

Case Series of Pleomorphic Carcinoma of the Lung Treated With Immune Checkpoint Inhibitors

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Abstract. Aim: We report, herein, three cases of pleomorphic carcinoma of the lung treated with immune checkpoint inhibitors. Case 1: A 73-year-old man was diagnosed as having pleomorphic carcinoma of the lung and treated with pembrolizumab alone. However, he showed no response and died 4 months after the initiation of the treatment. Case 2: A 66-year-old man was diagnosed as having pleomorphic carcinoma of the lung. He was started on a combination regimen of pembrolizumab plus carboplatin plus nab-paclitaxel, and a remarkable response was observed. Case 3: A 49-year-old man was diagnosed as having pleomorphic carcinoma of the lung. He was started on pembrolizumab monotherapy as second-line treatment. Eleven months after the treatment initiation, computed tomography revealed the decrease of tumor diameter. Conclusion: Immune checkpoint inhibitor therapy is expected to improve the prognosis of patients with pleomorphic carcinoma of the lung.

Pleomorphic carcinoma of the lung is one of the histological subtypes of sarcomatoid carcinoma, accounting for less than 1% of all cases of lung cancer (1). The response rate to cytotoxic agents is low, and the prognosis of patients with this type of cancer is poor (2-4). Recently, treatment with immune checkpoint inhibitors, administered either as monotherapy (5) or in combination with cytotoxic agents (6, 7), was demonstrated to be beneficial for patients with non-

small-cell lung cancer. Herein, we report the clinical courses of three patients with pleomorphic carcinoma of the lung who were treated with immune checkpoint inhibitors, either as monotherapy, or in combination with cytotoxic agents.

Case Reports

This case series is a part of a clinical study approved by the Ethics Committee, University of Toyama (approved number: R2020099), and we disclosed to patients about using clinical information and publication, in accordance with Ethical Guideline for Medical and Health Research Involving Human Subjects (Ministry of Health, Labour and Welfare, Japan).

Case 1. A 73-year-old man was referred to our hospital because of tumors in the left lower lobe of the lung and small intestine. His Eastern Cooperative Oncology Group performance status was good (PS 1). However, during the clinical course, he developed obstructive pneumonia and ileus, and underwent surgical resection of the left lower lobe and resection of the affected segment of the small intestine. Histopathological examination of the resected specimens revealed the diagnosis of pleomorphic carcinoma of the lung (cT4N0M1a, stage IVA) with small-intestinal metastasis. The tumors were negative for driver mutations, including of epidermal growth factor receptor (*EGFR*), ALK receptor tyrosine kinase (*ALK*), and ROS proto-oncogene 1, receptor tyrosine kinase (*ROS1*) but tumor programmed cell death 1 ligand 1 (PD-L1) expression, as assessed using 22C3 antibody, was positive [tumor proportion score (TPS): 80%-90%].

Pleural dissemination and abdominal subcutaneous metastasis became apparent after surgery (Figure 1A). Radiation therapy (45 Gy/25 fr) was administered for the abdominal lesion, and pembrolizumab monotherapy was initiated at the dose of 200 mg/day. No response was

