

[CASE REPORT]

Non-small Cell Lung Cancer Treated by an Anti-programmed Cell Death-1 Antibody without a Flare-up of Preexisting Granulomatosis with Polyangiitis

Takahiro Yamada¹, Takeshi Masuda¹, Kakuhiro Yamaguchi¹, Shinjiro Sakamoto¹, Yasushi Horimasu¹, Shintaro Miyamoto¹, Taku Nakashima¹, Hiroshi Iwamoto¹, Shintaro Hirata², Kazunori Fujitaka¹, Hironobu Hamada¹, Eiji Sugiyama² and Noboru Hattori¹

Abstract:

The safety and efficacy of anti-programmed cell death-1 (PD-1) antibodies in patients with granulomatosis with polyangiitis (GPA) still remain unclear. An 83-year-old man with GPA that was well controlled with immunosuppressive therapy was diagnosed with a postoperative recurrence of non-small cell lung cancer (NSCLC). Because the programmed cell death ligand 1 (PD-L1) tumor proportion score was 90%, pembrolizumab was administered. After 10 cycles, immune-related adverse events or GPA flare was not observed, and the patient showed an antitumor response. Anti-PD-1 antibody should therefore be considered a treatment option for PD-L1-high-expressing NSCLC patients with well-controlled GPA.

Key words: non-small cell lung cancer, anti-PD-1 antibody, pembrolizumab, granulomatosis with polyangiitis

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Introduction

A large number of clinical trials have shown the promising antitumor effects of immune checkpoint inhibitors (ICIs), e.g., anti-programmed cell death-1 (PD-1) antibodies and anti-programmed cell death ligand 1 (PD-L1) antibodies, and ICIs have been approved for the treatment of several types of cancers, including lung cancer. However, despite a study showing that 13.5% of patients with lung cancer have autoimmune diseases (AIDs) (1), these patients were excluded from clinical trials because of concerns over a flare-up of AIDs and the high incidence of immune-related adverse events (irAEs) from ICIs. Therefore, the efficacy and safety of ICIs in patients with AIDs have not yet been clarified in a prospective study. However, several retrospective studies have shown that ICIs are safe for patients with AIDs. Previous studies have reported AID flare-ups in 23-

50% of patients receiving ICIs (2-7). However, most of the patients in these studies had rheumatoid arthritis or psoriasis, while no patients demonstrating granulomatosis with polyangiitis (GPA) were enrolled.

GPA is an AID related antineutrophil cytoplasmic antibody (ANCA), which is histopathologically characterized by necrotizing vasculitis and granuloma formations. From 2005 to 2009, the incidence rate of GPA was reported to be as low as 2.1/100,000 person-years, but the number of patients with GPA has recently been increasing in Japan (8). A previous study revealed that the 10-year survival rate in GPA patients was 75-88%, and malignancy was responsible for 12% of all deaths (9, 10). Therefore, it is vital to understand how to best treat cancer patients with underlying GPA.

We herein report the first case of ICI administered to a GPA patient without a flare-up of either GPA or irAEs.

¹Department of Respiratory Internal Medicine, Hiroshima University Hospital, Japan and ²Department of Clinical Immunology and Rheumatology, Hiroshima University Hospital, Japan

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Correspondence to Dr. Takeshi Masuda, ta-masuda@hiroshima-u.ac.jp

Case Report

A 79-year-old man presented to our hospital in September 2014 with the chief complaints of fever and nasal bleeding. Laboratory tests revealed hematuria, proteinuria, and high titer of myeloperoxidase-ANCA (>100 U/mL). Based on these findings, he was clinically diagnosed with GPA. The administration of 40 mg/day prednisolone (PSL) was started. His GPA was well controlled, and the myeloperoxidase-ANCA test results had been negative since February 2015. Thereafter, immunosuppressive therapy was tapered down to 0.5 mg/day PSL and 4 mg/week methotrexate (MTX) without any flare-up of GPA.

In June 2017, he developed hemoptysis. The cytokeratin 19 fragment (CYFRA) level increased to 33.2 ng/mL, and computed tomography (CT) showed a pulmonary mass in the right lower lobe. After detailed examinations, he was diagnosed with non-small cell lung cancer (NSCLC), cT3N2M0, stage IIIB (Union for International Cancer Control TNM Classification, eighth edition). He underwent surgical resection of the right middle and lower lobes with re-

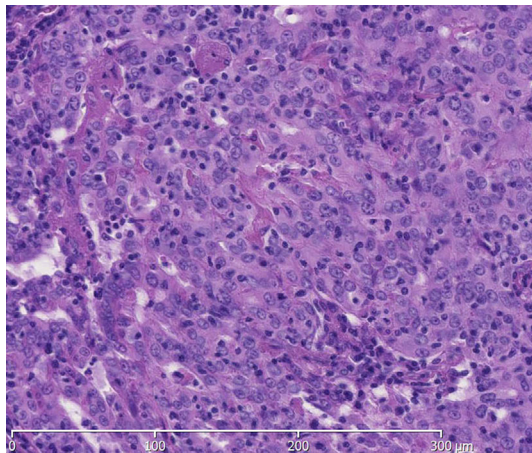


Figure 1. The pathological findings of lung cancer (Hematoxylin and Eosin staining).

