was positive with immunohistochemistry staining and fluorescent in-situ hybridization.

Treatment with crizotinib was started, with a PR which lasted for 2 years. Then the tumor progressed again, and crizotinib was switched to alectinib, which was also effective and the patient achieved a PR. Eight months later, enlargement of mediastinal nodes and pulmonary nodules were detected, suggestive of the development of resistance to alectinib. Transbronchial needle aspiration (TBNA) of the right lower paratracheal node was performed for a re-biopsy of the tumor. Only the cytological specimen was obtained, which revealed small-cell carcinoma (Fig. 2). Increased level of the tumor marker neuron-specific enolase was observed, but the Pro-GRP expression level was normal. She received chemotherapy with cisplatin–irinotecan combination. Although CT performed after two cycles showed size reduction of the mediastinal lymph nodes and some pulmonary masses, new small granular and scattered nodular shadows over both lung fields were found to be increased in size and number (Fig. 3).

Discussion

Known mechanisms that cause resistance to ALK-TKIs include ALK secondary mutations, ALK amplification and bypassing downstream signaling in, for example, epidermal growth factor receptor (EGFR) and insulin-like growth factor 1 receptor pathways. However, ~25% are mediated by unknown mechanisms (1), and new mechanisms of resistance have been actively investigated. In contrast, ~15% of

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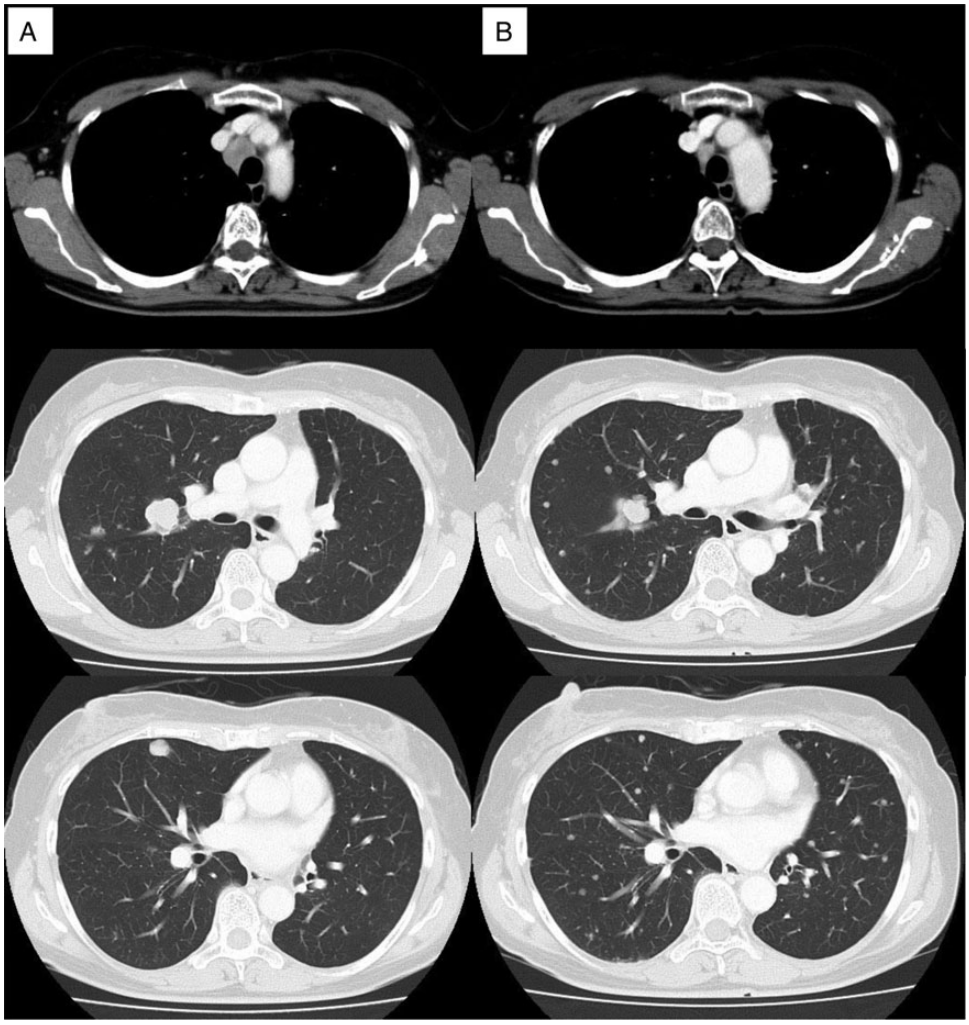

Figure 3. In computed tomography images before cisplatin–irinotecan, shown on the left side (A), the target lesion was reduced in size but nodular shadows scattered in both lung fields were increased in size and number than in CT images after cisplatin–irinotecan, shown on the right side (B).

resistance to first-generation EGFR-TKIs have been reported to consider the transformation to small-cell lung cancer (2,3).

Basic research and clinical data suggest that alectinib is effective against ALK-rearranged tumor with secondary mutation, which has already acquired resistance to crizotinib. In fact, alectinib is reported to have a high response rate of 55% in crizotinib-refractory tumors (4). Therefore, in the present case, an ALK secondary mutation was presumed to be the mechanism of the first resistance to crizotinib, which was then overridden by alectinib.

But the re-biopsy findings suggested that the subsequent resistance to alectinib was because of the transformation to small-cell carcinoma. To ensure this, the original surgical specimen was re-examined and confirmed to be devoid of any small-cell carcinoma component. A literature search using Pubmed yielded no such similar cases. However, in the present case, diagnosis of small cell carcinoma was made only based on morphological examination of the cytological specimens. Further, investigations such as immunohistochemical and genetic analyses of the specimens could not be adequately performed due to the limited quantity and quality of the sample. More invasive procedures to obtain specimens for molecular evaluations were judged to be clinically unjustified. Therefore, in this case, although the transformation of ALK-positive lung cancer to SCLC as an underlying cause of the acquired resistance to ALK-TKIs was strongly suggested, we could not make a definitive conclusion.

Cisplatin–irinotecan, which is the standard therapy for small-cell lung cancer in Japan (5), was administered, and the re-biopsied mediastinal lymph nodes and relatively large nodules were observed to be reduced in size. However, bilateral small granular and nodular shadows, likely to be pulmonary metastases, progressed. Since cisplatin–irinotecan combination is used also against NSCLC, it is difficult to determine which component of the tumor actually responded to the chemotherapy. However, the mixed response should be suggestive of the heterogeneity of the tumor.

The present case would support for attempts to re-biopsy of the tumor for selection of treatment, after acquired resistance. Nevertheless, as the heterogeneity of response to the cisplatin–irinotecan chemotherapy of the presented case suggests, the re-biopsied site only represents a partial picture of the resistance, and the mechanism of resistance may differ from one site to another.

Given the heterogeneity of the relapsed tumor, as well as the variety of acquired resistance mechanisms to target-based agents, re-biopsy via bronchoscope or needle aspiration might not always be appropriate. It is clinically challenging, however, to decide when to go on to more invasive diagnostic approach, such as

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thoracotomy (6). More research on the optimal diagnostic approach is warranted.

Conflict of interest statement

None declared.

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