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【 CASE REPORT 】

The Significant Antitumor Activity of Nivolumab in Lung Adenocarcinoma with Choriocarcinomatous Features

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Abstract:

We report the case of a 60-year-old Japanese man with a metastatic brain tumor that caused ataxia. As a consequence of resection of a cerebellar tumor, the tumor was diagnosed as a poorly differentiated adenocarcinoma with choriocarcinomatous features. The patient underwent bronchoscopy, leading to a diagnosis of the same histology as the brain tumor. After the administration of first-line chemotherapy and maintenance therapy due to progressive disease, he was given nivolumab and obtained a partial response; however, 11-months later, computed tomography showed tumor progression. Our experience suggests that nivolumab has strong activity, even in patients with a rare form of lung cancer.

Key words: nivolumab, choriocarcinoma, PD-1, PD-L1, acquisition of resistance

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Introduction

Primary pulmonary choriocarcinoma and primary pulmonary carcinoma with choriocarcinomatous features (PPCs) are rare diseases that carry a poor prognosis; PPCs in males are very rare. The first-line treatment of PPCs is resection; however, there is no standard regimen for advanced or recurrent PPCs (1). It is not clear how many cases of primary pulmonary carcinoma with choriocarcinomatous features are included in the literature about primary pulmonary choriocarcinoma because bronchoscopy specimens have been used in many reports and the amount of such specimens tends to be insufficient. In this case-since there are very few case reports about PPCs and the treatments are limited-we employed the concept of PPCs, based on the opinion of many researchers who have considered the two conditions to belong to the same disease category.

Nivolumab is a fully human immunoglobulin (IgG)4 programmed death 1 (PD-1) immune-checkpoint-inhibitor antibody. Nivolumab disrupts PD-1-mediated signaling to restore anti-tumor immunity. This type of chemotherapy is associated with a relatively high tumor response. The antibody has been reported to have strong activity as second-line treatment in patients with non-small-cell lung cancer (NSCLC) with different histologic features (2). Recently, an expanded phase-I trial showed a correlation between the pretreatment tumoral expression of a ligand of PD-1, programmed death ligand 1(PD-L1), and the response to anti-PD-1 therapy (nivolumab) (3), and that germ-cell tumors and poorly differentiated tumors demonstrate the high expression of PD-L1 (4). Continuous therapy with nivolumab may lead to the acquisition of resistance; some studies have described this mechanism of action.

We herein report, for the first time, the case of a patient with poorly differentiated adenocarcinoma with choriocarcinomatous features who underwent immunotherapy.

Case Report

A 60-year-old man was admitted to our hospital complaining of headache, ataxia and dizziness. Magnetic reso-

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nance imaging showed a space-occupying lesion of 3 cm in diameter in the cerebellum, which was suspected to be the cause of his symptoms (Fig. 1). Chest radiographs revealed a mass shadow at the right upper and middle lung field, and computed tomography (CT) revealed ipsilateral mediastinal and hilar lymphadenopathy (Fig. 2). The patient's blood test results, including his human chorionic gonadotropin (hCG) and carcinoembryonic antigen (CEA) levels (tumor markers), were all within normal limits.

Tumor resection performed under craniotomy led to a diagnosis of metastatic poorly differentiated adenocarcinoma with choriocarcinomatous features. A postoperative bronchoscopy specimen led to an identical diagnosis. Both types of neoplastic cells were genetically negative for epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and C-ros 1 (ROS1) mutations, and were immunophenotypically positive for thyroid transcription factor 1 (TTF-1). However, only the brain tumor specimen was positive for hCG (Fig. 3). After the diagnosis, the patient was treated with pemetrexed/cisplatin/bevacizumab as first-line chemotherapy and pemetrexed as maintenance therapy; however, progressive disease was observed after 5 months.

