Simultaneous Pseudoprogression and an Immune-related Adverse Event of Pulmonary Pleomorphic Carcinoma after Combined Therapy with Cytotoxic Anticancer Agents and Immune Checkpoint Inhibitor

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Abstract:

Pulmonary pleomorphic carcinoma is rare among lung tumors. Pulmonary pleomorphic carcinoma is resistant to chemotherapy. However, treatment with taxane anticancer agents and immune checkpoint inhibitors has been reported to be effective. When using immune checkpoint inhibitors, pseudoprogression and true progression are difficult to distinguish, and immune-related adverse events (irAEs) are common. We herein report a patient with simultaneous pseudoprogression and irAEs after combined therapy with cytotoxic agents and an immune checkpoint inhibitor for pulmonary pleomorphic carcinoma. Immune checkpoint inhibitors are effective against pulmonary pleomorphic carcinoma, but patients should be monitored for pseudoprogression and irAEs.

Key words: pleomorphic pulmonary carcinoma, immune checkpoint inhibitor, pseudoprogression, immune-related adverse event

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Introduction

Pulmonary pleomorphic carcinoma is one of the five subtypes of sarcomatoid carcinoma in the World Health Organization classification of lung tumors. Pulmonary pleomorphic carcinoma is defined as poorly differentiated non-small-cell lung cancer containing at least 10% spindle cells or giant cells. Since pulmonary pleomorphic carcinoma is rare (0.1-0.3% of all lung tumors), there are few reports concerning its treatment.

Pulmonary pleomorphic carcinoma is generally resistant to chemotherapy and has a poor prognosis (1). However, immune checkpoint inhibitors have occasionally demonstrated very good therapeutic efficacy (2, 3). Immune checkpoint inhibitors have been used to treat various malignant tumors, including lung cancer, and good therapeutic effects have been reported. However, these agents cause problems, such as pseudoprogression and immune-related adverse events (irAEs), that are not observed with conventional chemotherapy.

We herein report a case of pulmonary pleomorphic carcinoma that developed simultaneous pseudoprogression and irAEs after combined therapy with a cytotoxic agent and an immune checkpoint inhibitor. The pseudoprogression and irAEs were difficult to distinguish from true exacerbation of the cancer (4).
Figure 1. Preoperative positron emission tomography-computed tomography (PET-CT) showed accumulation in the tumor at the upper left lobe and left hilar lymph node (#11 L) (arrow).

Case Report

A 57-year-old man presented with left back pain. The patient had no remarkable history. He smoked 30 cigarettes per day (Brinkman index: 1,140) and consumed alcohol socially. He worked in the construction industry.

The history of the present illness

The patient had been aware of left back pain since around April 20XX. At that time, he underwent a medical examination and consulted a previous doctor because of an abnormal shadow on a chest imaging examination. A tumor was found in the upper lobe of the left lung, and the cytology of the bronchoscopic biopsy was Class III. Positron emission tomography-computed tomography (CT) showed accumulation in the tumor of the upper left lobe and the left hilar lymph node (#11 L) (Fig. 1). No findings suggested distant metastasis. Based on the examination, lung cancer was strongly suspected. Thus, the patient was referred to the Department of Respiratory Surgery at our hospital for treatment.

Left upper lobectomy was performed, and the diagnosis was pulmonary pleomorphic carcinoma pT3N1M0 Stage IIIA. Programmed cell death 1-ligand 1 (PD-L1) was highly expressed in the tumor (tumor proportion score 90%). Although postoperative adjuvant chemotherapy was planned, the tumor recurred early approximately three weeks after the operation. The patient was thus referred to our department for treatment.

Physical findings

The patient’s height and weight were 162.4 cm and 54.2 kg, respectively. A head and neck examination revealed no cervical lymphadenopathy and no other special notes. A chest examination revealed a palpable, 50-mm, elastic, slightly hard mass with heat and pain in the left anterior chest. An abdominal examination revealed a flat and soft abdomen with good intestinal peristaltic sounds and no spontaneous pain or tenderness. A limb examination revealed nothing special. The Eastern Cooperative Oncology Group performance status was 1.

The laboratory results included the following: white blood cells, 33,400/μL (neutrophils 90.0%); hemoglobin, 9.6 g/dL; platelets, 59.9×10⁴ /μL; sodium, 140 mmol/L; potassium, 4.0 mmol/L; chloride, 104 mmol/L; blood urea nitrogen, 7 mg/dL; creatinine Cre, 0.57 mg/dL; C-reactive protein, 21.49 mg/dL; aspartate aminotransferase, 18 U/L; alanine aminotransferase, 28 U/L; total bilirubin, 0.2 mg/dL; lactate dehydrogenase, 232 U/L; tumor marker, slightly elevated; and cytokeratin 19 fragment (CYFRA), 3.3 ng/mL (standard value 0.0-2.8).

