Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9612-17
Intern Med 57: 2223-2226, 2018
http://internmed.jp

【 CASE REPORT 】

Reversible Restrictive Lung Disease in Pseudomesotheliomatous Carcinoma in a Lung Harboring a *HER2*-mutation

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Abstract:
Pseudomesotheliomatous carcinoma of the lung is very rare, and reversible restrictive lung disease with pseudomesotheliomatous carcinoma has not yet been previously reported. We herein report a patient with *HER2*-positive non-small-cell lung cancer (NSCLC) showing pseudomesotheliomatous carcinoma who was successfully treated with bevacizumab combination chemotherapy. A 56-year-old Japanese woman with advanced NSCLC presented with dyspnea. We administered chemotherapy with cisplatin (75 mg/m^2) plus pemetrexed (500 mg/m^2) plus bevacizumab (15 mg/kg), followed by pemetrexed plus bevacizumab. After eight cycles of maintenance chemotherapy, chest CT demonstrated a marked tumor reduction and an improvement of the right lung volume. The vital capacity was thereafter found to have significantly increased according to pulmonary function tests.

Key words: HER2, lung cancer, pseudomesotheliomatous carcinoma, restrictive lung disease

(Intern Med 57: 2223-2226, 2018)
(DOI: 10.2169/internalmedicine.9612-17)

Introduction

Pseudomesotheliomatous carcinoma of the lung is very rare, with a reported incidence among all lung cancers of 0.46% (1). Reversible restrictive lung disease with pseudomesotheliomatous carcinoma in non-small cell lung cancer (NSCLC) patients harboring *human epidermal growth factor receptor-2* (*HER2*)-mutation has not yet been previously reported. Because of its rarity and clinical features, there are fewer evidence-based therapies available for pseudomesotheliomatous carcinoma of the lung compared to other types of NSCLC. A novel, effective treatment for NSCLC with pseudomesotheliomatous carcinoma is therefore needed.

We herein describe a patient with *HER2*-positive lung cancer showing pseudomesotheliomatous carcinoma who was successfully treated with bevacizumab combination chemotherapy and thereafter demonstrated a significant improvement in the symptoms of restrictive lung disease.

Case Report

A 56-year-old Japanese woman presented with dyspnea. She was not occupationally exposed to asbestos and had never smoked. Chest radiography and computed tomography (CT) revealed diffuse pleural thickening and a reduced volume of the right lung and narrowing of the intercostal spaces (Fig. 1A, C and D). A transbronchial lung biopsy of the mass was performed; the pathological diagnosis was adenocarcinoma. ^{18}F-fluorodeoxyglucose (FDG) positron-emission tomography (PET) demonstrated FDG accumulation in an area of diffuse pleural thickening (Fig. 1B). Molecular testing with next-generation sequencing revealed a *HER2* mutation in exon 20 insertion. We administered chemotherapy with cisplatin (75 mg/m^2) plus pemetrexed (500 mg/m^2) and bevacizumab (15 mg/kg) every 3 weeks, followed by pemetrexed plus bevacizumab. After eight cycles of maintenance chemotherapy, CT and PET demonstrated a marked tumor reduction and an improvement of diffuse

