Case Report

Bone Metastasis of Non-Small-Cell Lung Cancer Showing Pathological Complete Response to Osimertinib Monotherapy

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Keywords

Bone metastasis · Non-small-cell lung carcinoma · Osimertinib · Pathological complete response

Abstract

A 70-year-old man with lung adenocarcinoma had undergone right lower lobectomy and lymph node dissection. Only 6 months later under adjuvant uracil and fluorouracil therapy, the patient developed a solitary bone metastasis in the right 8th rib. Due to positive mutation of epidermal growth factor receptor (EGFR) exon 21 L858R in the primary cancer, the patient received osimertinib monotherapy, leading to massive calcification of the osteolytic bone metastasis with significant decrease of standard uptake value on positron emission tomography. After 12 months of osimertinib monotherapy, slight enlargement of the ground glass nodule, i.e., presumed noninvasive lung cancer, in the right upper lobe, and no further occurrence of metastatic foci made us to resect both the lung nodule and the bone metastasis. Pathological examination showed the lung nodule to be noninvasive adenocarcinoma and the bone metastasis to have no viable cancer cells. The patient was discharged on the 8th postoperative day without any complication. On developing a therapeutic strategy for advanced/recurrent EGFR mutation-positive lung adenocarcinoma, oncologists should note the possibility of pathological complete response to newly developed EGFR tyrosine kinase inhibitors including osimertinib for a presumed cure of oligometastatic lung adenocarcinoma.

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Introduction

Lung cancer is one of the most common malignancies in the world, with 1.8 million new cases and 1.6 million deaths each year [1]. These facts imply that lung cancer has extremely high malignant potential, and the vast majority of patients with lung cancer eventually die. Therefore, the 5-year survival rate of primary lung cancer is extremely poor being 21.7% [2].

The World Health Organization classifies lung cancers into adenocarcinoma, squamous-cell carcinoma, neuroendocrine tumor, large-cell carcinoma, adenosquamous carcinoma, sarcomatoid carcinoma, and other and unclassified carcinoma [3]. Lung cancer however is roughly grouped into small-cell lung carcinoma and non-small-cell lung carcinoma (NSCLC) from the difference of therapeutic strategy. Of the NSCLCs, the ratio of adenocarcinoma is increasing compared to those of other subtypes due to the spread of smoking cessation.

Chemotherapy has a great effect on small-cell lung carcinoma [4] but has nominal or limited efficacy against NSCLC [5]. Chemotherapy with severe side effects however has long been the mainstay in the treatment of NSCLC due to the limited number of available therapeutic options. Chemotherapy including some kind of a platinum agent is often discontinued due to the intolerable side effects even when favorable response to the chemotherapy continues.

During the past 2 decades, 2 major therapies with markedly different antitumor mechanisms compared to conventional chemotherapies have emerged in the treatment of NSCLC, that is, immune checkpoint inhibitors [6, 7] and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) [8]. Osimertinib is a potent irreversible EGFR TKI effective for NSCLCs expressing not only EGFR mutations but an EGFR T790M resistance mutation [9]. Here, we report a rare case of bone metastasis of NSCLC showing pathological complete response to osimertinib monotherapy.

Case Report

A 70-year-old man with a gradually growing nodule in the right lower lobe (Fig. 1a) was referred to our department. Positron emission tomography/computed tomography (PET/CT) showed a spiculated mass with a maximum standard uptake value of 11.0 and no other hot spots neither in the regional nodes nor in the distant organs. The serum carcinoembryonic antigen (CEA) level was as high as 47.3 (normal range: 0.0–5.0) ng/mL. Under the diagnosis of stage IB (T2aN0M0) NSCLC, the patient underwent a thoracoscopy-assisted right lower lobectomy and lymph node dissection. Pathological study showed the tumor to be adenocarcinoma (Fig. 1b) with positive mutation of EGFR exon 21 L858R without VRAF V600E mutation, ROS1 rearrangement, and PD-L1 expression. The patient started to receive an oral compound of uracil and tegafur, i.e., UFT, as an adjuvant therapy 2 months after the operation. Follow-up CT showed an osteolytic lesion in the right 8th rib, and confirmatory PET/CT also showed a presumed bone metastasis with a maximum standard uptake value of 5.4 (Fig. 2a). The serum CEA level at this point was as high as 46.7 ng/mL. After obtaining fully informed consent regarding antitumor mechanisms, efficacy, and side effects of the therapy, we treated the patient with osimertinib monotherapy (80 mg/day). An elevated serum CEA level of 55.5 ng/mL at the start of osimertinib monotherapy decreased to 11.7 ng/mL and to a normal range in 6 weeks and 6 months after the initiation of osimertinib monotherapy, respectively. Chest CT showed no size reduction of the rib metastasis but massive calcification clearly demarcating the affected rib with the osimertinib monotherapy for 12 months (Fig. 2b). A

Fig. 1. Image and pathological findings of NSCLC. **a** Spiculated mass with pleural indentation was observed on CT. **b** Magnified view of the resected lung tumor showed atypical cell proliferation in a papillary fashion. NSCLC, non-small-cell lung carcinoma; CT, computed tomography.

