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Case Report

Successful Chemotherapy for Diffuse Cystic Lung Metastases during Targeted Therapy with Osimertinib in a Patient with Non-Small-Cell Lung Cancer: A Literature Review and a Rare Case Report

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Keywords
Diffuse cystic lung metastasis · Non-small-cell lung cancer · Osimertinib

Abstract
Introduction: Diffuse lung cysts occur owing to several diseases; however, diffuse cystic lung metastases are very rare in the case of lung cancer. We report a rare case of diffuse cystic lung metastases from lung adenocarcinoma and reviewed previously reported cases of cystic lung metastases for lung cancer and determined their characteristics. ***Case Presentation:*** A 78-year-old Japanese woman with advanced lung adenocarcinoma was positive for the epidermal growth factor receptor gene mutation exon 21 L858R and had been treated with osimertinib. She presented with multiple bilaterally positioned thin-walled lung cysts and pneumothorax. Lung cysts were diagnosed as cystic lung metastases from lung cancer, and carboplatin, pemetrexed, and pembrolizumab were subsequently administered. All cysts markedly decreased in size, and some disappeared. ***Conclusion:*** Effective treatment methods for cystic lung metastases from lung cancer have not been reported. To our knowledge, this is the first case of cystic lung metastases that were successfully treated with chemotherapy.

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Introduction

Diffuse thin-walled (<4 mm thick) lung cysts are associated with several diseases, such as lymphangioleiomyomatosis, interstitial lung disorders, pulmonary lymphoproliferative disorders, and Birt-Hogg-Dube syndrome. Primary lung cancer and metastasis typically form nodules or thick-walled (>4 mm thick) cavities and rarely thin-walled cysts. Diffuse cystic lung metastases from sarcoma and benign metastasizing leiomyoma have been often reported [1]; however, their occurrence from lung cancer is rare. Here, we report a case of diffuse cystic lung metastases from lung adenocarcinoma that disappeared or decreased in size after successful chemotherapy.

Case Report

A 78-year-old Japanese woman without a past medical or smoking (including secondhand smoking) history presented with a cough that had persisted for a month. Chest X-ray and computed tomography (CT) scan revealed a nodule (9.5 × 4.6 cm) in the left upper lobe. Laboratory examination revealed elevated serum carcinoembryonic antigen (CEA) levels (474.7 ng/mL). Brain magnetic resonance imaging revealed multiple brain metastases. Whole-body positron emission tomography (PET)-CT demonstrated ^{18}F-fluorodeoxyglucose (FDG) uptake in lung tumors and bone metastases. A transbronchial lung biopsy revealed adenocarcinoma with immunohistochemistry positive for TTF-1 and Napsin A, indicating primary lung carcinoma. Lung adenocarcinoma of clinical stage IVB (T4N3M1c) was confirmed. Epidermal growth factor receptor (EGFR) gene mutation exon 21 L858R was found to be positive and program death-ligand 1 was expressed at low levels (1–24%). Osimertinib was administered as the first-line treatment, and the patient's condition remained stable. Partial response was subsequently observed in all lesions, and serum CEA levels simultaneously decreased significantly (32.4 ng/mL). After 18 months of osimertinib treatment, the patient presented with sudden right chest pain and dyspnea. Chest X-ray (Fig. 1) and CT scan (Fig. 2) showed right-sided pneumothorax and multiple bilateral thin-walled (<4 mm thick) cysts without nodules, respectively. Osimertinib was discontinued because of suspected adverse respiratory effects. The patient underwent chest tube placement for pneumothorax and week-long right lung expansion. Laboratory tests revealed an increase in serum CEA levels (252.7 ng/mL) (Fig. 3). One month after osimertinib discontinuation, the number and size of the lung cysts continued to increase (Fig. 1c). Therefore, the bilateral thin-walled diffuse cysts were considered lung metastases, while the appearance of pneumothorax was due to ruptured cystic metastasis. Carboplatin (AUC 5), pemetrexed (500 mg/m^2), and pembrolizumab (200 mg/body) were administered for recurrent cancer.

All diffuse lung cysts markedly decreased in size after chemotherapy initiation, while some disappeared, as shown by chest X-ray and CT scans (Fig. 1d, 2c). PET-CT imaging after two cycles of chemotherapy showed abnormal uptake of FDG in the primary lung cancer, bone, and lymph nodes but not in the remaining diffuse lung cysts (data not shown). During the 4-month follow-up, almost all cysts had disappeared, and some had shrunken. The patient has maintained this chemotherapy regimen to date.

