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【 CASE REPORT 】

Intracranial Response to Nivolumab in a Patient with PD-L1-negative Lung Adenocarcinoma

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Abstract:

We herein report the case of a 52-year-old man with stage IV lung adenocarcinoma. The patient was negative for epidermal growth factor receptor (EGFR) mutations and echinoderm microtubule-associated protein-like 4 (EML4) /anaplastic lymphoma kinase (ALK) rearrangement. He was treated with nivolumab as a third-line chemotherapy. After four cycles of nivolumab treatment, a partial response was observed in the brain and at the primary tumor site. Nivolumab treatment has been continued for 11 months without progression. Immunohistochemistry revealed that the programmed death-ligand 1 (PD-L1) expression was 0% (according to the tumor proportion score).

Our case indicates that the efficacy of programmed cell death 1 inhibitors is not solely predicted by the PD-L1 status, and that immune checkpoint inhibitors might be effective for the treatment of central nervous system metastasis.

Key words: brain metastasis, nivolumab, lung cancer

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Introduction

Central nervous system (CNS) metastasis is seen in 24-44% of patients with advanced non-small cell lung cancer (NSCLC) (1). The prognosis of patients with CNS metastasis is generally poor, and the efficacy of chemotherapy is limited in cases involving CNS metastasis because of the blood-brain barrier. Recently, several targeted therapies, including epidermal growth factor receptor-tyrosine kinase inhibitors and anaplastic lymphoma kinase-tyrosine kinase inhibitors, have been reported to be effective for the treatment of CNS metastasis from NSCLC with appropriate driver oncogenes.

Nivolumab is a recently-approved human immunoglobulin G-4 (IgG4) anti-programmed cell death 1 (PD-1) antibody. Nivolumab has shown long-acting efficacy for NSCLC in comparison to docetaxel; the programmed cell death-ligand 1 (PD-L1) expression in tumor cells was considered to predict the response to PD-1 antibody treatment in patients with NSCLC (2, 3). However, there has been little information on the efficacy of nivolumab in the treatment of CNS metastasis and PD-L1-negative NSCLC. Thus, we present the case of a patient with PD-L1-negative lung adenocarcinoma and CNS metastasis who responded to nivolumab.

Case Report

A 52-year-old man was referred to our hospital due to headache and dizziness. Brain magnetic resonance imaging

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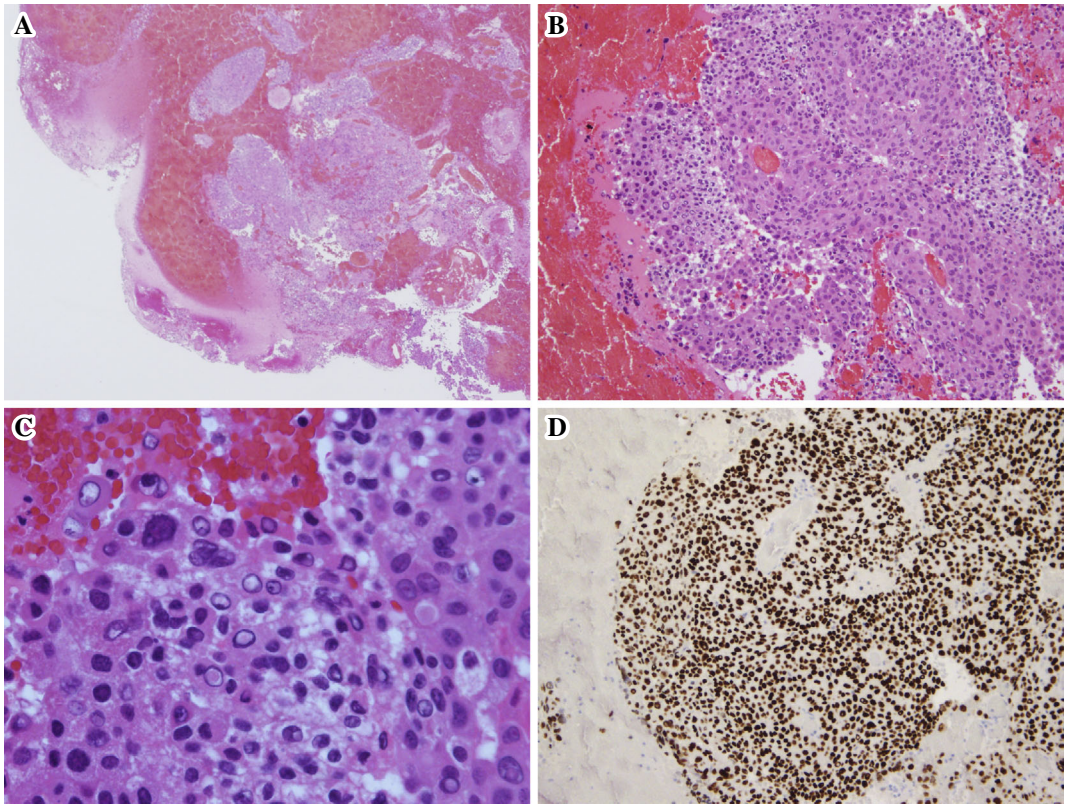

