Case Report

Gingival Metastasis of ALK Rearranged Non-Small Cell Lung Cancer

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Keywords

Lung cancer · ALK rearrangement · Gingival metastasis · Heterogeneity · Molecular targeted therapy

Abstract

Background: Metastasis to oral soft tissues is rare and account for only 0.1% of all oral malignancies. Oral cavity metastasis tends to be male-predominant, and lung cancer is the leading cause. Targeted therapies for advanced ALK rearranged non-small cell lung cancer (NSCLC) have shown a promising higher response than cytotoxic chemotherapy. Gingival metastasis usually shows poor prognosis. However using ALK inhibitor to ALK-positive advanced NSCLC may show longer survival. **Case:** A 64-year-old male who was diagnosed non-small cell carcinoma (NSCC) favoring adenocarcinoma presented with gingival metastasis. After first-line chemotherapy, ALK rearrangement was revealed in both primary lesion and gingival metastasis, and therefore the patient was treated with alectinib. Tumor response of the primary site and gingival lesion were obtained, however he presented with intestinal metastasis that lead to bowel obstruction and passed away. **Conclusion:** Our case showed good response to primary tumor and gingival metastasis but not to intestinal obstruction. ALK inhibitor often shows high response rate and long survival for ALK rearrangement NSCLC, however ALK rearranged positive NSCLC with gingival metastasis may have poor prognosis.

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Introduction

Oral metastatic tumors are rare and metastasis to oral soft tissues account for only 0.1% of all oral malignancies [1]. Metastasis to the soft tissues involves gingiva (57%), tongue (27%) and tonsil (8%) [2]. Leading tumor types of oral cavity metastasis among men are lung, followed by kidney and liver; in woman, breast, female genital organs, and lung [3].

Approximately 3–7% of patients with NSCLC have ALK rearrangement [4]. Targeted therapy for advanced ALK rearranged NSCLC have been developed and show a higher response and longer response duration than cytotoxic chemotherapy, by the first-generation ALK inhibitor, crizotinib and the second-generation, alectinib and ceritinib. In the longer follow-up, median survival time was shown more than 47 months [5]. Comparing ALK inhibitors in first-line setting, clinical trials showed the superiority of alectinib of ALK-positive advanced NSCLC [6, 7]. Gingival metastasis usually shows poor prognosis, however, we have known the survival in ALK positive NSCLC by using ALK inhibitor. We report a patient having gingival metastasis of ALK rearranged NSCLC treated with alectinib.

Case Report

A 64-year-old Japanese male patient presented with fever and cough. The patient had no smoking history with medical history of hypertension and diabetes. His Eastern Cooperative Oncology Group (ECOG) performance status was 1. A chest radiograph and subsequent computed tomography (CT) scan revealed a nodule in left lower lobe and mediastinal lymphadenopathy and transbronchial biopsy (TBB) revealed non-small cell lung cancer favoring adenocarcinoma, which was scattered spindle or polygonal cell proliferation below the bronchial epithelium accompanied with myxoid stroma (Fig. 1A). No evidence of glandular structure or cytoplasmic mucus was observed while thyroid transcription factor-1 (TTF-1) was positive in immunohistochemical (IHC) analysis. After one month, positron emission tomography-computed tomography (PET-CT) scan showed rapid growth of primary tumor and multiple metastatic lymph node. In addition, impending left bronchial obstruction, esophageal stenosis, multiple lung metastases, right pleural dissemination, peritoneal metastasis, and multiple bone metastases, which was determined to be adenocarcinoma of the left lower lobe at cT4N3M1c Stage IVB. Three days after diagnosis, patient presented to the emergency department complaining dyspnea. He was firstly treated with palliative radiotherapy for impending left bronchial obstruction. An indolent mass on his upper anterior gingiva was revealed (Fig. 2A) when performing dental treatment before using bisphosphonate. A gingival biopsy specimen also revealed similar tumor cells proliferating in the ulcer base as primary lesion (Fig. 2C). After radiotherapy, CT scan revealed rapid progression and he was treated with the first-line cisplatin (CDDP) /pemetrexed (PEM). Four days after first cycle, the IHC of ALK protein turned out to be positive (Fig. 1B). ALK Histofine IHC was also strongly positive in gingival biopsy (Fig. 2D). After one cycle, chemotherapy achieved progression disease (PD) (Fig. 1C), and he underwent second-line alectinib for 9 weeks. Reduction of the primary region, plural effusion (Fig. 1D) and gingival mass was obviously revealed (Fig. 2B), however presented aspiration pneumonia followed by acute respiratory distress syndrome due to bowel obstruction and passed away.

Discussion

We report a patient having gingival metastasis of ALK rearranged NSCLC treated with alectinib, which showed response to primary lesion and gingival metastasis but not to intestinal metastasis.

Metastasis of malignant tumors to the oral soft tissues account for 0.1% of all oral malignancies [1]. The most common site for metastasis is the attached gingiva (57%), followed by the tongue (27%), tonsil (8%), palate (4%), lip (3%), buccal mucosa (1%), and floor of mouth (<1%) [2]. Oral cavity tends to be male-predominant, and lung cancer is the leading cause. The leading primary tumor types among men are lung followed by kidney, and liver. In woman, top primaries are breast, genital organs, and lung [3]. In most patients, primary tumors have been detected before the metastatic spread to the oral cavity.

