CASE REPORT

Adenoid Cystic Carcinoma of the Lung with an EGFR Mutation

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Abstract

An 80-year-old woman was referred to our hospital due to the presence of a mass that was identified on a chest X-ray. A further investigation demonstrated advanced adenoid cystic carcinoma of the lungs. Anti-cancer chemotherapy with docetaxel was carried out and the lesion remained as stable disease. Subsequently, pleural effusion was detected, and an investigation of the pleural effusion revealed the existence of malignant cells with an epidermal growth factor (EGFR) mutation. Gefitinib was administered and the pleural effusion resolved. This is the first case of a positive EGFR mutation of adenoid cystic carcinoma of the lung with a favorable response to an EGFR-tyrosine kinase inhibitor.

Key words: lung cancer, EGFR, salivary gland, adenoid cystic carcinoma

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Introduction

Recent studies have clarified that non-small cell lung cancer (NSCLC) involves genetic mutations known to play critical roles in the progression to metastatic disease. Mutations in epidermal growth factor receptor (EGFR) are reported in patients with NSCLC, and the inhibition of tyrosine kinase demonstrates favorable outcomes. This EGFR mutation is typically found in cases of lung adenocarcinoma. However, other carcinomas, such as small cell carcinoma, have been reported to rarely be positive (1-4). We herein demonstrate lung adenoid cystic carcinoma, usually seen in the salivary glands, associated with an EGFR mutation that exhibited a good response to an EGFR-tyrosine kinase inhibitor (TKI), gefitinib.

Case Report

An 80-year-old woman was referred to our hospital due to a mass on a chest X-ray. Chest CT revealed a mass in left S3. Positron emission tomography (PET)/CT demonstrated an uptake of fludeoxyglucose (¹⁸F) (FDG) at the site of the mass as well as the uptake of FDG in the mediastinal lymph nodes and left inguinal lymph node. According to the patient’s request, she was referred to Aichi Medical University. A biopsy of the left inguinal lymph node was performed. The histology findings were compatible with atypical epithelial cell proliferation with a cribriform pattern, which is the characteristic finding of adenoid cystic carcinoma. Immunohistochemistry with TTF-1 was negative, although histology demonstrated an adenocarcinoma-like pathology. The carcinoma contained some S-100- and p63-positive tumor cells, considered to be myoepithelial differentiated tumor cells. There was no proven primary site except for the lungs in the clinical setting. Taking these findings into consideration, we diagnosed this case to be advanced adenoid cystic carcinoma of the lungs (Fig. 1).

Anti-cancer chemotherapy with docetaxel (60 mg/m²) was carried out eight times, and the lesion remained as stable
disease. Thereafter, the patient wished to return to our hospital. Three months later, an accumulation of pleural effusion was detected, and an investigation of the pleural effusion revealed the existence of malignant cells with an EGFR mutation (exon 19 deletion (L747-T751 deletion) by a PCR invader method (Fig. 2). Cytology of the pleural effusion made it difficult to differentiate from adenocarcinoma; therefore, we clinically diagnosed the patient’s status as progression of adenoid cystic carcinoma of the lung. Gefitinib (250 mg/day) was administered, and the pleural effusion resolved (Fig. 3). Unfortunately, an accumulation of pleural effusion again occurred six months after EGFR-TKI initiation, despite the continuation of EGFR-TKI, and she died seven months after the progression.

The EGFR mutation status of the inguinal lymph node was investigated using the peptide nucleic acid-locked nucleic acid (PNA-LNA) PCR clamp method at Aichi Medical University, although the results were negative. A re-examination with the PCR invader method demonstrated an EGFR mutation at exon 18 (G719S).

**Discussion**

We herein experienced a case of adenoid cystic carcinoma with an EGFR mutation. The administration of an EGFR-TKI, gefitinib, decreased the pleural effusion and size of tumor. To the best of our knowledge, this is the first case of a positive EGFR mutation in adenoid cystic carcinoma with a favorable response to a TKI.

NSCLC with EGFR mutations is known to be a driver mutation that plays a critical role in the pathogenesis of lung cancer. EGFR is expressed on the cell surface in a substantial percentage of NSCLCs. A good response achieved with EGFR-TKIs is seen in patients with somatic mutations within the EGFR-TK domain, particularly exon 19 deletions, exon 21L858R and exon 18G719X (5). In contrast, the exon 20 T790M mutation is associated with acquired resistance to TKI therapy (5). The EGFR mutation status is critical for the proper selection of chemotherapeutic drugs (6, 7). Current guidelines recommend testing all patients with metastatic NSCLC adenocarcinoma for the presence of activating EGFR mutations and the use of an EGFR-TKI as first-line therapy in patients with adenocarcinoma and a known EGFR mutation (8). Indeed, approximately 6-37% of adenocarcinoma patients have EGFR mutations. Ethnic differences exist, and the rate of EGFR mutations is frequently higher in patients from areas in East Asia (9).