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Received: June 5, 2017; Accepted: December 20, 2017; Advance Publication by J-STAGE: March 9, 2018
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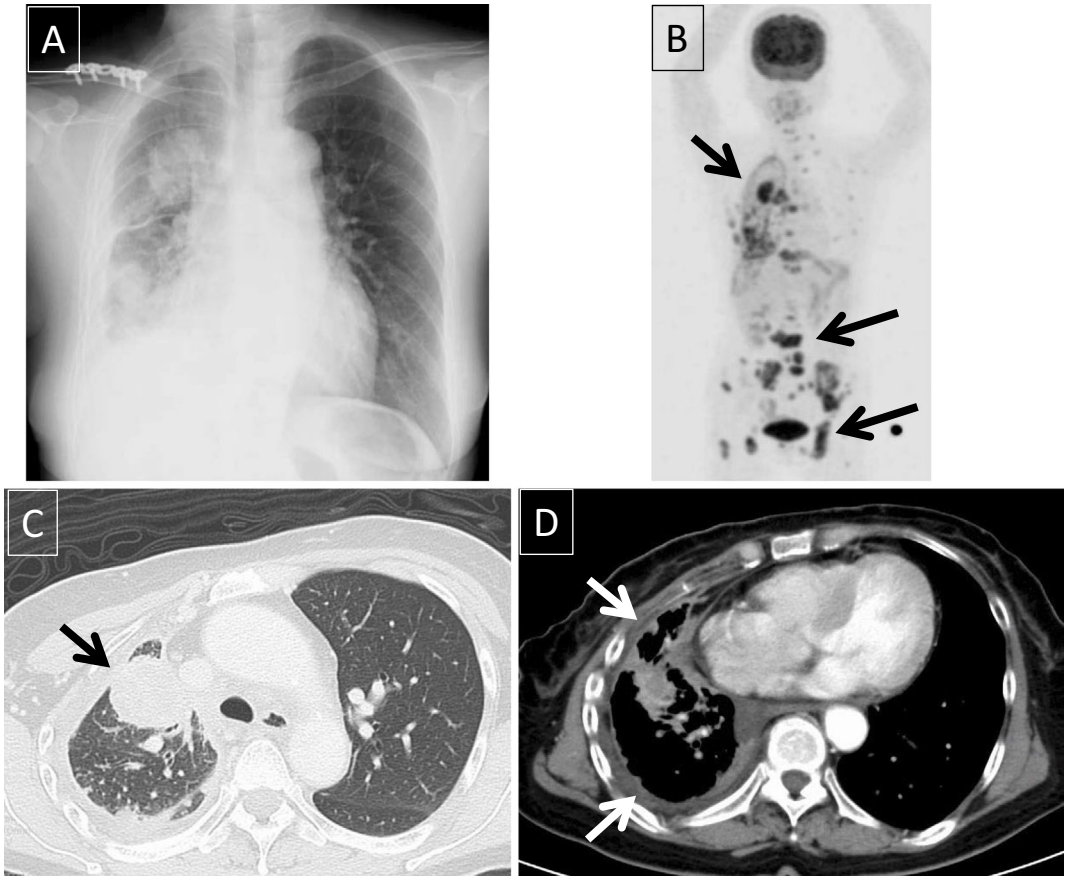

Figure 1. **A: Chest radiograpy showing a mass with diffuse pleural thickening and a reduced volume of the right lung. B: PET-CT demonstrating FDG accumulation in the mass and diffuse pleural thickening and multiple bones before chemotherapy (arrow). C, D: Chest CT demonstrating a mass and diffuse pleural thickening and reduced volume of the right lung with narrowing of the intercostal spaces (arrow).**

pleural thickening and the right lung volume (Fig. 2). The vital capacity and peak expiratory flow then was observed to significantly increase according to pulmonary function tests (Fig. 3).

Discussion

Reversible restrictive lung disease of lung cancer patients is generally observed in cases with malignant pleural effusion or obstructive atelectasis due to the presence of a tumor. However, reversible restrictive lung disease with pseudomesotheliomatous carcinoma as observed in our patient has not yet been reported. Pseudomesotheliomatous carcinoma was first reported by Harwood et al. in 1976, among lung cancer patients with extension to the pleura (2). Pseudomesotheliomatous carcinoma of the lung is very rare, with a reported incidence among all lung cancers of 0.46%. It was reported that 87% of pseudomesotheliomatous carcinoma patients had a smoking history and 76% of such cases had an asbestos exposure history (3). Smoking and asbestos have thus been considered as causes of pseudomesotheliomatous carcinoma carcinogenesis.

A case of pseudomesotheliomatous carcinoma harboring an *epidermal growth factor receptor* (*EGFR*) mutation without occupational asbestos exposure was recently reported, with narrowing of the intercostal spaces (4). Although previous pseudomesotheliomatous carcinoma reports did not describe the incidence of oncogenes, such as *EGFR* mutation or *HER2* mutation, the present case might indicate that the *HER2* mutation could play an important role in the development of pseudomesotheliomatous carcinoma of the lung, as our patient had no other risk factors (e.g., smoking history, asbestos exposure).