The patient started second-line chemotherapy with nivolumab, and a partial response was obtained after the first four cycles. However, CT showed progressive disease in a pulmonary lesion after 1 year (Fig. 4). Whole-body positron emission tomography revealed that the uptake of contrast medium only occurred in the right lung; thus, the right upper lobe was resected. A histological examination of the tumor in the right upper lobe-which had been diagnosed as poorly differentiated adenocarcinoma-revealed that the tumor partially contained infiltrating cluster of differentiation (CD) 8-positive and/or granzyme B-positive T cells, and that there were no choriocarcinomatous features. PD-L1 immunoreactivity tests revealed >50% positive cells before surgery but a decrease in the number of positive cells after the administration of nivolumab (Fig. 5). The patient is currently receiving nivolumab therapy is ongoing, and there has been no evidence of recurrence or side effects.

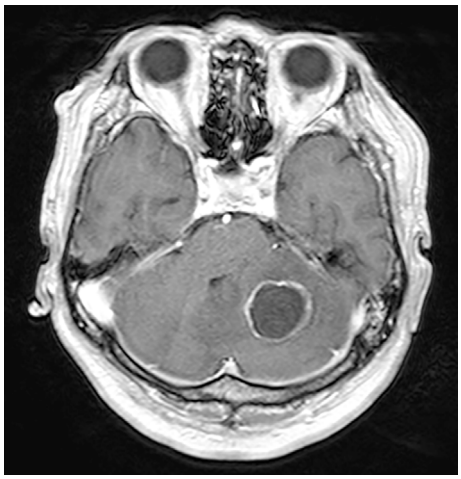

Figure 1. Magnetic resonance imaging at the first visit showing cerebellar metastasis.

Discussion

There have been some clinical reports on PPCs (1). A PubMed search revealed 55 case reports on PPCs. PPCs are highly malignant intrapulmonary tumors with a notoriously poor prognosis. The median survival time in 47 cases was only 8 months. Men showed worse survival than women. PPCs show a poor response to radiotherapy. Thus, combined treatment of surgery and chemotherapy offers a chance to improve survival. BEP (bleomycin/methotrexate/cisplatin) or platinum-based combination chemotherapy-in accordance with the first-line chemotherapy of non-small cell lung cancer-seem to be the most appropriate chemotherapy regimens (5).

The PD-1 receptor, which is expressed on activated T cells, is engaged by the ligands PD-L1 and PD-L2, which

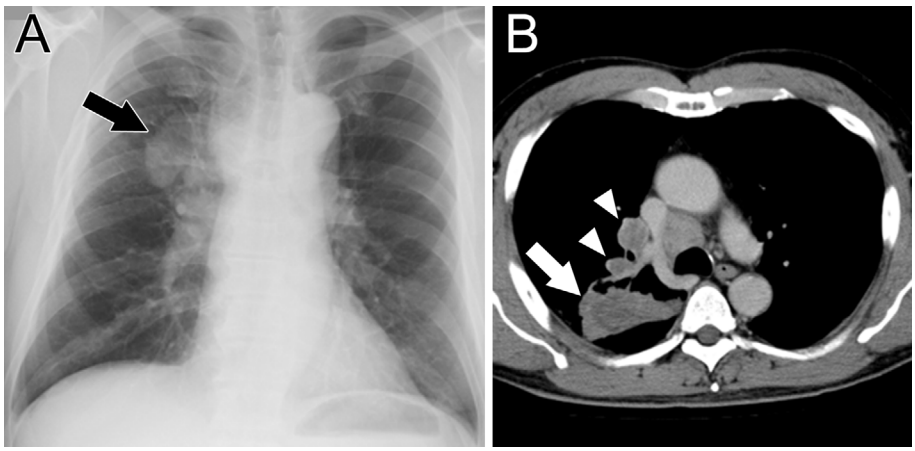

Figure 2. A chest radiograph showing a mass shadow in the right upper lung field (A), and computed tomography (CT) of the chest showing ipsilateral mediastinal and hilar lymphadenopathy (B). Large arrows indicate mass shadows. Small arrows indicate ipsilateral mediastinal and hilar lymphadenopathy.

