

Case Report

Different Response to Nivolumab in a Patient with Synchronous Double Primary Carcinomas of Hypopharyngeal Cancer and Non-Small-Cell Lung Cancer

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Keywords

Nivolumab · Programmed death 1 · Non-small-cell lung cancer · Pharyngeal cancer

Abstract

Nivolumab is a humanized IgG4 and programmed death 1 (PD-1) monoclonal antibody that has demonstrated antitumor efficacy in clinical trials of various malignant tumors including non-small-cell lung cancer and head and neck squamous cell carcinoma (SCC). However, patients with multiple primary malignancies were excluded in clinical trials. Thus, the efficacy of nivolumab in such patients has not been revealed yet. The programmed death ligand 1 (PD-L1) expression level is currently the main predictive biomarker of PD-1 inhibitors in various types of solid tumors and hematological malignancies. Here we describe a patient with synchronous double primary carcinomas of hypopharyngeal SCC and lung adenocarcinoma who exhibited different responses to nivolumab. After nivolumab treatment, hypopharyngeal SCC with moderate PD-L1 positivity by immunohistochemical staining showed a remarkable response; conversely, nivolumab was not effective against lung adenocarcinoma, which was

negative for PD-L1. This suggests that tumors with different PD-L1 expressions may exhibit different responses to PD-1 inhibitors when multiple primary malignancies are present within one patient.

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Introduction

Programmed death 1 (PD-1) is a cell surface receptor that is predominantly expressed on activated T and B cells [1–3]. When the PD-1 receptor on T cells binds its ligand, either programmed death ligand 1 (PD-L1) or PD-L2, the T cell receives an inhibitory signal and no longer mounts productive immune responses. Several studies have reported expression of PD-L1 on various human cancer cells, and its expression has been thought to play a major role in inhibiting the immune response in tumors [1, 4].

Nivolumab is a selective, fully human IgG4 monoclonal antibody that binds PD-1 and blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2. Nivolumab is well tolerated, with manageable toxicity, and exhibits substantial anticancer activity in various types of solid tumors [5–8]. However, the response of patients with multiple primary malignancies to nivolumab is not clear, as patients with more than one primary malignancy were excluded from clinical trials.

Here we report the clinical course of a patient with synchronous double primary carcinomas of non-small-cell lung cancer (NSCLC) and hypopharyngeal cancer who exhibited different responses to nivolumab.

Case Presentation

A 60-year-old man was admitted to Fujita Health University Hospital with a tumor in the upper lobe of the right lung in July 2013. He underwent exploratory thoracotomy and pleural dissemination was detected. Histological findings revealed adenocarcinoma of the lung and the stage was cT1cN0M1a, stage IVA. The patient was treated with cisplatin (75 mg/m²) and pemetrexed (500 mg/m²) every 3 weeks. However, he showed disease progression after 6 cycles. The patient then received docetaxel (60 mg/m²) every 3 weeks in January 2014 and continued up to 6 cycles. The lung adenocarcinoma of this patient was relatively slow-growing, and thus he remained treatment-free for 14 months without disease progression after docetaxel treatment. However, a subsequent computed tomography (CT) scan showed an enlarged lymph node in the right neck, and a lymph node biopsy revealed squamous cell carcinoma (SCC) in August 2015. We thus made a diagnosis of hypopharyngeal SCC (cT2N1M0, stage III) and started concurrent chemoradiotherapy with carboplatin (70 Gy in 7 weeks). The tumor shrank and CT scan after the chemoradiotherapy showed partial response. In March 2016, the tumor in the upper lobe of the right lung was enlarged, and we started nab-paclitaxel (100 mg/m²) given weekly for 3 weeks every 28 days. Nab-paclitaxel therapy was effective; however, the patient complained of progressive dyspnea and his neck lymph nodes were enlarged. We performed a lymph node biopsy, and pathological examination revealed SCC. Although nab-paclitaxel was still effective for lung adenocarcinoma, we decided to start nivolumab (3 mg/kg) every 2 weeks in August 2016.

After 4 cycles of nivolumab, tumor shrinkage was detected in the SCC of the neck lymph nodes; however, the adenocarcinoma in the upper lobe of the right lung showed no remarkable response. After 8 cycles, the SCC of the neck lymph nodes showed a durable response to

nivolumab; however, the size of the mass in the upper lobe of the right lung was slightly enlarged (Fig. 1). The responses to nivolumab between the two regions were different; however, the enlarged lymph neck mass that had caused progressive dyspnea was thought to have a larger impact on prognosis than the lung adenocarcinoma. Therefore, we decided to continue nivolumab, and the patient has continued nivolumab without serious side effects over 6 months.

