Remarkable response to pembrolizumab with platinum-doublet in PD-L1-low pulmonary sarcomatoid carcinoma: A case report

Hirokazu Taniguchi1,2 | Shinnosuke Takemoto1 | Mutsumi Ozasa1,3 |
Noritaka Honda1 | Takayuki Suyama1 | Yasuhiro UmeYama1 | Yosuke Dotsu1 |
Takumi Nakao1 | Kojima Tomohito4 | Hiroshi Gyotoku1 | Hiroyuki Yamaguchi1 |
Taiga Miyazaki5 | Noriho Sakamoto1 | Yasushi Obase1 | Minoru Fukuda1,6 |
Junya Fukuoka3 | Hiroshi Mukae1

1Department of Respiratory Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
2Molecular Pharmacology Program and Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA
3Department of Pathology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
4Department of Gastroenterology and Hepatology, Nagasaki University Hospital, Nagasaki, Japan
5Department of Infectious Diseases, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
6Clinical Oncology Center, Nagasaki University Hospital, Nagasaki, Japan

Correspondence
Shinnosuke Takemoto, Department of Respiratory Medicine, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki, 852-8501, Japan.
Email: shinnosuke-takemoto@umin.ac.jp

Abstract
Pulmonary sarcomatoid carcinoma (SC) is an aggressive subtype of lung cancer that exhibits resistance to cytotoxic chemotherapy. Although programmed cell death 1 (PD-1) inhibitors have been reported to show antitumor effects in patients with high programmed death-ligand 1 (PD-L1) expressing SC, the efficacy of combined therapy with PD-1 inhibitor plus cytotoxic chemotherapy has not previously been clarified. We herein report a case of SC with low expression of PD-L1 and few pre-existing tumor-infiltrating lymphocytes which showed a remarkable response to pembrolizumab plus cytotoxic chemotherapy as first-line treatment. Our findings suggest that combined treatment might enhance the immunogenic response, even in immunologically ignored SCs.

KEYWORDS
immunotherapy, programmed death-ligand 1, pulmonary sarcomatoid carcinoma

INTRODUCTION
Pulmonary sarcomatoid carcinoma (SC) is a rare type of non-small cell lung cancer (NSCLC) with a poor prognosis due to rapid tumor growth, early metastasis, and resistance to platinum-based standard chemotherapy.1,2 Novel therapeutic strategies for the treatment of SC are urgently needed to improve clinical outcomes.

Immune checkpoint inhibitors (ICIs) that block programmed cell death 1 (PD-1) and programmed death-ligand 1 (PD-L1), either as single agents or in combination, have led to revolutionary treatments for NSCLC.3–7 A recent retrospective study suggested that single use of PD-1 inhibitor was effective in SC patients as a second- or third-line treatment.8 However, the efficacy of PD-1 inhibitor with platinum-doublet, especially as first-line treatment, has not yet been elucidated.

Here, we report a patient with SC who showed a remarkable tumor response to PD-1 inhibitor, pembrolizumab with carboplatin (CBDCA) plus pemetrexed (PEM), regardless of PD-L1 tumor proportion score (TPS) 1%, and few tumor-infiltrating lymphocytes (TILs) and few PD-1+ immune cells were observed in tumor biopsy samples.
A 65-year-old male patient presented to our hospital with a history of a cough and hip joint pain. Computed tomography (CT) revealed a mass lesion in the left upper lung lobe and a large mass in the left pelvis. Radiographic and pathological evaluations of the biopsy samples from the left lung and pelvic tumors led to a diagnosis of advanced SC with bone metastasis (cT4N0M1c, cStage IVB, UICC version 8). Immunohistochemistry (IHC) analysis of the biopsy sample from the lung tumor demonstrated 1% PD-L1 expression on tumor cells (clone 22C3, Dako) (Figure 1(a),(b)), and no druggable driver mutations were observed.