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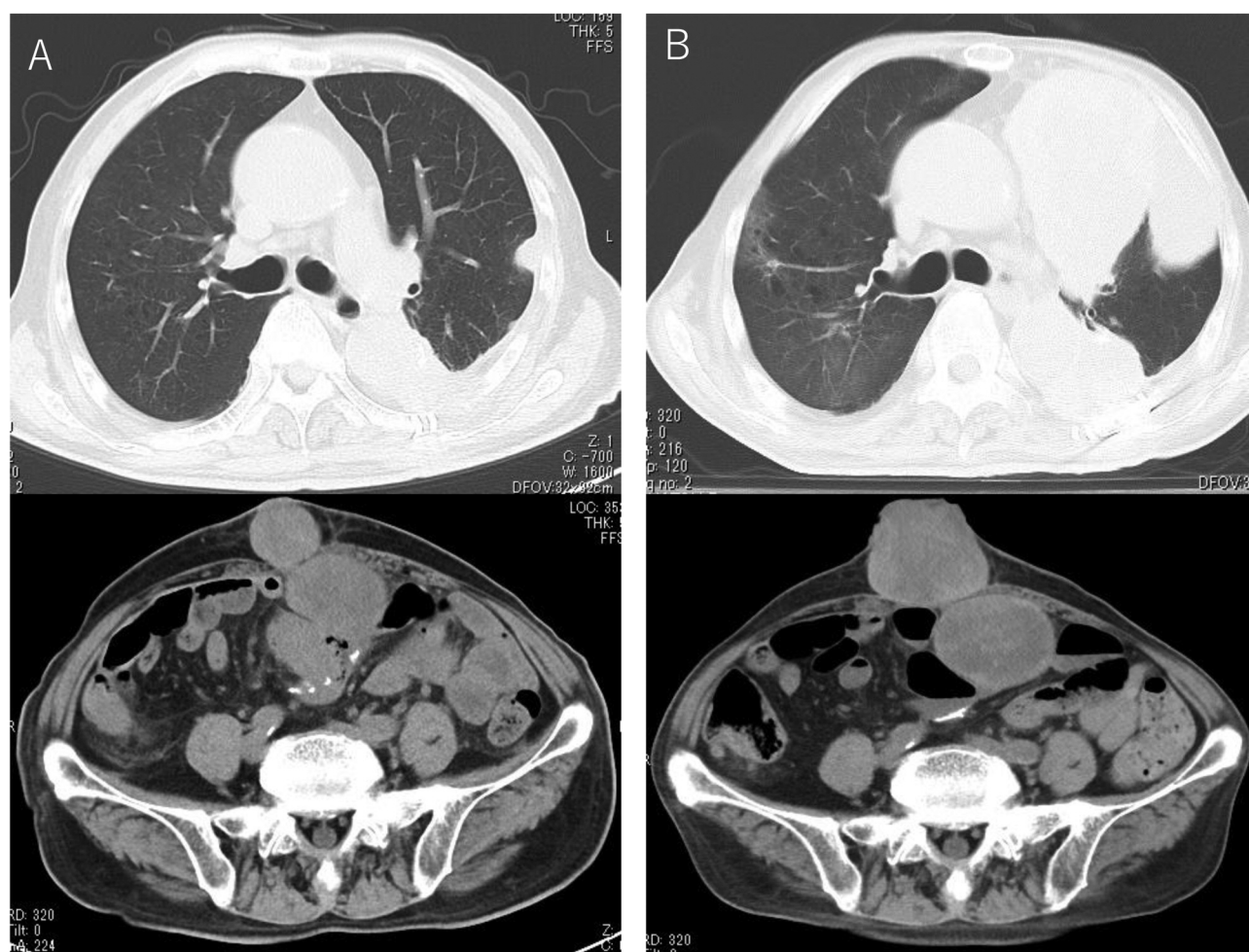


Figure 1. A: After surgical resection of the left lower lobe of the lung and involved segment of the small intestine, computed tomography showing pleural dissemination and abdominal subcutaneous metastasis in case 1. B: Computed tomography showing progression of the pleural dissemination and abdominal subcutaneous metastatic lesions after two cycles of pembrolizumab monotherapy. Upper and lower panels show pulmonary and abdominal lesions.

observed at the assessment conducted after two cycles of the therapy (Figure 1B), and the patient died 4 months after the initiation of pembrolizumab treatment.

Case 2. A 66-year-old man was admitted to a neighborhood hospital complaining of wheezing and breathlessness. Chest computed tomography revealed obstructive pneumonia due to a tumor in the left lung (Figure 2A). He was treated with antibiotics, and histopathological examination of a surgical biopsy of the tumor in the left lung revealed the diagnosis of pleomorphic carcinoma of the lung (cT4N2M0, stage IIIA). The tumor was negative for driver mutations, including of *EGFR*, *ALK*, and *ROS1* but tumor PD-L1 expression was positive (TPS: 90-100%). Combined therapy with pembrolizumab (200 mg/day), carboplatin (area under the curve: 6, day 1), and nab-

paclitaxel (100 mg/m²; days 1, 8, and 15) was initiated, and follow-up examination revealed tumor shrinkage. He was transferred to our hospital for treatment continuation.