HER2 mutation is a rare somatic mutation that represents 2-3% of lung cancers, and there has been no report of its comorbidity with pseudomesotheliomatous carcinoma showing intercostal space narrowing (5, 6). Regarding the outcomes of chemotherapy for advanced *HER2*-mutant lung cancers, Mazieres et al. reported the outcomes with conventional chemotherapy excluding *HER2* targeted drugs. The response rate and the median progression free survival for patients receiving first-line chemotherapy were 43.5% and 6.0 months [95% confidence interval (CI): 5.0-7.1], respectively (n=93) (7). In addition, Falchook et al. reported a case of advanced non-small cell lung cancer harboring a *HER2* mutation which achieved a sustained antitumor effect to la-

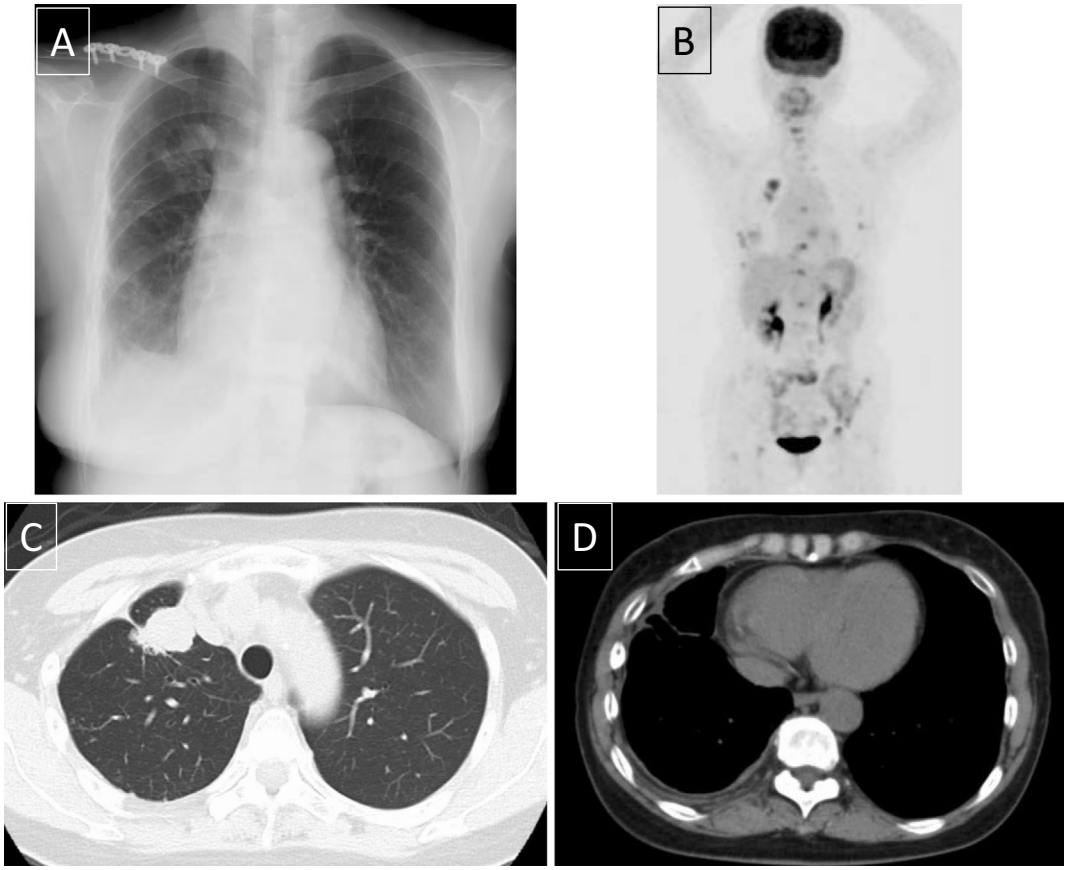

Figure 2. **Chest radiograpy and CT demonstrating a marked tumor reduction and an improvement of diffuse pleural thickening and the right lung volume after eight cycles of maintenance chemotherapy.**