Figure 1. **A: A histological examination revealed that the brain tumor was an adenocarcinoma (×20). B: A histological examination showed that the brain tumor was an adenocarcinoma (×100). C: A histological examination showed that the brain tumor was an adenocarcinoma (×400). D: An immunohistochemical analysis for thyroid transcription factor-1 (TTF-1) was positive.**

(MRI) showed brain tumors in the right cerebellum and right temporal lobe. Craniotomy was performed, and these brain tumors were diagnosed as adenocarcinoma (Fig. 1). Chest computed tomography showed a tumor in his right upper pulmonary lobe. A molecular tumor analysis was performed, and the patient was diagnosed with Stage IV cT1cN0M1c lung adenocarcinoma [per the Union for International Cancer Control's (UICC) TNM classification, 8th ed.]. epidermal growth factor receptor (EGFR) mutation and echinoderm microtubule-associated protein-like 4 (EML4) / anaplastic lymphoma kinase (ALK) rearrangement analyses were performed using a metastatic brain tumor sample; both were negative.

As the metastatic tumors in the right cerebellum remained after craniotomy, the patient underwent whole-brain radiation therapy (30 Gy/10 fr), followed by concurrent chemoradiotherapy consisting of cisplatin (80 mg/m^2, Day 1, every 4 weeks), vinorelbine (20 mg/m^2, Days 1 and 8, every 4 weeks) and thoracic radiotherapy (60 Gy/30 fr). After the concurrent chemoradiotherapy, the patient was treated with two cycles of consolidation chemotherapy consisting of cisplatin (80 mg/m^2, Day 1, every 3 weeks) and vinorelbine (20 mg/m^2, Days 1 and 8, every 3 weeks). However, at three months after the last cycle of consolidation chemotherapy, the metastatic tumor in the right cerebellum became enlarged. The metastatic tumor was treated with stereotactic body radiotherapy (SBRT). At three months after SBRT, the lung tumor became enlarged; he was then treated with combination chemotherapy consisting of carboplatin [6 area under the curve (AUC), every 3 weeks] and nab-paclitaxel (100 mg/m^2, Days 1, 8 and 15, every 3 weeks). However, after the third cycle of this regimen, the primary site in the right upper lung and the metastatic tumor in the right cerebellum progressed.

The patient was treated with nivolumab (3 mg/kg, Day 1) every two weeks as a third-line chemotherapy. After four cycles of nivolumab treatment, the metastatic brain tumor showed a partial response; this was reconfirmed by brain imaging two months later. The primary tumor site also showed a partial response (Fig. 2). We have continued to treat the patient with nivolumab for 11 months without progression in the brain or at the primary site.

Immunohistochemistry (Dako 22C3 assay), which was performed to determine the PD-L1 status of the metastatic brain tumor, revealed a tumor proportion score of 0% (Fig. 3).