His performance status was 0. After four cycles of the combination therapy, remarkable response was observed (Figure 2B), and maintenance treatment with pembrolizumab was still ongoing at 7 months after treatment initiation.

Case 3. A 49-year-old man visited a neighborhood hospital complaining of breathlessness, palpitations, and fever. Chest and abdominal computed tomography revealed tumors in the right upper lobe of the lung and right adrenal gland. Due to the rapid growth of the tumor in the right adrenal gland, surgical resection of the right adrenal gland was performed, and histopathological examination of the resected specimen

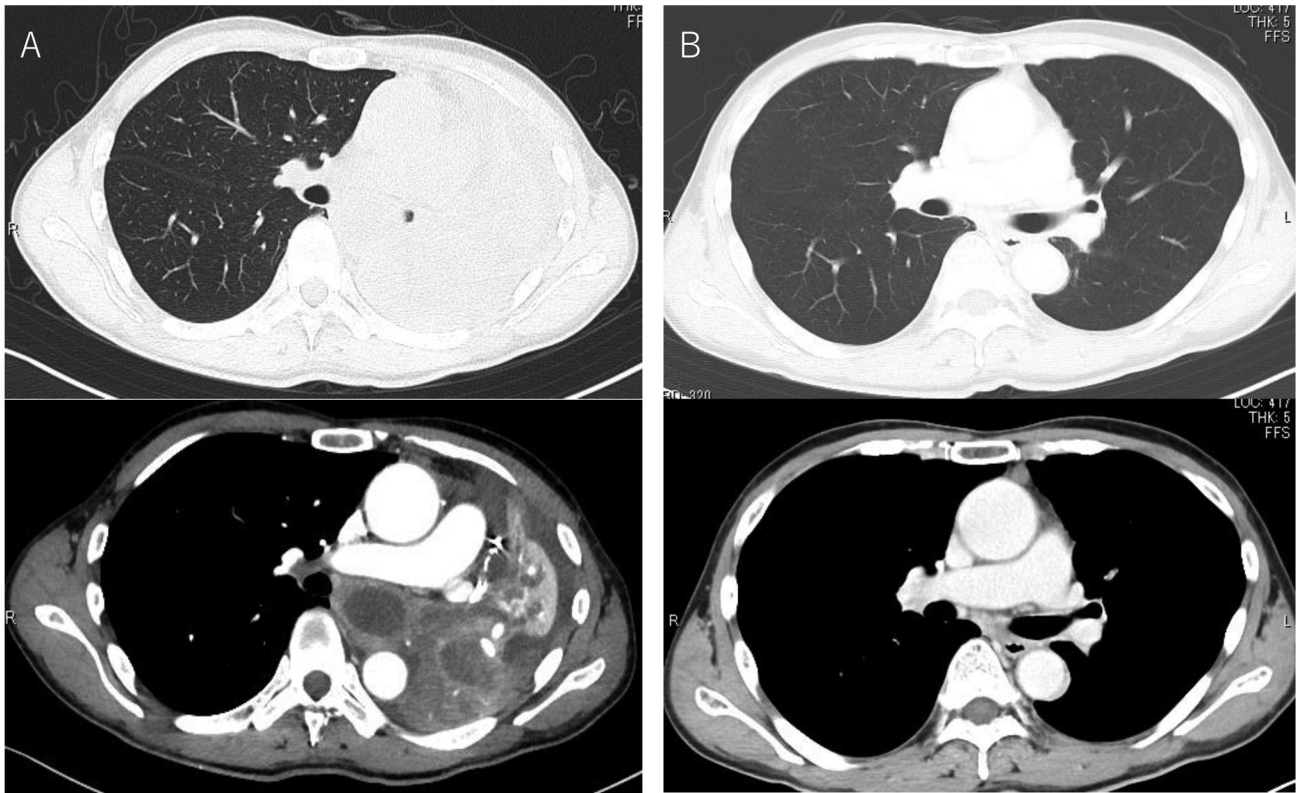


Figure 2. A: Computed tomography at first presentation of case 2 revealed a massive tumor in the left lower lobe and atelectasis and obstructive pneumonia of the left lower lobe. B: A decrease in size of the massive tumor in the left lower lobe was found on computed tomography after four cycles of combination therapy with pembrolizumab plus carboplatin and nab-paclitaxel. Upper and lower panels show pulmonary and mediastinal window settings.

revealed the diagnosis of pleomorphic carcinoma. He was then referred to our hospital for the purpose of systemic treatment.