Metastasis to soft tissues often grows rapidly causing pain, difficulty in chewing, dysphagia, and bleeding, however clinical distinction between benign and malignant lesion is difficult. In our case, asymptomatic gingival metastasis was found after detecting primary site. The clinical presentation could be deceiving and unusual, therefore, especially in cases with metastasis, searching oral cavity aggressively and performing biopsy is necessary since prognosis is dependent on the extent of metastasis. Mean survival is reported to be poor, which ranged from 7 to 8 months [8, 9]. Treatment strategies are often focused on quality of life, including local resection, radiotherapy as the local treatment and chemotherapy as the systemic treatment for other metastasis [3].

Pathogenesis of oral metastasis is unclear, but thought to be a multistage process in which cells detach themselves from the primary tumor and transported by lymphatic or blood vessels. In oral soft tissues, chronically inflamed mucosa, especially gingiva, has rich capillary network, which can trap the malignant cells and cause metastasis [10]. A successful metastatic colony is the result of a process known as the “invasion-metastasis cascade”, which involves the invasion of the tumor into the peripheral tissue leading to intravasation of cancer cells into blood or lymphatic vessels [11]. Invasion and dissemination are basic features of cancer cells, achieved mainly by “epithelial-to-mesenchymal transition” (EMT), where cancer cell acquire a mesenchymal phenotype [12]. In present case, IHC analysis of vimentin of TBB turned out to be positive, which showed the mesenchymal cell differentiation. This may suggests the possibility of EMT. Since gingival metastasis showed similar tumor cells proliferating in stroma as primary lesion, the primary lesion may had been easy to metastasize to intestine submucosal stroma and showed metastasis to intestine that led to bowel obstruction. In addition, histopathologic study and immunohistochemistry revealed NSCLC, favoring adenocarcinoma, which led to the detection of ALK rearrangement. Our case indicates the importance of performing immunohistochemistry when histological type is unclear.

Rearrangements of ALK gene accounts for approximately 3–7% of NSCLC patients with higher rates observed in younger, never or light smokers of adenocarcinoma [4]. Rapid development of targeted therapies for advanced ALK rearranged NSCLCs have shown higher response and longer response duration than cytotoxic chemotherapy. Currently, the first-generation ALK inhibitor, crizotinib, the second-generation, alectinib and ceritinib, and the third-generation, brigatinib have received the approval from the Food and Drug Administration (FDA) for the treatment. Alectinib is an oral highly selective ALK TKI with an objective response rate (ORR) of 93.5% for crizotinib-naïve patients in phase I-II trial (AF-0001JP) [13]. Treatment was continued, reaching a 3-year progression-free survival (PFS) of 62%, and a 3-year overall survival (OS) of 78% [14]. Furthermore, phase III trial compared alectinib versus crizotinib showed superiority of alectinib verses crizotinib: lower chance of progression (41

vs. 68%), higher 12-month event-free survival rate (68.4 vs. 48.7%), and higher response rate (82.9 vs. 75.5%) [7]. In our case, we introduced alectinib expecting longer survival and possibility of higher response rate than palliative radiotherapy, which is one of the treatment. Median OS of Palliative thoracic radiotherapy in NSCLC is known to be approximately 4–12 months [15]. The patient was able to undergo alectinib and showed good response to primary tumor and gingival metastasis, however intestinal metastasis showed progression causing bowel obstruction. One of the reasons could be the rapid progression of the tumor. Gingival metastasis often indicates tumor aggressiveness, and in our case, pathological findings that mesenchymal cells accounted for most of the tumor also suggests aggressiveness. In addition, tumor heterogeneity of ALK fusion could be suggested since primary lesion and gingival metastasis, ALK IHC of which was strongly positive, responded to alectinib, but not to intestinal metastasis.

Conclusion

Gingival metastasis is a rare type of metastasis that often indicate poor prognosis despite of local resection, radiotherapy, and chemotherapy. ALK inhibitor often shows high response rate for ALK rearrangement NSCLC, which leads to longer survival than non-driver mutation NSCLC. Our case did not response to ALK inhibitor and this suggests ALK rearranged positive NSCLC with gingival metastasis may have poor prognosis.

Acknowledgement

The authors would like to thank Enago (<https://www.enago.jp>) for the English language review.

Statement of Ethics

The authors have no ethical conflicts to disclose. Written informed consent has been obtained from the patient.

Disclosure Statement

Yusuke Okuma: Research funding, Chugai Pharmaceutical Co. Ltd. and Takeda Co. Ltd.

Funding Sources

None.

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Fig. 1. Histopathologic study of TBLB showed scattered spindle or polygonal cell proliferation below the bronchial epithelium accompanied with myxoid stroma (A). The tumor cells were immunoreactive for ALK protein (B). CT scan before (C) and after (D) introducing alectinib. Reduction of the primary region and plural effusion was revealed.

Fig. 2. Physical examination showing mass on his upper anterior gingiva before treatment (A). Reduction of the lesion was seen after introducing alectinib (B). Histopathologic study of gingival biopsy revealed similar tumor cells proliferating in the ulcer base as primary lesion (C). ALK immunostaining was also strongly positive (D).