gional lymph node dissection. The tumor had sheet-like neoplastic spindle cells that were immunohistochemically negative for thyroid transcription factor 1, napsin A, p40, cytokeratin 5/6, CD 56, synaptophysin, and chromogranin A (Fig. 1). Finally, he was diagnosed with large cell lung carcinoma, p-T3N2M0, stage IIIB. The PD-L1 tumor proportion score, which was determined using the anti-PD-L1 antibody clone 22C3, was 90%. Neither any epidermal growth factor receptor gene mutation or anaplastic lymphoma kinase gene arrangement was detected. As a result, it was decided that he should be followed closely without chemotherapy.

Approximately 8 months after the surgery, he complained of right back pain. The CYFRA level again had increased to 13.2 ng/mL (Fig. 2), and CT showed a tumor in the right chest wall, along with nodules in the left lung, mediastinal lymphadenopathy and a mass in the left adrenal gland. ¹⁸F-fluorodeoxyglucose (¹⁸FDG) positron emission tomography revealed an ¹⁸FDG uptake in these lesions (Fig. 3). Based on these findings, he was diagnosed with a recurrence of lung cancer. At that time, the activity of GPA was low e.g. he had no symptoms due to GPA and laboratory abnormalities including myeloperoxidase-ANCA. Based on these results, pembrolizumab, an anti-PD-1 antibody, was started at a dosage of 200 mg/body every 3 weeks, as the first-line systemic treatment. Three months after the initiation of the therapy, a good partial antitumor response was achieved (Fig. 4), and the CYFRA level decreased (Fig. 2). At the time of writing this report, pembrolizumab therapy was maintained for more than 6 months with no adverse events, including no GPA flare-ups.

Discussion

We herein present the first case of NSCLC with GPA that was treated with anti-PD-1 antibody without any adverse events, including no flare-ups of GPA. The patient's GPA was well controlled, and at the initiation of pembrolizumab, he had a negative ANCA test result and no symptoms due to

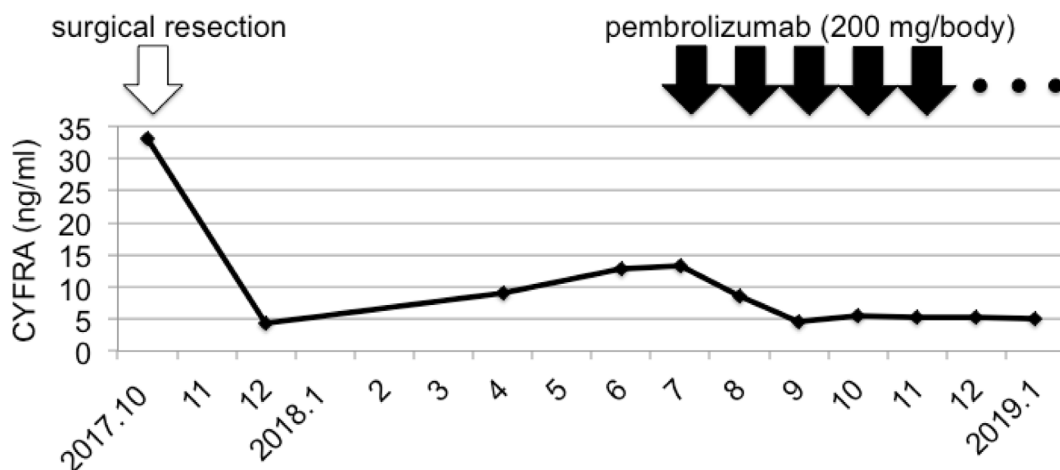


Figure 2. The treatment for lung cancer and the changes in the tumor marker levels are shown.

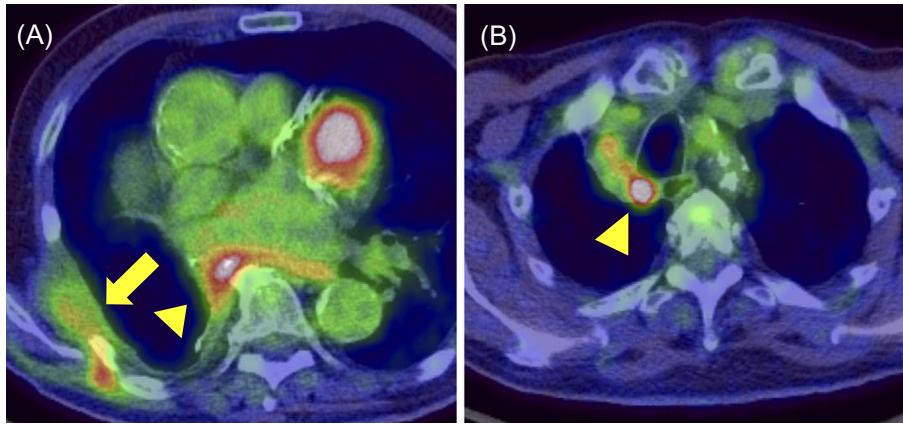


Figure 3. (A) and (B) ^{18}F -fluorodeoxyglucose positron emission tomography revealed a fluorodeoxyglucose uptake in the right chest wall (arrow) and mediastinal lymph nodes (arrowheads).