He was diagnosed at our hospital as also having pleomorphic carcinoma of the lung (cT3N0M1b, stage IVA). Although his performance status was good (PS 1), the tumor in the right upper lobe showed rapid growth and a new tumor appeared in the left adrenal gland. Systemic chemotherapy was initiated with carboplatin (area under the curve: 6, day 1) plus nab-paclitaxel (100 mg/m²; days 1, 8, and 15) and four cycles were administered. However, the primary tumor showed progression and bone metastases appeared, necessitating radiation therapy for the bone lesions (30 Gy/10 fr). The tumors were negative for driver mutations of *EGFR*, *ALK*, *ROS1*, and *BRAF* but tumor PD-L1 expression was strongly positive (TPS: 60%-70%). Next-generation sequencing (Foundation One) revealed mutations of *BRCA2*, *RBM10*, and *TP53* genes but no actionable gene mutations, and a high tumor mutation burden (42 mutations/Mb). Pembrolizumab monotherapy was initiated at the dose of 200 mg/day. Assessment at 11 months after the initiation of treatment revealed the decrease of tumor diameter (Figure

3). Pembrolizumab therapy was still ongoing at 12 months after the initiation of treatment.

Discussion

We have presented three cases of pleomorphic carcinoma of the lung that were treated with immune checkpoint inhibitors, administered either as monotherapy or in combination with cytotoxic agents. Two patients, including one who received pembrolizumab monotherapy and one who received pembrolizumab in combination with cytotoxic agents, showed long survival, while the third patient who received pembrolizumab monotherapy failed to show any response to the immune checkpoint inhibitor therapy.

While the response to cytotoxic agents is reported to be poor in patients with pleomorphic carcinoma of the lung (2-4), there have been several reports of cases treated successfully with immune checkpoint inhibitors (8-12). Although publication bias should be considered, immune checkpoint inhibitors are expected to be effective against pleomorphic carcinoma of the lung.