**CASE REPORT**

A 65-year-old male patient presented to our hospital with a history of a cough and hip joint pain. Computed tomography (CT) revealed a mass lesion in the left upper lung lobe and a large mass in the left pelvis. Radiographic and pathological evaluations of the biopsy samples from the left lung and pelvic tumors led to a diagnosis of advanced SC with bone metastasis (cT4N0M1c, cStage IVB, UICC version 8). Immunohistochemistry (IHC) analysis of the biopsy sample from the lung tumor demonstrated 1% PD-L1 expression on tumor cells (clone 22C3, Dako) (Figure 1(a),(b)), and no druggable driver mutations were observed.
The patient received four cycles of pembrolizumab (200 mg/bodyweight) with CBDCA (AUC 5) plus PEM (500 mg/m²) after palliative local radiotherapy (40 Gy/20 Fr.) to his left pelvis. The tumor in the left lung shrunk significantly and the left pelvic bone metastasis underwent ossification after four cycles of treatment (Figure 2(a),(b)). However, treatment was discontinued because the patient developed pneumonitis and colitis which were considered to be severe immune-related adverse events (iRAEs) (Figure 3(a)–(c)). The patient commenced immunosuppressive treatment with 60 mg of prednisolone 38 days after the initiation of the fourth cycle of treatment. His pneumonitis and colitis fortunately improved; however, the tumor in his left lung had a significant regrowth 84 days after the initiation of prednisolone (Figure 2(c)), whereas the site of bone metastasis was stable, probably due to prior irradiation. After the iRAEs had subsided, the patient received docetaxel (60 mg/m²) plus ramucirumab (10 mg/kg) as second-line treatment because the tumor size had evidently increased in size at that point. However, the mass in the left lung significantly increased after two cycles of docetaxel plus ramucirumab treatment (an increase in diameter from 93 mm before treatment to 125 mm after treatment). The patient chose not to receive third-line therapy and continued with best supportive care due to a decrease in performance status.

IHC review of the biopsy samples from the left lung and pelvic tumor at the time of diagnosis showed that there were few TILs including CD8⁺ T cells (NCL-L-CD8-4B11, Leica Microsystems), CD4⁺ T cells (NCL-L-CD4-1F6, Leica Microsystems), and PD-1⁺ cells (NAT105, Abcam) in both biopsy samples obtained from the primary lung cancer site and metastatic site of the left pelvis (Figure 4(a)–(h)). Written informed consent for the publication of this case report was obtained from the patient. This case study was approved by the Institution Review Board of the ethics committee of our institution (Approval #20122147).

DISCUSSION

PD-1 inhibitors have demonstrated novel therapeutic success by overcoming tumor-induced T cell inhibition. CD8⁺ positive T cells are considered a critical component of antitumor immune response, and increased levels of CD8⁺ TILs have previously been reported to be associated with better outcomes in 552 patients with NSCLC. Pre-existing CD8⁺ T cells distinctly located at the invasive tumor margin have been demonstrated to predict the response to ICIs in several types of cancers. Expression of PD-L1 on tumor cells has also been shown to be a predictive factor for the efficacy of PD-1 inhibition in many solid tumors, including NSCLC. Inflammatory cytokines
such as IFN\(\gamma\) upregulate PD-L1 expression in various cell types and TILs release IFN\(\gamma\) as an adaptive immune resistance.\(^{13}\) Thus, TILs or expression of PD-L1 on tumors have been reported as predictive markers for the effectiveness of PD-1 inhibitors. A previous study reported that the response rate of PD-1 inhibitors tended to be lower in the lower PD-L1 expression cases in SCs.\(^8\)

On the other hand, recent clinical trials showed that the addition of PD-1 or PD-L1 inhibitor with platinum-doublet resulted in significantly longer overall and progression-free survival (PFS) than placebo with platinum-doublet across all categories of PD-L1 expression in patients with NSCLC.\(^{4,5}\) In addition to direct antitumor effects, a combination of PD-1 inhibitor with cytotoxic chemotherapy has previously been reported to enhance the immunogenic response by the release of potentially immunogenic tumor antigens, promotion of the infiltration of CD8\(^+\) T cells, and increasing the ratio of cytotoxic lymphocytes to regulatory T cells,\(^{14-16}\) even in patients with NSCLC that lacked pre-existing T cell infiltrates or low PD-L1 expression, as in the present case.