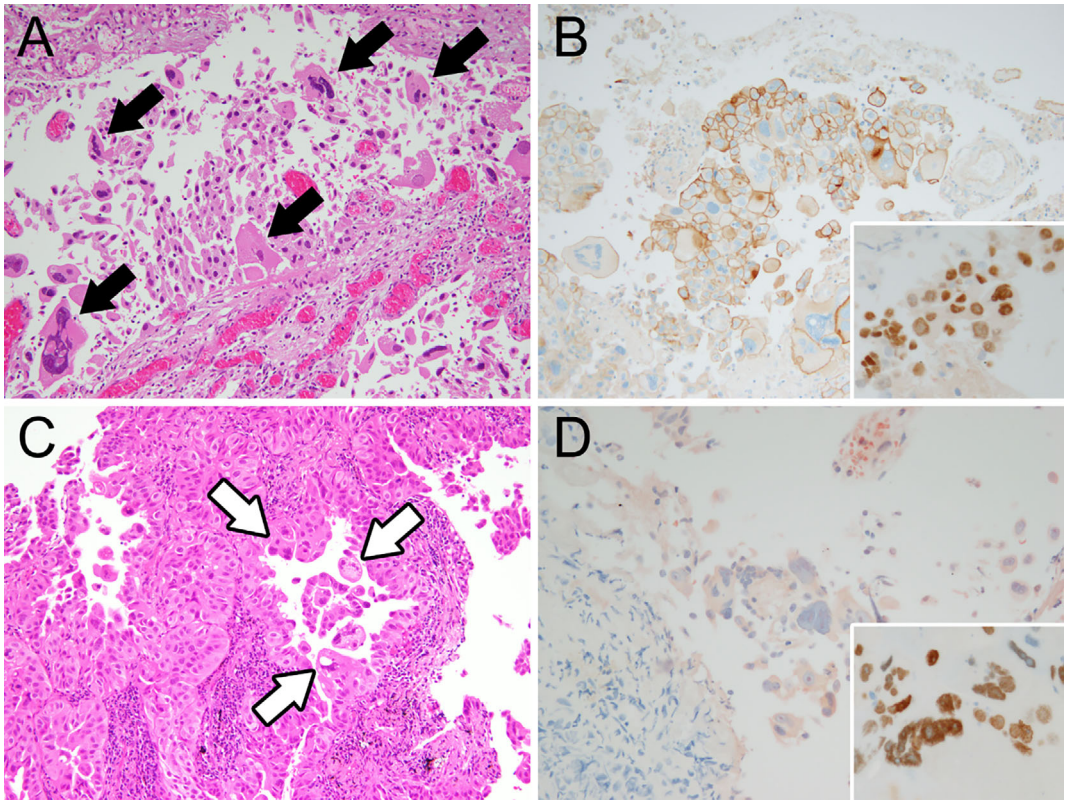

Figure 3. **Cerebellar metastasis of lung adenocarcinoma (A, B). The primary lesion shown by bronchoscopy (C, D). The expression of hCG and TTF-1. (B, D). Representative micrographs of the tumors. Hematoxylin and Eosin staining at an original magnification of ×20 and bizarre multinucleated giant cells are indicated by black and white arrows, respectively (A, C). The focal expression of hCG shown at an original magnification of ×20. Both specimens showed poorly differentiated adenocarcinoma with choriocarcinomatous features. Only the choriocarcinomatous features of the metastatic lesion were positive for hCG. Both the adenocarcinoma component and the choriocarcinomatous features of both lesions were positive for TTF-1 at an original magnification of ×40.**