We investigated the expression of PD-L1 in the tumor tissue of the upper lobe of the right lung, pleural metastases, and neck lymph nodes by immunohistochemistry using a rabbit antihuman PD-L1 antibody (clone 28-8, Ab205921). We detected 30% positive staining for PD-L1 expression in the SCC of the neck lymph nodes (Fig. 2). Conversely, the expression of PD-L1 in the lung adenocarcinoma tissue of the pleural metastases was 0%.

Discussion

This report demonstrates different responses to nivolumab in a patient with double primary tumors of lung adenocarcinoma and hypopharyngeal SCC. The number of patients who are diagnosed with multiple primary cancers has been increasing because of improved diagnostic modalities and increased numbers of patients who live longer after the first diagnosis. Patients with multiple primary malignancies are not rare. However, the response to chemotherapy, including nivolumab, for such cases is unclear, because patients with two or more malignancies are generally excluded from large randomized trials.

Several studies have reported that the degree of expression of PD-L1 was associated with an increased response rate in various types of tumors. In CheckMate 057, a randomized phase III trial of nivolumab compared with docetaxel in non-squamous advanced NSCLC, the median overall survival (OS) was significantly higher in the nivolumab group compared with the docetaxel group [6]. The PD-L1 expression level was strongly associated with improved efficacy in patients treated with nivolumab. In patients with low PD-L1 expression (<10%), there was no difference in the median OS between the two treatment arms. In the CheckMate 141 trial, which was the first randomized trial of recurrent/metastatic SCC of the head and neck, the median OS was 7.5 months in the nivolumab group versus 5.1 months in the standard therapy group [7]. Importantly, patients with a PD-L1 expression $\geq 1\%$ had a higher benefit regarding OS and objective response rate.

In the present case, nivolumab was effective against hypopharyngeal SCC that was positive for PD-L1; however, it was not effective against lung adenocarcinoma with PD-L1-negative expression. Nivolumab binds to the PD-1 receptor on activated T cells and prevents binding of the cancer cell-derived PD-L1 and PD-L2; this binding then restores the patient's own antitumor immune response by T cells. Immunotherapy strategies that inhibit the PD-1 pathway will be effective in cases of patients with potentially tumor-reactive T cells. Tumor immunogenicity differs widely among the same cancer types in different patients and among different cancer types [9]. Therefore, the response patterns of PD-1 inhibitors can differ from targeted tumors within one patient. In our case, the difference in the expression level of PD-L1 between the different cancer types was effective to predict a response to nivolumab.

PD-L1 expression is not always associated with a good response to PD-1 inhibitors. Therefore, there has been a critical need for more efficient biomarkers that can predict a response to PD-1 inhibitors. The tumor mutation burden (TMB), which is the total number of mutations per coding area of a tumor genome, is a promising biomarker that predicts response to immunotherapy. The phase III CheckMate 026 trial assessed the efficacy of

nivolumab compared to standard first-line platinum-based chemotherapy in patients with advanced NSCLC whose tumors expressed PD-L1 $\geq 1\%$ [10]. This trial did not meet its primary endpoint; however, exploratory analyses of this trial indicated that the high-TMB subgroup had a greater response rate and longer progression-free survival with nivolumab than with standard chemotherapy, and PD-L1 expression and TMB were not directly linked. Therefore, combination testing of PD-L1 expression and TMB could be helpful for physicians in identifying a larger percentage of patients who might respond to PD-1 inhibitors.

In conclusion, we note that the efficacy of PD-1 inhibitors for patients with multiple primary malignancies has not been established yet. However, it is possible that multiple primary malignancies in one patient may show different responses in the treatment of PD-1 inhibitors, especially when the PD-L1 expression level of each tumor is different.

Acknowledgment

Immunohistochemical staining and scoring of PD-L1 were performed at Pathology Institute Corp. (Toyama, Japan).

Statement of Ethics

The patient provided written informed consent for publication of this case report, and the privacy policy was fully explained.

Disclosure Statement

Dr. Hida obtained research grants from Ono Pharmaceutical, Novartis Pharma, Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, AstraZeneca, Nippon Boehringer Ingelheim, Pfizer, Bristol-Meyers Squibb, Clovis Oncology, Eisai, Takeda Bio, Dainippon Sumitomo Pharma, Abbvie, Merck Serono, MSD, Kyowa Hakko Kirin, Daiichi Sankyo, and Astellas, and has received personal fees from Ono Pharmaceutical, Novartis Pharma, Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, AstraZeneca, Nippon Boehringer Ingelheim, Pfizer, Clovis Oncology, and Bristol-Meyers Squibb. Dr. Kuroda obtained a research grant from Chukyo Clinical Center. All other authors have no conflicts of interest.