Salivary gland-type lung carcinomas are uncommon, representing less than 1% of all lung tumors. The annual incidence of tracheal cancer is approximately 0.1 per 100,000. Adenoid cystic carcinoma and mucoepidermoid carcinoma are the two most common subtypes, and salivary gland-type lung carcinomas are generally reported to have a good prognosis (10-12). In addition, adenoid cystic carcinomas of the tracheobronchial tree are identical to adenoid cystic carcinomas of the salivary glands. Adenoid cystic carcinomas typically form polypoid lesions in the trachea or main stem bronchi; however, they may form infiltrative plaques with longitudinal or circumferential extension and often breach the cartilaginous plate. Occasionally, adenoid cystic carcinoma can present with multiple episodes of recurrence with late metastasis. The primary treatment modalities are surgery and radiation therapy, although no randomized trials have been conducted to date. It is uncertain if chemotherapy al-
Figure 2. Progression of adenoid cystic carcinoma. Compared to the findings observed in Fig. 1, pleural effusion progressed on a chest X-ray (A). Chest CT (D and E) revealed the progression of the mass in left S3 and the accumulation of pleural effusion. PET/CT demonstrated the uptake of FDG in the mass as well as the uptake of FDG in the left pleura (B). Pleural effusion cytology revealed many clusters of atypical cells, which demonstrated increased levels of nucleus/cytoplasm ratio and chromatin (C). On cytology, differentiation between adenocarcinoma and adenoid cystic carcinoma was difficult.

Figure 3. Clinical course after the initiation of EGFR-TKI treatment. Gefitinib (250 mg/day) was administered. Compared to the previous chest X-ray shown in Fig. 2, pleural effusion had resolved (A) and the primary site of adenoid cystic carcinoma had decreased (B and C).

ters the natural history of metastatic adenoid cystic carcinoma at any site (10-12). Although carcinomas other than that of the lungs have not been reported to be EGFR-TKI-sensitive, there are several trials investigating EGFR mutations in adenoid cystic carcinoma. In one study, based on screening for salivary gland carcinoma, two drug-sensitizing EGFR exon 19 deletion mutations (E746-A750 deletion) were identified in a case of adenoid cystic carcinoma and
mucoepidermoid carcinoma of the parotid gland. The authors found that one of 11 patients had EGFR mutations (13). In contrast, Macarenco and colleagues demonstrated that none of the 12 patients in their series had EGFR mutations in cases of adenoid cystic carcinoma (14). Moreover, Huo and colleagues reported that no EGFR mutations were detected in 24 cases of lung adenoid cystic carcinoma (15). In the current case, we identified an exon 19 deletion, which is similar to the findings of previous reports. There is a difference in the rate of occurrence of EGFR mutations between ethnic groups regarding adenocarcinoma of the lung. Therefore, whether ethnic factors influence the EGFR mutational status in these tumors must be determined, and it is necessary to investigate the frequency of EGFR mutations in cases of adenoid cystic carcinoma in Asian patients.

We found a discrepancy in the results of EGFR mutation tests in the present case. Goto and colleagues reported that the results of their study showed that all five EGFR mutation tests had comparable success rates (over 90%) using formalin-fixed samples. However, it should be recognized that even when utilizing the same technologies, differences in the reagents, DNA quality, software programs and, crucially, primer design and amplicon size have a significant influence on the direct sequencing success rate and potential for detecting mutations (16). Additionally, multiple EGFR mutations in a single tumor have been reported. Kobayashi and colleagues reported that 14% of EGFR mutated tumors had multiple EGFR mutations (17). Another plausible explanation is that docetaxel inhibited a specific population of EGFR mutated tumors.

The present case clearly demonstrates the merit of EGFR-TKI therapy. As noted above, however, ethnic differences exist. Indeed, Asian patients have a high incidence rate of EGFR mutations in cases of adenocarcinoma compared to Caucasians. Therefore, we recommend EGFR mutation screening in patients with rare tumors of the lungs, although 24 cases of lung adenoid cystic carcinoma in Asians have recently been reported to have no EGFR mutations (15). The clinical course of the present case demonstrates that EGFR-TKI treatment can improve the clinical outcome in cases of advanced adenoid cystic carcinoma of the lung. Investigations of the EGFR mutation status are required in such cases, although the positive rate is low, and more studies are needed to determine the role of EGFR mutations in the onset of adenoid cystic carcinoma of the lung in Asian patients.

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

References