are expressed by tumor cells and infiltrating immune cells (6). Germ-cell tumors and poorly differentiated adenocarcinoma show the relatively high expression of PD-L1 (4, 7). This result is consistent with the PD-L1 expression in both the adenocarcinoma component and choriocarcinomatous features of the bronchoscopy specimen before nivolumab therapy. Nivolumab is a fully human IgG4 PD-1 immune-checkpoint-inhibitor antibody that disrupts PD-1-mediated signaling and restores anti-tumor immunity (8). A meta-analysis by Topalian et al. showed that the activity of nivolumab is correlated with the expression of PD-L1 (8). Topalian et al. found no significant relationship between the PD-L1 expression and the clinical features, including the histology (8). The acquisition of resistance to nivolumab is thought to be the reason why the choriocarcinomatous features disappeared while the adenocarcinoma component remained in the resected specimen after the start of nivolumab therapy. The mechanism underlying the development of resistance to nivolumab is not clear; however, a growing body of evidence suggests the absence of CD8-positive T cells to be one of the major causes of anti-PD-1 therapy failure. Recent studies have suggested that growing tumors are frequently infiltrated by immune cells-notably CD8 positive T cells-and that these cells probably contribute to the control of tumor growth in humans (9-11). Another mechanism of tumor regrowth is overcoming the reinvigoration provided by anti-PD1 therapy to exhausted tumor-associated lymphocytes, such as severe exhaustion, the expression of co-inhibitory receptors, and the expression of PD1-independent inhibitory pathways (12).

In the present case, a histological examination revealed poorly differentiated adenocarcinoma, including giant cell-like trophoblasts in the metastatic tumor of the brain and primary lesion. The metastatic tumor of the brain had hCG-positive cells. The patient's serum levels of hCG were not increased and specimens from bronchoscopy and the resected tumor did not contain hCG-positive cells, while bizarre multinucleated giant cells were found to have proliferated in both specimens. We hypothesize that the absence of hCG-positive cells in the transbronchial lung biopsy specimen of the primary lesion occurred by chance, and was a consequence of the small number of cells that were collected in the biopsy. CD8-positive and granzyme B-positive T cells were found to have infiltrated the tumor in the resected specimen, representing the cytotoxic effect of lymphocytes on cancer cells. After the continuous administration