Imaging results

Chest X-ray revealed left pleural effusion (postoperative pleural effusion was considered), and reduced permeability of the upper left lung field was observed. After resection of the upper lobe of the left lung and combined resection of the left second and third ribs, contrast-enhanced CT revealed an irregularly shaped tumor measuring 62×34 mm in the left anterior chest (Fig. 2). Swelling of the left axillary lymph node and the right adrenal gland was also observed.

Pathological findings (surgical specimens)

A pathologic examination of the biopsy revealed crude nuclear chromatin and polygonal, rhombic, and spindle-shaped tumor cells with round nuclei and eosinophils that proliferated in a solid and bundled manner. No clear flat or glandular epithelium was evident. Immunostaining was cytokeratin (CK) 7 (+), CK5/6 (+), thyroid transcription factor-1 (TTF-1) (-), and NapsinA (-). Although immunostaining showed squamous epithelial traits, the morphology suggested sarcomatoid carcinoma. Taken together, these findings suggested pleomorphic carcinoma.

Progress after hospitalization

Based on the test results, the patient was diagnosed with postoperative recurrence of pulmonary pleomorphic carcinoma. The PD-L1 expression rate of the tumor was high (tumor proportion score 90%), indicating the use of immune
checkpoint inhibitors. Treatment with an immune checkpoint inhibitor alone was considered. However, recurrence was observed at an early stage after surgery, so combination therapy with a cytotoxic agent and an immune checkpoint inhibitor was necessary to obtain a greater antitumor effect. Therefore, carboplatin (AUC6)+nab-paclitaxel (nab-PTX, 100 mg/m²)+pembrolizumab (200 mg/body) therapy was initiated. Since marked malaise appeared and persisted from day 5 of treatment, the scheduled administration of nab-PTX on day 8 was discontinued. On the same day, no problems with blood laboratory values were noted.

Contrast-enhanced CT was performed on day 9 because of pain and warmth in the left anterior chest. An increase in the left anterior chest mass and right adrenal metastasis was observed (Fig. 3). Although the evaluation was early, the tumor size increased, and the performance status decreased despite the treatment. Thus, we judged the disease to be difficult to control. We decided that supportive care was best and discontinued the anticancer drugs.

From approximately day 17, the general malaise increased, food intake became difficult, and the level of consciousness dropped sharply from day 19. Blood sampling on day 20 showed a marked decrease in the renal function (blood urea nitrogen, 69 mg/dL; Cre, 7.66 mg/dL), which was diagnosed as organ failure due to the progression of the pulmonary pleomorphic carcinoma. Due to severe physical distress, continuous sedation was started on day 24 for symptom relief. The patient died on day 32. A pathological autopsy was performed to confirm the cause of death.

Pathological anatomical results

At the site of pneumonectomy in the left upper thoracic cavity, there was a tight adhesion between the residual lung and pleura, and the pleura was difficult to remove by hand. On the cut surface, a solid mass with a white to yellowish-white tone was observed over the entire upper part of the lower lobe of the left lung. Most of the tumor consisted of degenerative and necrotic tissue and scar tissue with moderate to severe inflammatory cell infiltration.

On high magnification, the area with the remaining tumor cells was less than 5% of the tumor. Infiltration of lymphocytes and neutrophils was observed in the remaining tumor cells. Necrotic and degenerating tumor cells were also observed. Therefore, the histological findings were considered indicative of active change (Fig. 4a).

Immunohistochemically, the infiltrating lymphocytes were mainly cluster of differentiation 3 (CD3)-positive T cells mixed with CD20-positive B cells. In the T-cell lineage, CD8-positive cells were more abundant than CD4-positive cells, and infiltration of T-cell intracytoplasmic antigen-1 (TIA-1)-

Figure 2. Computed tomography at the time of recurrence showed a 62×34-mm irregular mass in the left anterior chest (arrow, left panel). The inside of the mass exhibited a heterogeneous contrast effect. The left axillary lymph nodes and right adrenal gland were enlarged (arrow, right panel).

Figure 3. Computed tomography on day 9 of treatment showed an increase in the left anterior chest mass and right adrenal metastasis (arrow).
Figure 4. Lung and adrenal gland findings from the pathological autopsy. (a) Histopathological sections of the upper part of the lower lobe of the left lung (scale bar: 1,000 μm). The area where tumor cells remained accounted for less than 5% of the tumor. Infiltration of lymphocytes and neutrophils was observed in the remaining tumor cells, and necrotic and degenerating tumor cells were also observed (arrow). (b) Histopathological sections of the right adrenal gland (scale bar: 500 μm). It was mainly composed of degenerated and necrotic tissue (arrow). No obvious residual tumor was observed.

Figure 5. Immunohistochemical staining of lung tissue at the autopsy (scale bar: 100 μm). The infiltrating lymphocytes were predominantly CD3-positive T cells, and a mixture of cells of B-cell lineage showing CD20 positivity was observed. In the T-cell lineage, CD8-positive cells were more abundant than CD4-positive cells, and infiltration of TIA-1-positive lymphocytes was also observed. In the right adrenal gland, a solid mass showing a yellowish cut surface with a major axis of approximately 20 mm was observed. The mass was mainly composed of degenerated and necrotic tissue, with no obvious residual tumor (Fig. 4b).