Discussion

Lung adenocarcinoma is a common histological type of lung cancer. Its characteristics indicated by CT images commonly include a peripheral tumor mass or ground-glass nodule in a primary lesion and multiple nodules in lung metastases. Diffuse lung

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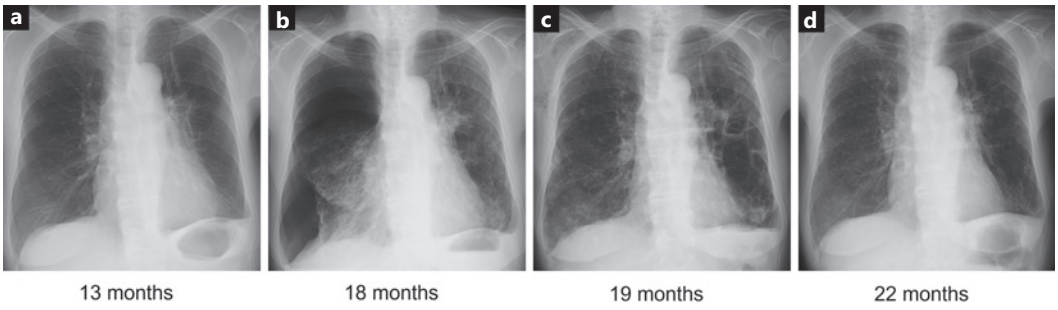

Fig. 1. Chest X-ray during chemotherapy chest X-ray showing the lungs at the initiation of osimertinib therapy at 13 months (**a**), appearance of pneumothorax at 18 months (**b**), enlargement of the cysts with osimertinib withdrawal at 19 months (**c**), and disappearance of the cysts after four cycles of second-line therapy at 22 months (**d**).

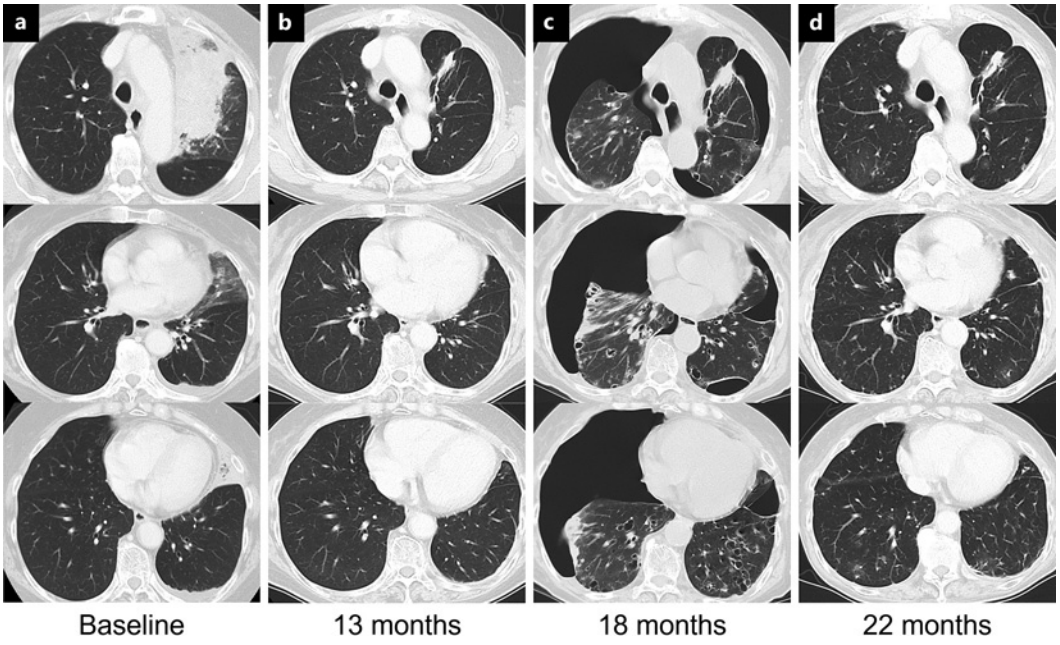

Fig. 2. CT scan during chemotherapy CT scan showing the baseline before the initiation of osimertinib (**a**), the presence of a nodule in the left upper lobe of the lung at 13 months from the initiation of osimertinib therapy (**b**), the appearance of pneumothorax and diffuse cysts at 18 months (**c**), and the disappearance of the cysts after four cycles of second-line therapy at 22 months (**d**). CT, computed tomography.

cysts can occur in several diseases. Only 6 cases of diffuse cystic metastasis from lung cancer after systematic chemotherapy have been reported (Table 1) [2–7], of which adenocarcinoma was the predominant histological type (5 of 6 cases). All patients received targeted therapy (tyrosine kinase inhibitors or immune checkpoint inhibitors) before the presentation of diffuse cystic lung metastases. The present case also involved the diagnosis of adenocarcinoma and targeted therapy with osimertinib. Three patients received chemotherapy for cystic metastases, but the sizes of their lung cysts remained the same or increased after treatment, indicating that platinum doublet with/without