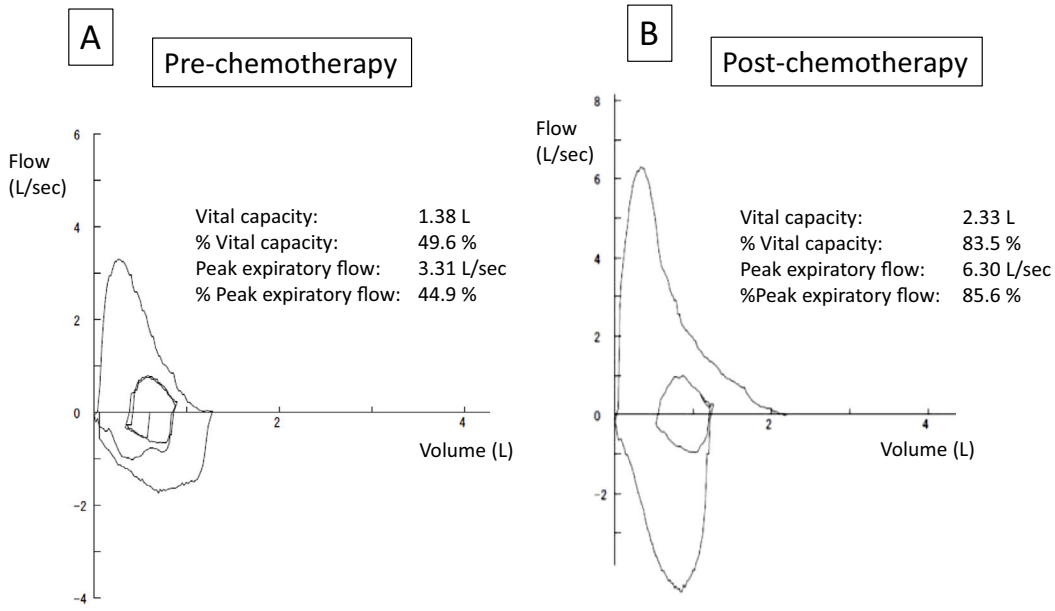

Figure 3. **Pulmonary function tests showing a significant improvement in the vital capacity and peak expiratory flow.**

patinib and trastuzumab in combination with bevacizumab (8). In the present case, we performed bevacizumab combination chemotherapy. The findings of this case suggest that bevacizumab containing chemotherapy may play an important role in the successful treatment of pseudomesotheliomatous carcinoma of the lung harboring a *HER2*-

mutation.

Regarding prognostic factors, Tomizawa et al. reported that *HER2* mutations were not associated with the prognosis of non-small-cell lung cancer patients, suggesting a negative prognostic role for the co-existence of a *TP53* mutation (9).

The present report is the first to described a case of *HER2*-positive lung cancer showing pseudomesotheliomatous carcinoma that was successfully treated with cisplatin plus pemetrexed and bevacizumab chemotherapy with a significant improvement in the symptoms of restrictive lung disease.

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

References

1. Kobashi Y, Matsushita T, Irei T. Clinicopathological analysis of lung cancer resembling malignant pleural mesothelioma. Respirology **10**: 660-665, 2005.
2. Harwood TR, Gracey DR, Yokoo H. Pseudomesotheliomatous carcinoma of the lung. A variant of peripheral lung cancer. Am J Clin Pathol **65**: 159-167, 1976.
3. Attanoos RL, Gibbs AR. 'Pseudomesotheliomatous' carcinomas of the pleura: A 10-year analysis of cases from the Environmental Lung Disease Research Group, Cardiff. Histopathology **43**: 444-452, 2003.
4. Takahara Y, Nishiki K, Nakase K, et al. A case of diffuse pleural invasion of pseudomesotheliomatous carcinoma with *EGFR* mutation diagnosed by thoracoscopic biopsy. J Jpn Soc Respir Endoscopy **38**: 183-189, 2016.
5. Stephens P, Hunter C, Bignell G, et al. Lung cancer: intragenic *ERBB2* kinase mutations in tumours. Nature **431**: 525-526, 2004.
6. Arcila ME, Chaft JE, Nafa K, et al. Prevalence, clinicopathologic associations, and molecular spectrum of *ERBB2* (*HER2*) tyrosine kinase mutations in lung adenocarcinomas. Clin Cancer Res **18**: 4910-4918, 2012.
7. Mazieres J, Barlesi F, Fileron T, et al. Lung cancer patients with *HER2* mutations treated with chemotherapy and *HER2*-targeted drugs: results from the European EUHER2 cohort. Ann Oncol **27**: 281-286, 2016.
8. Falchook GS, Janku F, Tsao AS, Bastida CC, Stewart DJ, Kurzrock R. Non-small-cell lung cancer with *HER2* exon 20 mutation: regression with dual *HER2* inhibition and anti-VEGF combination treatment. J Thorac Oncol **8**: e19-e20, 2013.
9. Tomizawa K, Suda K, Onozato R, et al. Prognostic and predictive implications of *HER2*/*ERBB2*/*neu* gene mutations in lung cancers. Lung Cancer **74**: 139-144, 2011.