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Case Report

Diffuse Cystic Metastases in the Lung after Nivolumab Treatment in a Patient with Non-Small Cell Lung Cancer: A Case Report

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Keywords
Non-small cell lung cancer · Diffuse cysts · Immune checkpoint inhibitor · Radiology · Diagnosis

Abstract
Although diffuse cysts in the lung can be found in many diseases, they are uncommon in metastatic lung adenocarcinoma. They are even more unusual after the administration of immune checkpoint inhibitors. A case of lung adenocarcinoma that developed diffuse cysts in the lungs during treatment with nivolumab is reported. The patient was a 60-year-old woman with postoperative recurrent lung adenocarcinoma in mediastinal lymph nodes and pleural dissemination. After first-line treatment with cisplatin, pemetrexed, and bevacizumab, computed tomography (CT) showed disease progression. Treatment was then switched to nivolumab. After 5 courses of nivolumab, CT showed multiple ground-glass nodules in her lungs. After 4 more courses of nivolumab, the ground-glass nodules increased in size, and cystic air spaces appeared in their centers. The patient did not have any symptoms. Laboratory tests showed no evidence of infection or nivolumab-induced pneumonitis. Sialyl Lewis X-i antigen increased, and positron emission tomography showed abnormal uptake of ^{18}F-fluorodeoxyglucose in these lesions. Considering this evidence, the cystic lesions were diagnosed as multiple lung metastases. Various differential diagnoses should be considered when diffuse cystic lesions are found in the lungs after the administration of immune checkpoint inhibitors.

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Introduction

Diffuse cysts in the lung can be found in many diseases, but rarely in metastatic lung adenocarcinoma [1]. The presence of diffuse cysts after the administration of immune checkpoint inhibitors is even more unusual. A case of lung adenocarcinoma that developed diffuse cystic lesions in both lungs during treatment with nivolumab is presented.

Case Report/Case Presentation

A 60-year-old woman with no history of neoplastic disease was noted to have an abnormality on a screening chest X-ray. Computed tomography (CT) showed a lung tumor in the right middle lobe. Tumor tissue obtained by transbronchial lung biopsy was diagnosed as lung adenocarcinoma. Positron emission tomography (PET) scan and brain magnetic resonance imaging (MRI) did not show distant metastases. A right middle lobectomy was performed. The pathological stage was T1bN1M0 stage IIA. Epidermal growth factor receptor (EGFR) gene mutation and translocation of anaplastic lymphoma kinase gene were both negative. The programmed death-ligand 1 (PD-L1) tissue proportion score was 5% by PD-L1 IHC 28-8 Pharm Dx (SRL, Inc., Tokyo, Japan). After surgical resection, carboplatin and TS-1 were administered as adjuvant chemotherapy [2]. Unfortunately, mediastinal lymph node metastases and pleural dissemination were seen on PET-CT 18 months after the surgical resection. Cisplatin, pemetrexed, and bevacizumab were administered as the first-line treatment for recurrent cancer. The patient was treated with 4 courses of these three agents, followed by pemetrexed as maintenance treatment. After 4 courses of maintenance treatment, CT showed disease progression. Nivolumab was then administered as second-line treatment. After 5 courses of nivolumab, multiple ground-glass nodules were identified (Fig. 1). Four more courses of nivolumab were administered. Subsequent CT showed that these ground-glass nodules were increasing in size, and cystic air spaces appeared in the centers of these ground-glass nodules (Fig. 2). PET-CT showed abnormal uptake of ^{18}F-fluorodeoxyglucose