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Fig. 1. Computed tomography (CT) scans before and after 8 cycles of nivolumab treatment. **a, b** CT scan showing the lymph node metastasis of the squamous cell carcinoma in the right neck (**a**) and its shrinking after nivolumab therapy (**b**). **c, d** CT scan showing the lung adenocarcinoma in the right upper lobe (**c**) and its slightly increased size after nivolumab therapy (**d**).

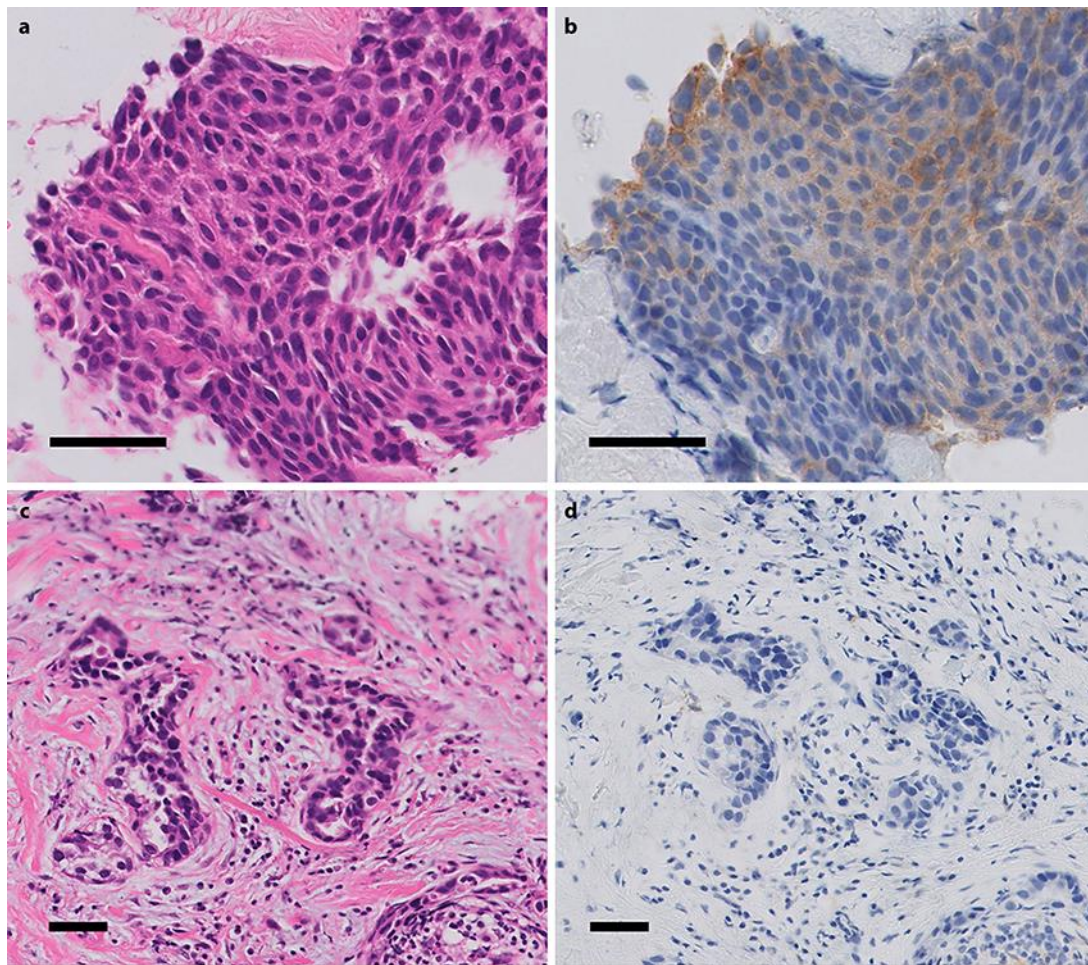


Fig. 2. **a** High magnification of the biopsied lymph node showing squamous cell carcinoma metastasis from the hypopharynx (hematoxylin and eosin staining; scale bar, 20 μm). **b** Area identical to **a** showing membranous PD-L1 staining in 30% of tumor cells (scale bar, 20 μm). **c** Moderately differentiated adenocarcinoma of the lung associated with desmoplastic reaction (hematoxylin and eosin staining; scale bar, 50 μm). **d** Area identical to **c** showing negative PD-L1 immunohistochemical staining (scale bar, 50 μm).