These findings indicated a strong immune response in the tumors. The PD-L1 expression rate was 90% in the surgical material, which is consistent with an immune response to the tumor induced by pembrolizumab.

positive lymphocytes was observed (Fig. 5).
In both kidneys, inflammatory cells mainly composed of lymphocytes and plasma cells gathered in a nest-like manner were observed in the entire cortical region, mainly in the interstitium around the renal tubule. Lymphocytes extending into the renal tubular epithelium, rupture of the tubular basement membrane, and obscuration were observed, indicating tubular interstitial nephritis. Immunohistochemically, the infiltrating lymphocytes were predominantly CD3-positive T cells, with mixed CD20-positive B cells. In the T-cell lineage, more CD8-positive cells were found than CD4-positive cells, and infiltration of TIA-1-positive lymphocytes was observed. Lymphocytes positive for CD8 and TIA-1 penetrated between the tubular epithelium, suggesting renal tubular epithelial damage had been caused by these lymphocytes. HE: Hematoxylin and Eosin staining, PAM: periodic acid-methenamine-silver staining

In the present case, a retrospective examination of the surgical specimen showed the formation of a follicular-like structure consisting of a collection of lymphocytes around the tumor. This organized tertiary lymphoid structure consisted of tumor-infiltrating immune cells, and the structure was considered an ectopically formed lymphoid formation in nonlymphoid tissues. The presence of such a structure reportedly enhances the treatment responsiveness of immune checkpoint inhibitors (6). In addition, PD-L1 was extensively expressed in the tumor, making the tumor more likely to respond to treatment with immune checkpoint inhibitors.

Pseudoprogression and an irAE occurred at the same time in this case. Pseudoprogression is a phenomenon in which lesions appear to be exacerbated as a reaction to tumor immunity. The autopsy in this case revealed the infiltration of CD8-positive and TIA-1-positive lymphocytes in the tumor cells, and an immune response to the tumor was observed. Therefore, the growth of the tumor was deemed pseudoprogression. To differentiate between true exacerbation and pseudoprogression, an evaluation should include the per-

**Figure 6.** Renal findings at the autopsy (scale bar: 50 μm). Immunohistochemically, the infiltrating lymphocytes were predominantly CD3-positive T cells with mixed CD20-positive B cells. In the T-cell lineage, more CD8-positive cells than CD4-positive cells were found, and infiltration of TIA-1-positive lymphocytes was also observed. The lymphocytes positive for CD8 and TIA-1 penetrated between the tubular epithelium, suggesting renal tubular epithelial damage had been caused by these lymphocytes. HE: Hematoxylin and Eosin staining, PAM: periodic acid-methenamine-silver staining
formance status, general condition, tumor volume change, and biopsy findings. However, effective methods for distinguishing between tumor exacerbation and pseudoprogression have not yet been established, and distinguishing between them in actual clinical practice is difficult (4).

irAEs are a side effect associated with the use of immune checkpoint inhibitors and can occur in almost any organ in the body. High antitumor effects are often observed when irAEs occur at an early stage (7, 8). In this case, fatigue increased from day 17. Renal damage appeared as an irAE around the same period, and the uremia symptoms were caused by the renal damage. The irAE appeared early after immune checkpoint inhibitor administration. Pathologically, almost a complete response was attained, consistent with previous reports.

In the present case, because of the early postoperative recurrence, we initially thought that the tumor growth during chemotherapy was exacerbation due to treatment failure and that the worsening of the general condition was also due to the tumor growth. However, the autopsy results showed that pseudoprogression and an irAE had occurred. Pseudoprogression was not included in the differential diagnosis because the speed of recurrence and the speed of tumor growth led to suspicion of true exacerbation. Furthermore, an irAE was not considered in the differential diagnosis because the exacerbation of the general condition was thought to have been due to the exacerbation of the pleomorphic carcinoma. In addition, the two conditions occurred at about the same time, making them difficult to distinguish and diagnose. In this case, no steroids were administered. Steroids are generally given to alleviate the symptoms of cancer and are also used to treat irAEs. If steroids had been administered for symptom relief and the renal function had improved as a result, we might have been able to recognize the irAE for what it was. When using immune checkpoint inhibitors, the possibility of pseudoprogression and irAEs should always be considered.

**Conclusion**

We encountered a case in which pulmonary pleomorphic carcinoma was treated with an immune checkpoint inhibitor, resulting in a high antitumor effect. However, pseudoprogression and an irAE occurred at the same time, and these conditions were difficult to distinguish from true exacerbation. We expect immune checkpoint inhibitors to have a high therapeutic effect on pulmonary pleomorphic carcinoma, but distinguishing pseudoprogression from true tumor exacerbations is difficult when the lesion site grows. irAEs should also be carefully considered.

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

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