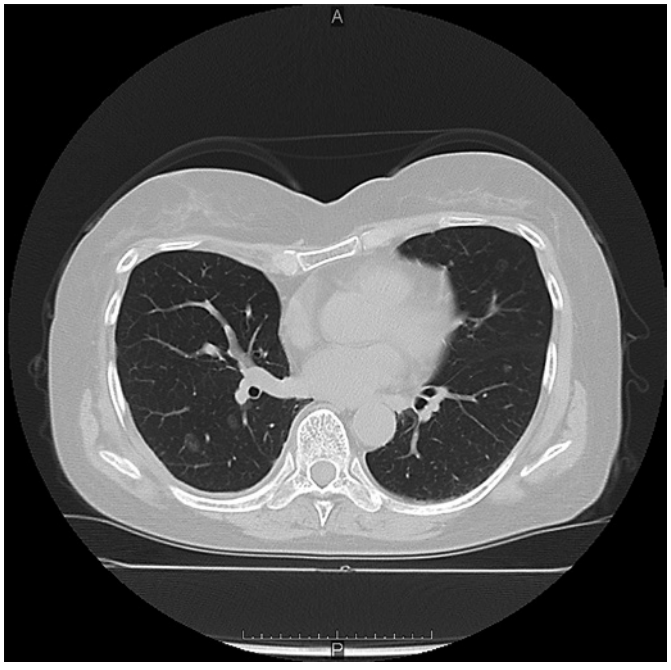

Fig. 1. Multiple ground-glass nodules appear on CT after 5 courses of nivolumab.

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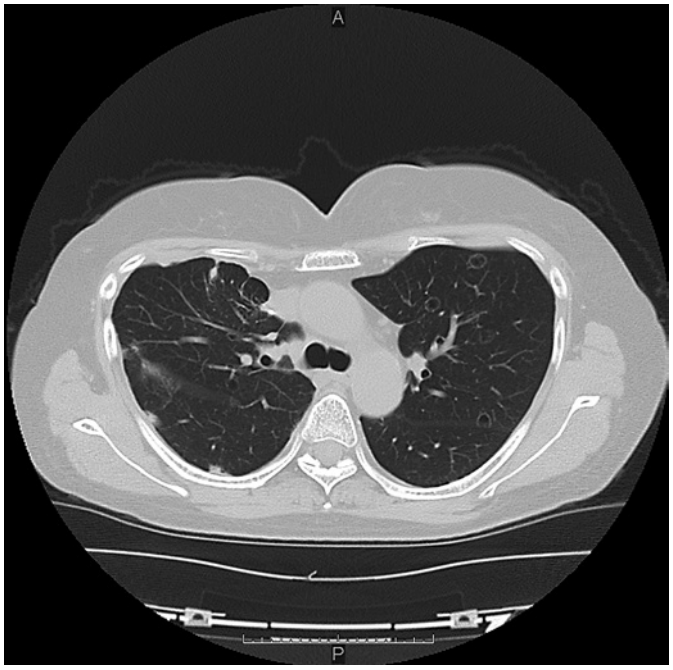

Fig. 2. Ground-glass nodules have become larger, and cystic air spaces have appeared in their centers.

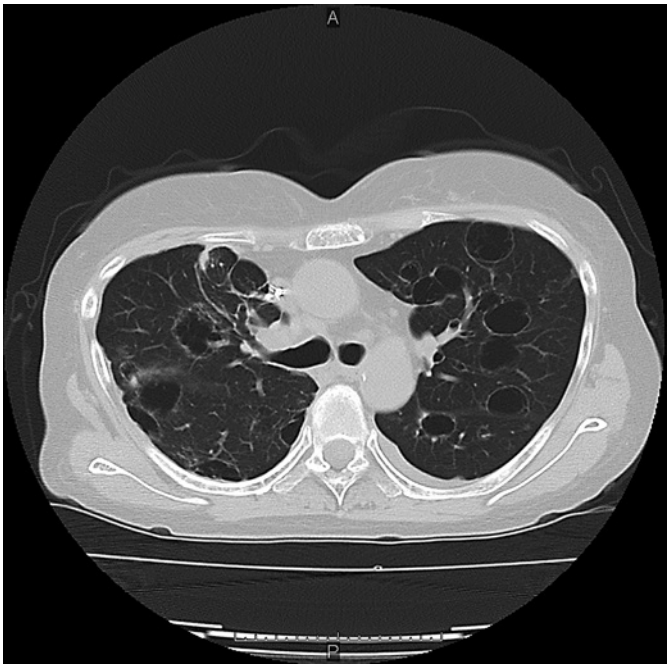

Fig. 3. Cystic lesions have spread and increased in number.

in these multiple ground-glass nodules with cystic air spaces and pleural dissemination. The patient had no respiratory symptoms. On laboratory testing, the white blood cell count was 5,300/mm^3, C-reactive protein was 0.03 mg/L, sialylated carbohydrate antigen KL-6 was 329 U/mL, and sialyl Lewis X-i increased from 250 to 500 U/mL. Based on this clinical evidence, these multiple lung nodules with cystic air spaces were considered lung metastases. The chemotherapy was switched to docetaxel and ramucirumab. After 7 courses, multiple brain metastases appeared on MRI, and whole-brain radiation therapy was then conducted. Her performance status deteriorated, and she received best supportive care.