Discussion

PD-1 inhibitors nivolumab and pembrolizumab are novel immune checkpoint inhibitors that have been recently approved in Japan. Nivolumab is approved for previously

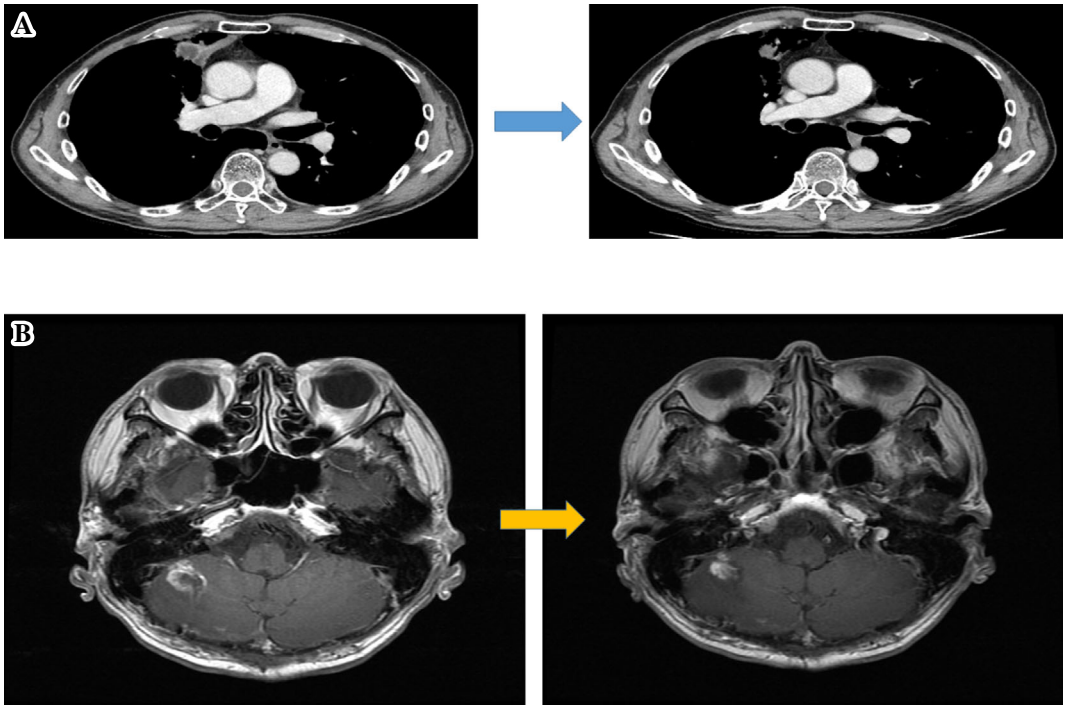

Figure 2. **A: The patient's primary tumor showed a partial response after four cycles of nivolumab treatment. B: A partial response was observed in the metastatic brain tumor after four cycles of nivolumab treatment.**

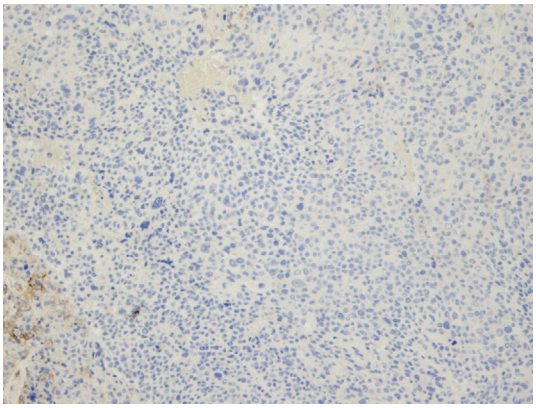

Figure 3. **Immunohistochemistry (Dako 22C3 assay) of the metastatic brain tumor to determine the PD-L1 status revealed a tumor proportion score of 0%.**

treated non-small cell carcinoma regardless of the PD-LI status, whereas pembrolizumab is approved for both treatment-naïve and previously treated non-small cell carcinoma, but is limited to cases involving PD-L1-positive tumors.