Fig. 2. Image and pathological findings of the bone metastasis. **a** Osteolytic change and FDG accumulation were observed in the right 8th rib on PET/CT. **b** PET/CT showed calcification and decrease of FDG uptake in the affected rib. **c** Cut slices of the resected rib showed no evident tumor and whitish oval and polygonal lesions (arrows). **d** Low-magnified view of the affected rib showed no viable cancer remnants and massive calcification (arrow) corresponding to the whitish and polygonal lesions observed on cut slices. PET/CT, positron emission tomography/computed tomography; FDG, fluorodeoxyglucose.

slight increase in size of the preexisting ground glass nodule in the right upper lobe (Fig. 3a, b), ipsilaterality of the 2 lesions, and oligometastatic concept made us to treat the patient with surgery both to the lung nodule and the affected rib, leading to the pathological diagnosis of noninvasive adenocarcinoma of the lung lesion (Fig. 3c) and no viable cancer-cell remnants in the bone lesion (Fig. 2c, d). The patient was discharged from the hospital 8 days after the operation without any complication. Due to the patient's request, the patient was followed up without any systemic treatments.

Fig. 3. Image and pathological findings of the noninvasive adenocarcinoma. **a** CT showed a small ground glass nodule in the right upper lobe. **b** CT showed slight enlargement of the ground glass nodule. **c** Magnified view of the nodule showed atypical cells growing in a lepidic fashion. CT, computed tomography.

Discussion

The eighth edition Tumor, Node, Metastasis staging system distinguishes single extrathoracic metastasis (M1b) from multiple extrathoracic metastases (M1c), defining the former as stage 4a and the latter as stage 4b [10]. When adding some aggressive local therapy to systemic therapy, patients with stage 4a NSCLC shows a more favorable clinical outcome, i.e., prolonged survival or even presumed cure than those with stage 4b NSCLC. In other words, stage 4a NSCLC is regarded as oligometastatic disease despite the lack of a clear definition of oligometastasis [11]. Surgical oncologists therefore should take the possible cure of patients with stage 4a NSCLC into consideration on developing the therapeutic strategy.

Under an adjuvant therapy with UFT, this patient developed bone metastasis only 6 months after surgery. Strictly speaking, solitary bone metastasis in this case should be called oligorecurrence. Although even a clinical effect of local therapy on oligometastasis itself has not yet been fully evaluated, both oligometastasis and oligorecurrence with prior no or nominal systemic therapy should have similar characteristics that oncologists can aim to cure them with effective systemic therapy followed by some definitive local therapy. In this case, we treated the patient with surgery after confirming the marked response of bone metastasis to osimertinib monotherapy. Oligometastatic or oligorecurrent NSCLC should be treated with surgery, when feasible and appropriate, after confirming the relatively long-term efficacy of some kind of systemic therapy against the metastatic or recurrent focus.

Chemotherapy has long been recommended for patients with advanced or recurrent NSCLC. Chemotherapy can be discontinued once the target foci have completely disappeared. Chemotherapy however generally causes various side effects which heal in a relatively short time or last for a long time, leading to reluctant interruption or discontinuation of the therapy even if the target foci respond well to the chemotherapy.

NSCLC patients with a programmed death 1 ligand and EGFR mutation can be treated with immune checkpoint inhibitors [6, 7] and EGFR-TKIs [8, 9], respectively. These 2 types of therapeutic agents have completely different mechanisms of action from those of chemotherapeutic agents and can often be administered for a long time until cancer progression. Various EGFR-TKIs are now available in the treatment of malignant tumors. Of these, gefitinib, erlotinib, afatinib, and osimertinib, that is, first, second, and third generation TKIs, respectively, can be used in the treatment of patients with NSCLC. Each drug has more efficacy and less toxicity than those of chemotherapeutic agents. The advent of gefitinib surprised oncologists around the world with both its overwhelming effect and the development of lethal interstitial

pneumonia. EGFR T790M, the main mechanism of TKI resistance, leads to the development of afatinib and osimertinib. Of these, osimertinib has an excellent antitumor effect with least adverse effects compared with those of afatinib [9].

Evaluation of an antitumor effect on bone metastasis is generally difficult that Response Evaluation Criteria in Solid Tumor [12] classifies bone metastases as nontarget lesions. In fact, we could speculate the bone metastasis to respond well to the osimertinib monotherapy with the PET/CT findings but could not preoperatively evaluate the bone metastasis having no viable cancer cells due to the lack of shrinkage of the bone metastatic focus. Pathological complete response of bone metastasis observed in this case does not mean but possibly suggests the cure of the recurrent NSCLC. In conclusion, we experienced a rare case of bone metastasis of NSCLC showing pathological complete response to osimertinib monotherapy.

Statement of Ethics

The paper is exempt from Ethical Committee approval due to the nature of reporting based on daily clinical practice. Informed written consent was obtained from the patient for the publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H. Shintani contributed the design of the report. S. Oura drafted the manuscript. T. Yamaguchi treated the patient. S. Makimoto revised the manuscript. All the authors have read and approved the final version of the manuscript.

Data Availability Statement

All data generated during this study are included in this article. Further inquiries can be directed to the corresponding author.

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