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Thirty-eight months after the recurrence, she died from brain metastases due to the lung cancer. Three months before her death, CT showed that the cystic lesions had increased in size (Fig. 3).

Discussion/Conclusion

Lung adenocarcinoma is the most common histological type of non-small cell lung cancer. The general appearance of lung adenocarcinoma on CT is a ground-glass nodule in a primary lesion and multiple nodules in lung metastases. If diffuse cystic lesions in a lung cancer patient are found after a relatively short period of time, the common radiological differential diagnoses include desquamative interstitial pneumonia, usual interstitial pneumonia, lymphocytic interstitial pneumonia, pneumocystis pneumonia, and pulmonary cystic metastasis [1]. A few reports have mentioned that metastatic lung adenocarcinoma presented as multiple thin-walled cavities [3–5]. Song et al. [3] reported the occurrence of cavitation of lung metastases following EGFR-tyrosine kinase inhibitor therapy. They noted that these diffuse cystic changes on imaging can occur following effective targeted therapy. Wan et al. [4] reported a case of diffuse cystic lung adenocarcinoma with a pathological diagnosis. Their case demonstrated diffuse cystic lesions in both lungs at the first visit. They mentioned the difficulty of differential diagnosis. Zhang et al. [5] reported a case with rapidly progressive diffuse cystic lesions diagnosed as metastatic lesions of lung adenocarcinoma. The similarity between these cases is that they were all nonsmokers. This may have some effect on this type of carcinogenesis that results in multiple cysts. With regard to immune checkpoint inhibitors, there have been only a few cases that developed multiple cystic lesions in the lung [6, 7]. Rampinelli et al. [7] reported a case considered an atypical response to nivolumab. Their case showed lung metastases replaced by cystic lesions on imaging. They discussed the cyst development mechanism and mentioned the interaction between PD-L2 and repulsive guidance molecule domain family member B expressed in lung tissues [8]. On the other hand, Gorospe et al. [6] reported a case with cystic lesions considered to be nivolumab-induced pneumonitis.

In the present patient, chemotherapy and immune checkpoint inhibitor therapy were administered for her recurrent cancer before the appearance of cystic lesions. However, interstitial pneumonia, nivolumab-induced pneumonitis, and pneumocystis pneumonia were considered to have been ruled out because the inflammatory reaction and sialylated carbohydrate antigen KL-6 did not increase. Sialyl Lewis X-i increased again at the appearance of cystic lesions. The present patient did not show a clinical response to nivolumab, and her diffuse cystic lesions presented following the development of ground-glass nodules. According to these findings, these cystic lesions were diagnosed as multiple lung metastases.

After the administration of immune checkpoint inhibitors, diffuse cystic lesions can arise as an atypical response [7], immune-related pneumonitis [6], infection, and pulmonary metastases. The diagnosis is a challenging step. The limitation of this report is that a pathological diagnosis was not obtained. Lung biopsy should likely be performed if there is rapid progression of cystic lesions.

In summary, a case of lung adenocarcinoma developing a rare radiographic finding of diffuse cystic lesions after the administration of nivolumab was presented. This case indicates that various differential diagnoses should be considered when diffuse cystic lesions appear in the lung after the administration of immune checkpoint inhibitors.

Statement of Ethics

Written, informed consent was obtained from the patient for the publication of this case report.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization and investigation: Satoshi Muto. Resources: Yuki Ozaki, Takuya Inoue, Naoyuki Okabe, Yuki Matsumura, Takeo Hasegawa, Yutaka Shio. Supervision: Hiroyuki Suzuki. Writing: Satoshi Muto and Hiroyuki Suzuki.

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