Case Report

Genetic Heterogeneity of EGFR Mutation in Pleomorphic Carcinoma of the Lung: Response to Gefitinib and Clinical Outcome

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Somatic epidermal growth factor receptor (EGFR) mutations in exons 19 and 21 have been found in non-small cell lung cancer (NSCLC) and are associated with the therapeutic response to gefitinib in patients with advanced NSCLC. We report a case of pleomorphic carcinoma of the lung with different EGFR mutations. Prior to gefitinib treatment, an exon 19 deletion of EGFR mutation was positive in the specimens obtained from pleural effusion and left cervical lymph node, histologically proven to be adenocarcinoma. However, the response to gefitinib was poor and the patient died of progressive disease 4 months after the initiation of gefitinib therapy. Postmortem examination revealed the major histological component to be of the sarcomatoid or pleomorphic type with scant mixed adenocarcinoma, resulting in a histological diagnosis of pleomorphic carcinoma of the lung. Although the adenocarcinomatous tissue was still positive for exon 19 deletion of EGFR mutation alone, sarcomatous components had both the exons 19 deletion and 20 T790M mutation concomitantly, thought to be a gefitinib resistance mutation. Pulmonary pleomorphic carcinoma is a rare NSCLC composed of biphasic and heterogeneous malignant cell populations. The present case suggested that expression of different EGFR mutations is related to the biphasic histological appearance in pulmonary pleomorphic carcinoma.

Key words: EGFR – T790M – pulmonary pleomorphic carcinoma

INTRODUCTION

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that is strongly expressed in non-small cell lung cancer (NSCLC). Somatic EGFR mutations in exons 19 and 21 have been found in NSCLC and are associated with the therapeutic response to gefitinib in patients with advanced NSCLC, especially adenocarcinoma (1–4). Several Phase II trials of EGFR-tyrosine kinase inhibitors (TKIs) in patients positive for such EGFR mutations have yielded high response rates (5,6). On the other hand, recent studies have shown that the threonine-to-methionine substitution at amino acid position 790 (T790M) in exon 20 is related to gefitinib resistance (4,7,8). The secondary resistance mutation T790M has been identified in around 50% of progressing patients (4,9).

We experienced a case of NSCLC initially diagnosed as pulmonary adenocarcinoma presenting with EGFR exon 19 deletion mutation, but showed rapid regrowth and fatal outcome despite daily treatment with 250 mg of gefitinib. Postmortem examination indicated a scant adenocarcinomatous cell population still harboring an EGFR exon 19 deletion mutation, but the tumor cell population mainly consisted of spindle/sarcomatous components with both the exons 19 deletion and 20 T790M mutation in EGFR,
resulting in the histological diagnosis of pleomorphic carcinoma of the lung. Here, we present the clinical course and the response to gefitinib in this case.

CASE REPORT

A 58-year-old man who had never smoked visited our department because of a persistent non-productive cough in December 2006. Physical examination revealed left cervical lymph node swelling and chest radiography showed a giant mass in the left upper field (Fig. 1A). A diagnosis of pulmonary adenocarcinoma was made on the basis of the pathological findings of neck lymph node biopsy (Fig. 3A) and bronchofiberscopic cytology. Abdominal computed tomography revealed a right adrenal metastatic tumor. The patient underwent one course of systemic chemotherapy (cisplatin and docetaxel) from 20 December 2006. After the one course of systemic chemotherapy, chest radiography revealed an increase in size of the tumor and left pleural effusion (Fig. 1B), indicating progressive disease and downstaging of performance status (performance status = 3). As deletion mutation in exon 19 of EGFR was present in both neck lymph node and pleural fluid specimens, gefitinib (250 mg/day) was given. Chest radiography revealed transient decreases in the tumor size and pleural effusion (Fig. 1C). Three months after initiation of gefitinib treatment, the size of the thoracic mass and effusion increased again (Fig. 1D) and abdominal computed tomography also revealed enlargements of right adrenal and left post-abdominal metastatic masses (Fig. 2A and B). The patient died 1 month later and the autopsy findings indicated that the tumors from progressing thoracic and abdominal masses consisted mainly of a homologous sarcomatoid spindle-cell component. In the thoracic lesion, there was a scant component of malignant epithelial cells (likely adenocarcinoma). Thus, the disease had two histological elements, resulting in diagnosis of pulmonary pleomorphic carcinoma (Fig. 3B and C). The homologous sarcomatoid spindle-cell component had both an exons 19 deletion and 20 T790M mutation of EGFR. On the other hand, the adenocarcinomatous tumor component still had the 19 deletion.