The Checkmate 057 trial showed that the PD-L1 status was a predictor of the efficacy of nivolumab in non-squamous NSCLC. The response rate to nivolumab in PD-L1 negative patients was 9% (3). In the Checkmate study, PD-L1 status was ascertained immunohistochemically with Dako 28-8 assays. The Keynote 001 trial showed that PD-L1 status was also a predictor of the efficacy of pembrolizumab in non-small cell carcinoma. The response rate of PD-L1-negative patients to pembrolizumab was 8.1 % (4). In the Keynote trial, the PD-L1 status was assessed immunohistochemically using Dako 22C3 assays. In the Blueprint PD-L1 IHC Assay Comparison Project, the results of 22C3 and 28C8 assays were found to be highly correlated with the PD-L1 status of tumor cells (5). According to the results, the PD-L1 status as analyzed by immunohistochemistry (22C3 assays) seems to be a predictor of the efficacy of nivolumab.

The patient in the present case has shown a long-lasting response to nivolumab, in spite of his PD-L1-negative status. This point suggests that the efficacy of PD-1 inhibitors is not predicted by the PD-L1 status alone.

Information about the efficacy of PD-1 inhibitors in the treatment of CNS metastasis is limited. Dudnik et al. retrospectively reviewed the efficacy of nivolumab in five patients with CNS metastasis from NSCLC, and found a complete response in one patient, and a partial response in another patient (6). The authors reported that these responses were durable and that they were concordant with the systemic responses. The patient's PD-L1 status was not analyzed in this retrospective study. Goldberg et al. reported the results of a phase II trial to investigate the efficacy and safety of pembrolizumab for patients with melanoma or NSCLC and untreated brain metastases. All of the NSCLC patients who were enrolled in this trial had PD-L1-positive tumor tissue. In this trial, responses were achieved in six [33%; 95% confidence interval (CI): 14-59] of the 18 NSCLC patients with brain metastasis (7).

The mechanism underlying the effect of PD-1 inhibitors

on CNS metastases is unknown. Furthermore, no data are available about the cerebrospinal fluid concentrations of PD-L1 inhibitors. However, Baruch et al. reported that PD-1 immune checkpoint blockade evoked an interferon-γ-dependent systemic immune response in mouse models of Alzheimer's disease, and led to the clearance of cerebral amyloid-β plaques and the improvement of cognitive performance (8). This result suggests that immune checkpoint inhibitors could be effective for CNS diseases.

This case report is associated with some limitations. First, it is possible that the brain lesion represented radiation necrosis due to stereotactic body radiotherapy and whole-brain radiation therapy. However, Minniti et al. reported that the median time to symptomatic and asymptomatic radiation necrosis was 11 months and 10 months, respectively, after stereotactic radiosurgery for brain metastasis (9). The brain lesion in our case emerged earlier than these data; we thought that there was a high probability that the brain lesion represented brain metastasis. Second, it was possible that the PD-L1 status at the start of nivolumab treatment had changed after the administration of several chemotherapy regimens and radiotherapy. However, in the Keynote-010 trial, pembrolizumab provided superior overall survival, regardless of whether new or archival samples were used to assess PD-L1. These data suggested that a new biopsy might not be required, and in Japanese clinical practice, it is common for the PD-L1 status to be assessed in the second-line setting using archival samples (10).

In conclusion, to our knowledge, this is the first case report to show a promising effect of nivolumab in a patient with intracranial metastasis from PD-L1-negative NSCLC. Our case indicates that the efficacy of PD-1 inhibitors is not solely predicted based on the PD-L1 status, and that immune checkpoint inhibitor therapy might be effective for NSCLC patients with CNS metastasis. These findings should be confirmed by prospective clinical trials. Furthermore, biomarkers to predict the efficacy of immune checkpoint inhibitors, and the mechanism underlying the effects of immune checkpoint inhibitors on CNS disease should be clarified by further research.

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

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