There are some limitations in the case reported here. The samples that were evaluated might not have captured the whole tumor microenvironment completely because they were obtained by needle biopsy, although the same results were obtained from two other tumor sites. Another limitation is that the tumor shrinkage might partially have been due to the abscopal effect wherein local irradiation can reduce the size of the nonirradiated site mediated by the immune system.\(^{17}\)

In conclusion, pembrolizumab with CBDA plus PEM demonstrated antitumor activity in SC with low PD-L1 expression and few TILs. Further studies using a large cohort are needed to elucidate whether this therapeutic approach contribute to the survival of patients with SC across all categories of PD-L1 expression and pre-existing TILs.

ACKNOWLEDGMENTS
We would like to thank Editage (www.editage.com) for English language editing.
CONFLICT OF INTEREST
The authors report no conflicts of interest related to this work.

ORCID
Hirokazu Taniguchi  https://orcid.org/0000-0003-2414-8344
Shinnosuke Takemoto  https://orcid.org/0000-0003-0373-0618
Minoru Fukuda  https://orcid.org/0000-0002-5321-1843

REFERENCES
1. Vieira T, Antoine M, Ruppert AM, Fallet V, Duruisseaux M, Giroux Leprieur E, et al. Blood vessel invasion is a major feature and a factor of poor prognosis in sarcomatoid carcinoma of the lung. Lung Cancer. 2014;85(2):276–81.
2. Vieira T, Girard N, Ung M, Monnet I, Cazes A, Bonnette P, et al. Efficacy of first-line chemotherapy in patients with advanced lung sarcomatoid carcinoma. J Thorac Oncol. 2013;8(12):1574–7.
3. Gadgeel S, Rodríguez-Abreu D, Speranza G, Esteban E, Felip E, Démine M, et al. Updated analysis from KEYNOTE-189: Pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer. J Clin Oncol. 2020;38(14):1505–17.
4. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, de Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018;378(22):2078–92.
5. West H, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter H, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMPower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20(7):924–37.
6. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 2019;393(10183):1819–30.
7. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373(17):1627–39.
8. Domblides C, Leroy K, Monnet I, Mazières J, Barlesi F, Gounant V, et al. Efficacy of immune checkpoint inhibitors in lung sarcomatoid carcinoma. J Thorac Oncol. 2020;15(5):860–6.
9. Schalper KA, Brown J, Carvajal-Hausdorf D, McLaughlin J, Velcheti V, Syrigos KN, et al. Objective measurement and clinical significance of TILs in non-small cell lung cancer. J Natl Cancer Inst. 2015;107(3). https://doi.org/10.1093/jnci/dju045.
10. Teng MW, Ngio SF, Ribas A, Smyth MJ. Classifying cancers based on T-cell infiltration and PD-L1. Cancer Res. 2015;75(11):2139–45.
11. Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJM, Robert L, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014;515(7528):568–71.
12. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Coszi T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016;375(19):1823–33.
13. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252–64.
14. Zitvogel L, Apetoh L, Ghiringhelli F, Kroemer G. Immunological aspects of cancer chemotherapy. Nat Rev Immunol. 2008;8(1):59–73.
15. Rosell M, Cereda V, di Bari MG, Formica V, Spila A, Jochems C, et al. Effects of conventional therapeutic interventions on the number and function of regulatory T cells. Onco Targets Ther. 2013;2(10):e2705.
16. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013;39(1):1–10.
17. Reits EA, Hodge JW, Herberts CA, Groothuis TA, Chakraborty M, Wansley EK, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. J Exp Med. 2006;203(5):1259–71.