Figure 1. Serial findings of chest radiography. (A) Before systemic chemotherapy, the giant mass occupied the left upper field. (B) After one course of systemic chemotherapy (cisplatin plus docetaxel), the tumor and left pleural fluid had increased. (C) One month after gefitinib treatment, the tumor and left pleural fluid had decreased. (D) Three months after initiation of gefitinib treatment, the tumor had increased again.
The occurrence of a sarcomatoid or pleomorphic component, with giant or spindle cells, is an uncommon but well-documented feature of NSCLC (10,11). These pleomorphic carcinomas account for 0.3% of all pulmonary malignancies (12). The tumors in the present case were found to be composed of a mixture of two basic cellular elements: adenocarcinoma and sarcomatous cells. At autopsy, more than 95% of the malignant tissues were composed of sarcomatoid...
tissues with only a scant amount of adenocarcinoma tissue. If there had been no adenocarcinomatous tissue component on postmortem examination, it would have difficult for us to diagnose the pleomorphic carcinoma.

Epidermal growth factor receptor gene analysis in the present case revealed that adenocarcinoma cells had an exon 19 deletion and sarcomatous cells had both the deletion 19 and 20 T790M EGFR mutations. The initial minor response to gefitinib in the present case seemed to be the reduction of adenocarcinoma elements harboring the exon 19 deletion. Recent studies using resected specimens indicated that exon 19 deletion or exon 21 L858R EGFR mutations was positive in two patients among three patients with pleomorphic carcinoma (13,14), although a presence of T790M, a secondary resistance mutation, was not examined. The expression of T790M in our case seemed to be related with the fatal outcome and rapid progression. It is likely that the expression of T790M mutation was induced only in sarcomatous cells after gefitinib administration and the tumor cells harboring the mutation had been enriched over time during the period of treatment. In general, it has been reported that progression-free survival time after initiation of EGFR-TKIs was 8–10 months in NSCLC patients with positive EGFR mutations (5,6). Compared with those reports, the response to gefitinib in the present case was small and transient. We speculated that tumor volume of adenocarcinoma initially taken from this patient was small or that the exon 19 deletion-positive cells in the present case were present at a low frequency.

Detection of T790M was actually reported in tumors from patients previously untreated with EGFR-TKIs, although it appeared to be extremely rare (4,9). We did not have evidence of the presence of T790M before therapy in the present case. However, it was possible that T790M mutation existed at a low frequency at the time of initial diagnosis. In future, careful examination of EGFR gene status using surgically resected specimens previously untreated with EGFR-TKIs in patients with pleomorphic carcinoma may provide new insight into the frequency of T790M in the sarcomatous elements.

Pleomorphic cell carcinoma has the concurrent presence of malignant epithelial and homologous sarcomatoid spindle cells co-expressing cytokeratin and vimentin to various degrees. Several immunohistochemical studies using pleomorphic carcinoma of the lung specimens suggested that sarcomatoid cells are metaplastic changes derived from transdifferentiation of malignant epithelial cells, because sarcomatoid cells retained variable phenotypic expression of epithelial markers (15,16). In the present case, the sarcomatoid tissue also exhibited exon 19 deletion mutant alleles concomitant with T790M in exon 20. It is still unclear whether early T790M acquisition is specific for sarcomatoid tissue. In addition, there was no information about the relationship between biological and EGFR gene differences between sarcomatoid and malignant epithelial elements.

In summary, we described a case of pulmonary pleomorphic carcinoma with two different histological types exhibiting EGFR mutations conferring ‘sensitivity’ and ‘resistance’ to EGFR-TKIs. This case suggests that pulmonary pleomorphic carcinoma is composed of dual and heterogeneous cell populations both biologically and with regard to EGFR gene status.

Conflict of interest statement
None declared.

References

EGFR mutation heterogeneity of pleomorphic carcinoma