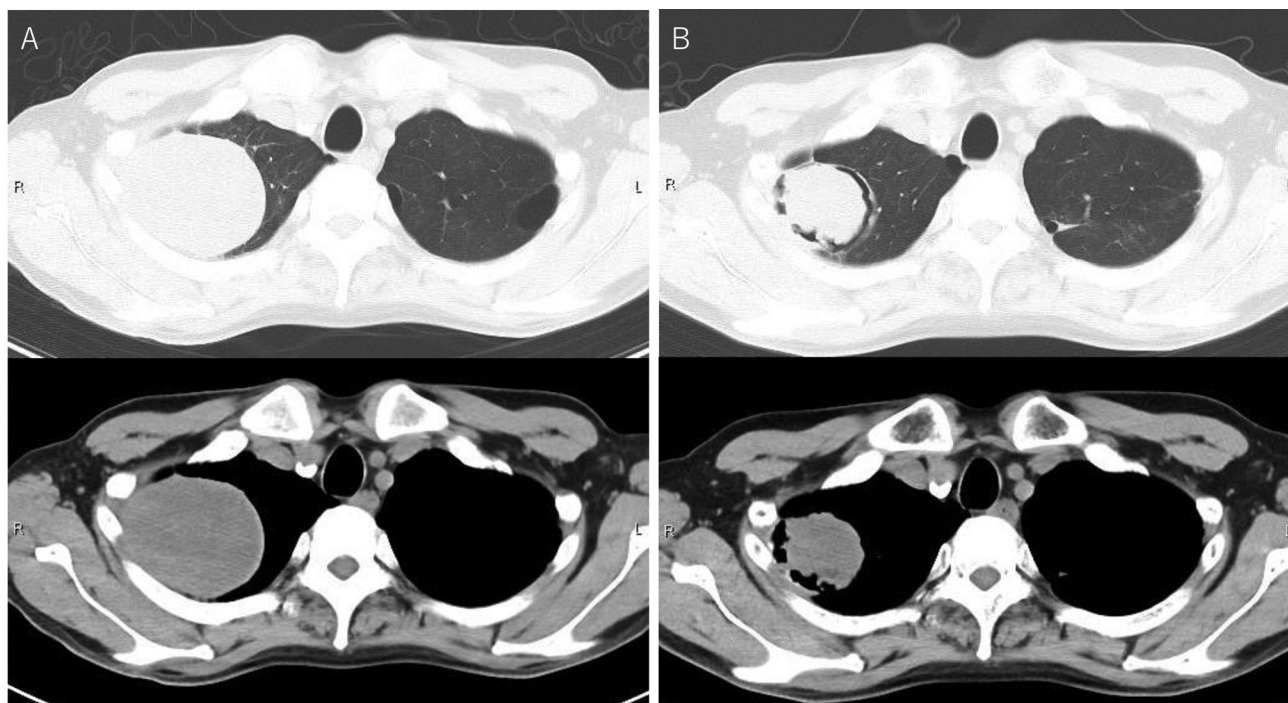


Figure 3. A: Computed tomography showing a tumor in the right upper lobe. B: A decrease of the tumor diameter was found on computed tomography at 11 months after the initiation of treatment. Upper and lower panels show pulmonary and mediastinal window settings.

The efficacy of immune checkpoint inhibitors in patients with non-squamous cell non-small cell lung cancer (13) is associated with PD-L1 expression, but this is not the case in patients with squamous cell non-small-cell lung cancer (14). Tumor PD-L1 expression is reported to be frequently positive in pleomorphic carcinoma of the lung (15, 16), especially in the sarcomatoid component (16). One retrospective analysis showed an association between positive tumor PD-L1 expression and longer survival after the initiation of immune checkpoint inhibitor therapy (17), suggesting that tumor PD-L1 expression may be a favorable biomarker of the efficacy of immune checkpoint inhibitor therapy in patients with pleomorphic carcinoma of the lung.

On the other hand, although all three cases showed positive tumor PD-L1 expression, one patient failed to show any response to pembrolizumab monotherapy. Kanazu *et al.* also reported similar observations in cases treated with nivolumab (8). These findings suggest that predictive factors other than tumor PD-L1 expression may exist for the response to immune checkpoint inhibitor therapy in patients with pleomorphic carcinoma of the lung. Tumor mutation burden (18), peripheral immune cell phenotypes, including the presence of BCL2 like 11 (BIM)⁺PD1⁺CD8⁺ T-cells (19), PD-L1⁺CD11b⁺ cells (20), PD1⁺CD4⁺ T-cells (21), CD62L^{low}CD4⁺ T-cells (22), PD-L1⁺CD14⁺ monocytes (23), and clinical parameters, including

the serum levels of lactate dehydrogenase, the neutrophil/lymphocyte ratio and serum C-reactive protein (24-27), have been investigated as possible predictors of the efficacy of immune checkpoint inhibitor therapy in patients with non-small-cell lung cancer. However, there is as yet no clear evidence of the association between these factors and the clinical benefit of immune checkpoint inhibitor therapy in patients with pleomorphic carcinoma of the lung.

In conclusion, although pleomorphic carcinoma of the lung is refractory to cytotoxic agents, immune checkpoint inhibitors are expected to improve the prognosis of patients with this disease. Development of predictive biomarkers for the efficacy of immune checkpoint inhibitor therapy in patients with pleomorphic carcinoma of the lung is desired.

Conflicts of Interest

All Authors declare that they have no conflicts of interest.

Authors' Contributions

KH and MI contributed to preparation of the article. KH, K Tokui, KA, IM, NT, CT, SO, KK, SI, TM, RH, and SN were involved in medical treatment. SM and K Tobe reviewed the final version of the article.

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