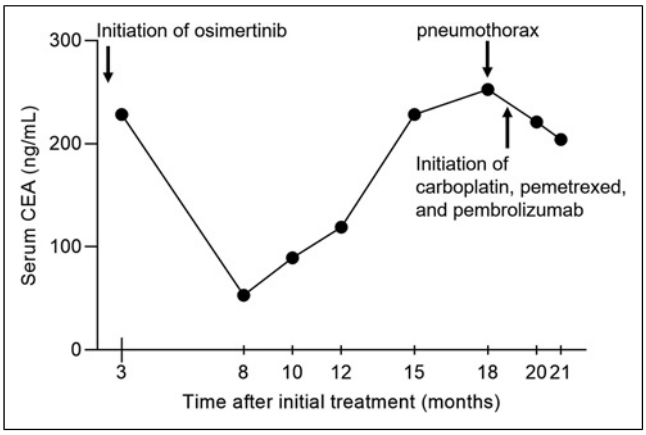

Fig. 3. Dynamic monitoring of CEA and its timeline serum CEA levels indicate the clinical response of the initial treatment, disease progression, and second line of therapy. CEA, carcinoembryonic antigen.

bevacizumab and docetaxel plus ramucirumab might be ineffective for cystic lung metastases. However, the efficacy of platinum doublet plus immune checkpoint inhibitors has not been reported. In previous studies, platinum doublet plus pembrolizumab resulted in longer progression-free survival and overall survival and higher overall response rate than pembrolizumab monotherapy or platinum doublet administration in patients with EGFR mutation-positive lung cancer who had failed on EGFR-tyrosine kinase inhibitor therapy [8, 9]. Therefore, we chose carboplatin, pemetrexed, and pembrolizumab to treat cystic lung metastases. Subsequently, these bilateral diffuse cysts disappeared or decreased in size, and serum CEA levels decreased.

The mechanisms underlying the appearance of diffuse cystic lung metastases remain unclear. Mermershtain et al. [10] reported that the occurrence of pulmonary cystic metastases can be related to effective targeted therapy. In fact, the previously reported 6 cases and our case used tyrosine kinase inhibitors or immune checkpoint inhibitors immediately before the appearance of diffuse cystic lung metastases. Two hypotheses regarding cystic metastasis have been previously proposed. First, diffuse cysts are formed owing to ischemic necrosis of the terminal bronchioles and alveoli caused by tumor cell infiltration of small vessels and capillaries [11]. Second, obstruction of tumor cells in the terminal and respiratory bronchioles creates a check valve, resulting in excessive peripheral ventilation [12]. In the former hypothesis, alveolar structures are necrotic, and the disappearance of cysts is not expected. Meanwhile, in the latter, cyst formation may be reversible once the check valve is released. In our case, diffuse lung cysts shrank with chemotherapy, and some disappeared, suggesting that chemotherapy alleviated the tumor obstruction in the bronchioles, eliminated the check valve, and resulted in cyst reduction.

PET-CT showed the absence of FDG accumulation in the lung cysts possibly owing to the small size of tumor cells speculated to obstruct the bronchioles. The possibility of modification by treatment cannot be ruled out because PET-CT was performed after chemotherapy.

In summary, we report the first case of diffuse cystic lung metastasis that disappeared or decreased in size with the administration of platinum doublet plus immune checkpoint inhibitor chemotherapy. This study establishes a novel treatment for cystic lung metastases. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534711).

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Table 1. Summary of the cases representing diffuse cystic lung metastases from lung carcinoma after CTx

Author	Age/ sex	Histological type	Mutation	PD-L1	CTx before/after presentation of cysts		Cysts size after treatment	Follow-up
Albahary et al. [2]	40/F	Adenocarcinoma	ALK	NA	Crizotinib	NA	NA	NA
Ryu et al. [3]	56/F	Adenocarcinoma	NA	NA	Gefitinib	NA	Increase in size	PFS more than 15 months
Sakhri et al. [4]	35/F	Adenocarcinoma	exon 19 deletion del E746-A750	NA	Erlotinib	CDDP+PEM+BEV	NA	Died after 27 months
Song et al. [5]	39/M	Adenocarcinoma	exon 21 T/G hybrid positivity	NA	Erlotinib	CBDCA+PEM	No change	NA
Rampinelli et al. [6]	72/M	Squamous cell carcinoma	NA	NA	Nivolumab	NA	NA	NA
Muto et al. [7]	60/F	Adenocarcinoma	negative	5%	Nivolumab	DTX+RAM	Increase in size	Died after 38 months
Present case	78/F	Adenocarcinoma	exon 21 L858R	1–24%	Bsimertinib	CBDCA+PEM +pembrolizumab	Decrease in size	Alive

CTx, chemotherapy; F, female; M, male; ALK, anaplastic lymphoma kinase; NA, not available; CDDP, Cisplatin; PEM, pemetrexed; BEV, bevacizumab; CBDCA, carboplatin; DTX, docetaxel; RAM, ramucirumab; PFS, progression-free survival.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors met the ICMJE criteria for authorship. A.M., T.O., T.T., Y.S., M.N., S.I., and Y.Ka. contributed to the study design and wrote the manuscript. A.K. and Y.Ki. conceived the study and revised the manuscript. All authors approved the final version of the manuscript.

Data Availability Statement

The data used to support the findings of this study are included in the article. Further inquiries can be directed to the corresponding author.

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