Rapid and Long-term Response of Pulmonary Pleomorphic Carcinoma to Nivolumab

Satoru Senoo¹, Takashi Ninomiya¹, Go Makimoto¹, Kazuya Nishii¹, Hirohisa Kano¹, Hiromi Watanabe¹, Yusuke Hata¹,², Toshio Kubo¹, Takehiro Tanaka³, Katsuyuki Hotta⁴, Yoshinobu Maeda⁵ and Katsuyuki Kiura¹

Abstract:

Pulmonary pleomorphic carcinoma (PPC) is a rare very aggressive subtype of non-small cell lung cancer. We herein report a case of PPC that showed a rapid response to nivolumab. The patient, whose multiple tumors had progressed very aggressively, was treated with nivolumab, an anti-programmed cell death-1 (PD-1) antibody. The tumors dramatically shrank after one cycle of nivolumab. The tumors were positive for programmed cell death ligand 1 (PD-L1). An immunohistochemical analysis revealed numerous PD-1⁺, CD68⁺ and CD206⁺ macrophages. This PD-1 antibody may be a good treatment option, especially in tumors that express PD-L1 and which show PD-1⁺ macrophage infiltration.

Key words: pulmonary pleomorphic carcinoma, immune checkpoint inhibitor, PD-1, PD-L1, FGFR

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Introduction

Pulmonary pleomorphic carcinoma (PPC) is a rare subtype of non-small cell lung cancer that is characterized by an aggressive clinical course (1). PPC is generally resistant to cytotoxic agents, which results in a poor prognosis in most cases. The response rate is reported to be as low as 0-17%, and the disease control rate is only 15-42% (2, 3). Although some case reports have used cytotoxic agents with or without bevacizumab (4), none have proven the efficacy of these regimens. Currently, there is no established treatment other than surgical resection. However, the indication for surgical resection is limited to selected patients due to the aggressive progression of PPC. We herein report a case of PPC harboring a fibroblast growth factor receptor (FGFR) gene copy number increase in which treatment with nivolumab was successful. We also provide the immunohistochemical profile of the macrophages around the patient’s tumors.

Case Report

A 62-year-old man who was an ex-smoker presented to our hospital in June 2016 with complaints of fever and chest pain. He had undergone treatment for diabetes mellitus and percutaneous coronary intervention for acute myocardial infarction at 58 years of age. The patient had smoked cigarettes for 38 years before quitting at 58 years of age. His grandfather had diabetes mellitus. Computed tomography (CT) revealed a solitary 5.0-cm pulmonary mass in the right upper lobe, lymphadenopathy in the mediastinum, a 1.0-cm nodule in the pancreatic tail, and a 1.0-cm nodule in the left adrenal gland. The primary tumor on the right upper lobe was located centrally and had invaded the mediastinum and intervertebral foramen of the second thoracic spine. Although an edge of the tumor was near the thoracic spinal cord, the patient had no symptoms of spinal disorder. He...
underwent bronchoscopy and was pathologically diagnosed with PPC. The tumor had neoplastic spindle cells that were immunohistochemically negative for thyroid transcription factor 1 and p40, with a partial adenocarcinoma component (Fig. 1A). The clinical stage was cT4N3M1b (left lung, pancreas, left adrenal gland, and erector spinae muscle) and stage IV (Union for International Cancer Control TNM Classification, seventh edition). Epidermal growth factor receptor gene mutations and anaplastic lymphoma kinase gene translocation were not detected. Subsequently, the patient was enrolled in clinical trials for comprehensive screening of cancer genes (UMIN000010234 and UMIN000017003), and an increase in the \( \text{FGFR} \) gene copy number (5.37 copies) was detected in the primary tumor.

The patient was treated with one cycle of carboplatin and pemetrexed in July 2016, but progression occurred only 1 month later. The primary tumor had progressed and approached the spinal cord. The metastatic lesions in the pancreas, left adrenal gland, and erector spinae muscle had also progressed rapidly, and a new metastatic lesion had appeared on the right rib. The patient was treated with nivolumab as second-line therapy in August 2016. Soon after the initiation of nivolumab therapy, the patient complained of right chest pain (numerical rating scale: 9/10) and required acetaminophen. The pain stopped the next day, and the patient was able to continue nivolumab without any other adverse events. The right upper lobe tumor was found to have dramatically shrunk just 2 weeks after one cycle of nivolumab (Fig. 2A), and additional shrinkage was seen on X-rays after another 2 weeks of treatment (Fig. 2B and C). A partial response (Response Evaluation Criteria in Solid Tumors ver. 1.1) was confirmed after seven cycles by CT (Fig. 3). In addition, all of the metastatic lesions had shrunk. Hypothyroidism (grade 1, Common Terminology Criteria for Adverse Events, ver. 4.0) was the only adverse event. At the time of writing, nivolumab therapy has been maintained for more than 1 year. No symptoms of spinal disorder have been reported to date. The tumor tested positive for the expression of programmed cell death ligand 1 (PD-L1) using the anti-PD-L1 antibody clone 28-8 (expression level: 70%, Fig. 1B). The expression level of PD-L1, determined using the anti-PD-L1 antibody clone 22C3, was 20% (data not shown). The tissues examined for the expression of PD-L1 were collected at the time of the diagnosis, before the start of treatment. Immunofluorescence staining showed that the cells around the tumors expressed CD68, CD206 and pro-
Discussion