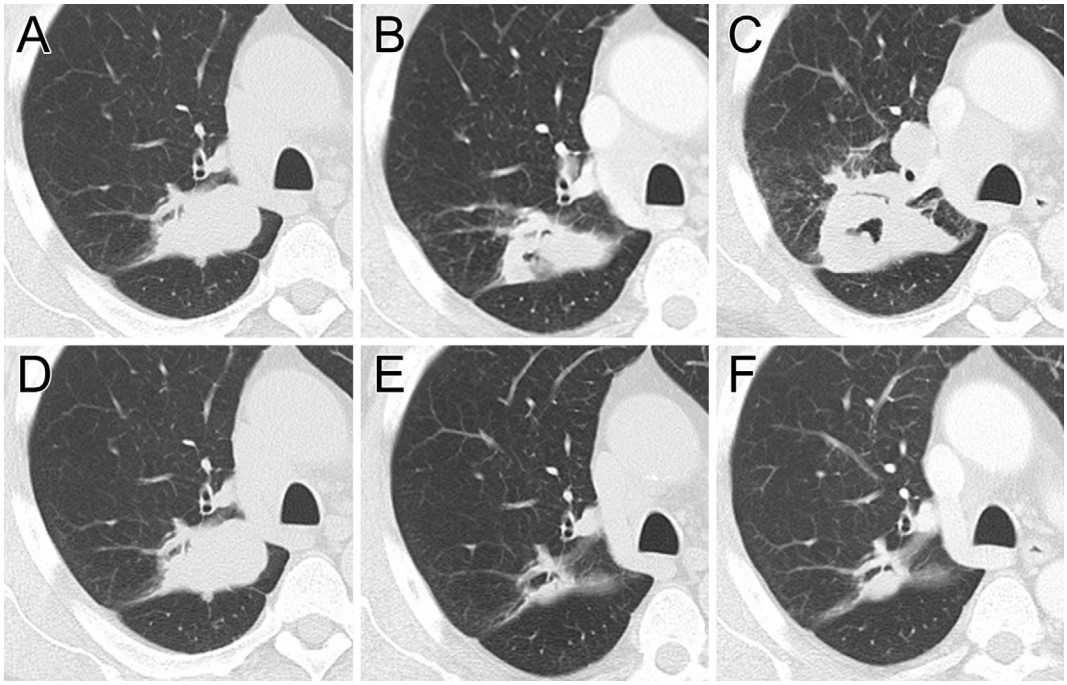

Figure 4. **Computed tomography showing the significant regression of the tumor in the lung after chemotherapy. A) At the start of first-line chemotherapy. CT showed a partial response before maintenance therapy. (B) The size of the tumor in the lung increased after 5 months (C). The patient started treatment with nivolumab as second-line chemotherapy. (D) A partial response was obtained after the first four cycles (E). CT showing progressive disease in a pulmonary lesion at the end of the 25th cycle (F).**

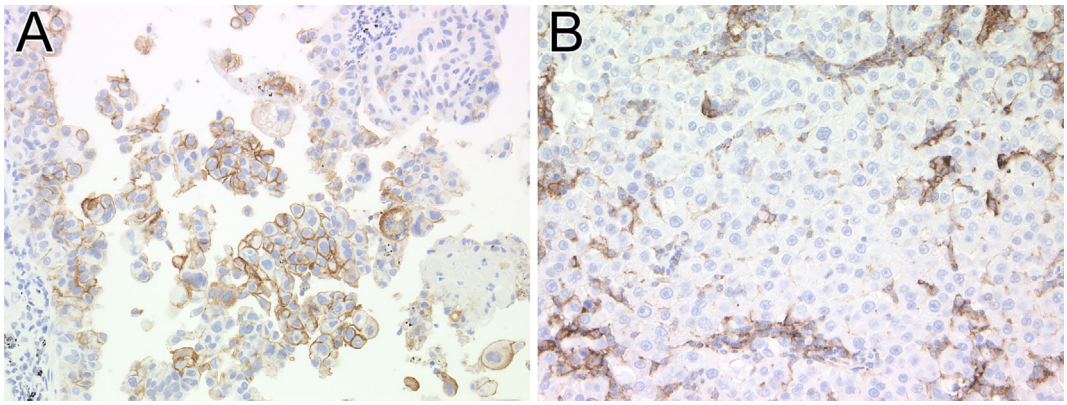

Figure 5. **Anti-PD-L1 immunostaining (PD-L1 IHC 22C3 pharmDx and PD-L1 IHC 28-8 pharmDx) of the bronchoscopy and specimen and a specimen of the resected tumor (A). Membrane staining of the bronchoscopy specimen. More than 50% of the tumor cells (including adenocarcinoma component and choriocarcinomatous features) were positively stained (B). Membrane staining of the resected specimen. Less than 50% of the tumor cells were positively stained.**

of nivolumab, the PD-L1 expression in the lung cancer cells decreased to <50%. We hypothesize that this type of acquisition of resistance may reflect the expression of co-inhibitory receptors or the expression of PD1-independent inhibitory pathways, as a consequence of the lower expression of PD-L1 in the resected specimen.

Some studies have shown that PD-L1 may be a predictive biomarker in anti-PD-1/PD-L1 therapy because PD-L1-positive patients respond better than PD-L1-negative patients (7, 13). This finding suggests that nivolumab should be started earlier for cases with a poor prognosis or with the high expression of PD-L1. Although local therapies, such as surgery after chemotherapy, are effective for stage-IV NSCLC, there is no evidence that such treatments are a good option (14). Little is known about immunotherapy combined with topical treatments for stage-IV NSCLC. However, based on our case, we are of the opinion that immunotherapy may have a better effect on long-term survival

if it is combined with conventional treatment. Thus, long-term follow-up of our patient is needed until relapse occurs. This will help to clarify whether the combination of immunotherapy and local therapy (e.g., surgery, radiotherapy) has a survival benefit for stage-IV NSCLC in comparison conventional chemotherapy. In the future, prospective studies and meta-analyses could provide evidence that such novel combined therapies improve the prognosis of lung cancer.

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

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