Nivolumab and pembrolizumab are anti-PD-1 monoclonal antibodies. Nivolumab treatment has been associated with longer progression-free survival and overall survival in comparison to docetaxel in patients with non-squamous non-small cell lung cancer, especially in those with PD-L1 expression levels of ≥5% or ≥10% (5). Pembrolizumab has been correlated with a higher objective response rate and longer progression-free survival in comparison to cytotoxic therapies in patients with non-small cell lung cancer with high PD-L1 expression levels (≥50%) in a phase III trial (6). The expression of PD-L1 in tumor cells has been considered as an indication for anti-PD-1 antibody treatment. Because patients with adenocarcinoma or squamous cell carcinoma accounted for a large proportion (almost 90%) of the patients in these trials, the high efficacy of these drugs in treating both adenocarcinoma and squamous cell carcinoma with high PD-L1 expression levels could be demonstrated. However, patients with PPC were not a major group in these trials; thus, the relationship between the efficacy of these drugs and the expression of PD-L1 in PPC patients is not well-understood. Two single-arm phase II clinical studies of...
immune checkpoint inhibitors (nivolumab or pembrolizumab) for sarcomatoid carcinoma of the lung are ongoing in Japan (UMIN000023433 and UMIN000027629). PPC is a subtype of sarcomatoid carcinoma of the lung and these studies include PPC. We await the findings of these studies.

PPC responds remarkably well to PD-1 inhibitors (7-11). In these cases, PD-1 receptors that responded to nivolumab or pembrolizumab had high PD-L1 expression levels. It is possible that the expression of PD-L1 in PPC is an indication for anti PD-1 antibody treatment. Kim et al. evaluated the PD-L1 expression in 41 cases of PPC using immunohistochemistry, in addition to the numbers of CD8+ and PD-1+ tumor-infiltrating lymphocytes (TILs) (12). PD-L1 was highly expressed in PPC tumors (90.2%), and the level of CD8+ or PD-1+ TILs and the ratio of PD-1+/CD8+ TILs were higher in male patients, smokers and older patients. In our case, the tumor cells were positive but not highly positive for PD-L1 (clone 28-8 and clone 22C3 detected PD-L1 expression levels of 70% and 20%, respectively), which is one reason for the response to nivolumab.

Gordon et al. reported that PD-1+ tumor-associated macrophages (TAMs) exhibited an M2-like surface profile, whereas PD-1+ TAMs tended to show an M1-like profile (13). In a mouse model, the blockade of PD-1/PD-1 increased macrophage phagocytosis, reduced tumor growth and prolonged survival (13). In our case, most cells around the tumors expressed CD68, indicating that these cells were macrophages. In addition, the CD206 expression revealed that these macrophages were M2-TAMs and expressed PD-1. Phagocytosis of these macrophages and tumor shrinkage may be induced by PD-1/PD-L1 blockade from nivolumab.

Holdman et al. reported that myeloid-derived suppressor cell (MDSC) infiltration during mammary tumorigenesis in bigenic mice with an introduced oncogene and FGFR gene was significantly enhanced in comparison to transgenic mice harboring only the oncogene, and that FGFR inhibitor treatment resulted in the disappearance of the MDSCs from the residual mammary gland (14). Liu et al. reported that treatment with other FGFR inhibitors inhibited the proliferation and lung metastasis of 4T1 mouse mammary tumor cells and reduced the number of MDSCs in the tumor microenvironment and systemic circulation (15). These results suggest that the FGF pathway is highly involved in MDSC infiltration. MDSCs activate M2-TAMs and regulatory T cells but inhibit CD8+ T cells and NK cells, leading to immune evasion in the tumor microenvironment. It is possible that in our case, M2-TAMs were activated by MDSCs, and that the MDSC infiltration was related to the FGF pathway.

Our patient required local therapy to avert a spinal disorder, particularly after progression during first-line chemotherapy. However, we prescribed systemic chemotherapy because the other lesions in the pancreas, left adrenal gland, and erector spinae muscle had also progressed rapidly, and a new metastatic lesion had appeared. The rapid response to nivolumab enabled us to prevent a spinal disorder and to simultaneously achieve systemic control of the PPC. The chest pain observed in our case was also attributed to an excessive immune response. The PD-L1 expression in the tumors and the PD-1 expression in macrophages around the tumors may result in a strong immune response and good shrinkage.

In conclusion, anti PD-1 antibodies shrink tumors rapidly and should be actively used for PPC expressing PD-L1 and associated with PD-1+ macrophages. A more detailed investigation into the mechanisms underlying the increase in the FGFR gene copy number and PD-1+ M2-TAMs with PD-1 inhibitors is warranted.

Author’s disclosure of potential Conflicts of Interest (COI), Katsuyuki Hotta: Honoraria, Eli Lilly Japan, Pfizer and Chugai Pharmaceutical. Katsuyuki Kiura: Honoraria, Eli Lilly Japan, Nihon Kayaku, AstraZeneca, Daiichi-Sankyo Pharmaceuticals, Chugai Pharmaceuticals, Taiho Pharmaceuticals and Sanofi-Aventis.

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