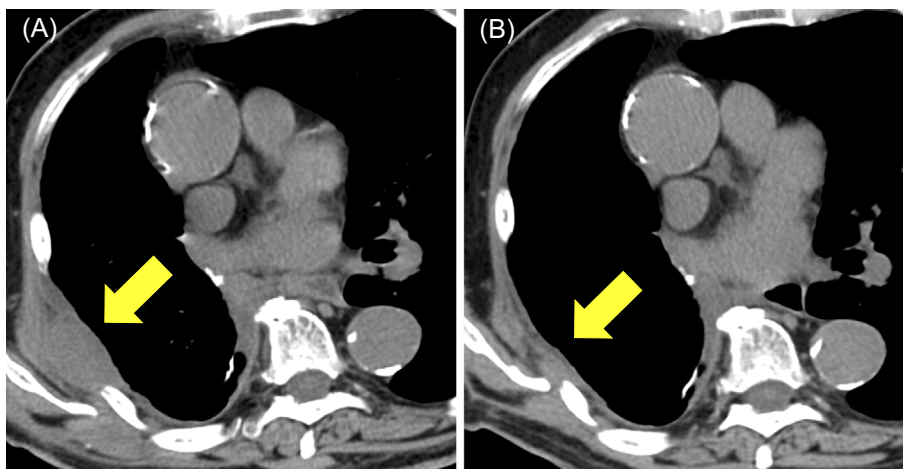


Figure 4. Chest computed tomography before (A) and after (B) the four cycles of pembrolizumab treatment. The arrows indicate the presence of tumors in the right chest wall.

GPA. We consider this to be the reason why he did not experience any GPA flare-ups after the administration of anti-PD-1 antibody. A previous study that investigated the safety of administering anti-PD-1 or -PD-L1 antibodies in 56 NSCLC patients with AIDs showed the incidence of AIDs flare-ups to be 23% (5). That study also reported a significantly lower incidence in patients with asymptomatic AIDs than in patients with symptomatic AIDs [18% (8/45) vs. 50% (5/10), $p=0.04$]. Therefore, patients with asymptomatic AIDs would be at a lower risk of flare-ups with ICI treatment. Most of the patients enrolled in that study had rheumatoid arthritis or psoriasis, and patients with GPA were not included. However, another report showed that patients with asymptomatic eosinophilic granulomatosis with polyangiitis, which belongs to ANCA-related vasculitis as well as GPA, did not develop any flare-ups through 17 cycles of pembrolizumab therapy (11). Therefore, it would be reasonable to consider that the risk of flare-ups would be low in patients with asymptomatic GPA. In addition, a previous study demonstrated that the PD-1 expression on helper T cells from the peripheral blood is higher in patients with active GPA

than in those with quiescent GPA (12). This result indicates that PD-1 is a negative costimulator in patients with GPA and it might counterbalance the presence of persistent T-cell activation. Therefore, we consider that the risk for a flare-up of GPA by inhibiting PD-1 would be higher in patients with active GPA than in those with quiescent GPA.

In the present case, the patient's GPA was treated with immunosuppressive therapy of PSL and MTX, which are considered to reduce the effect of anti-PD-1 antibody. However, we observed a partial antitumor response. A previous study showed that both the progression-free survival and overall survival of patients receiving ICI treatment were significantly longer in patients administered less than 10 mg of PSL than in those administered more than or equal to 10 mg of PSL (13). This cutoff value of PSL (i.e., 10 mg/day) was considered to be in the range of physiologic adrenal replacement, and ICI treatment with less than 10 mg PSL has been observed to overcome any deleterious effects to the immune system. The effect of immunosuppressive agents, such as MTX but not PSL, has yet to be evaluated; however, limited treatment (i.e., 0.5 mg/day PSL and 4 mg/week MTX) in

this patient was shown to result in a favorable antitumor effect.

In this case, no flare-up of GPA was observed. However, in a previous case, ICIs induced GPA as an irAE in an ANCA-positive melanoma patient (14). We are currently not able to predict the onset of an AIDs flare-up in patients receiving ICI treatment. A previous study showed that a flare of preexisting AIDs in patients receiving ICIs occurred from 1 to 260 days after the initiation of ICIs (5). Therefore, we should pay attention to the occurrence of any flare-ups of AIDs for a long period of time after the initiation of ICI treatment.

Conclusion

We herein described the first known NSCLC patient with asymptomatic GPA treated by ICIs who did not experience any GPA flare-ups. The patient achieved a good antitumor response through ICI administration while receiving a limited dose of immunosuppressive therapies. This case suggests that we should consider administering ICIs to asymptomatic GPA patients treated with immunosuppressive therapies under an equivalent of 10 mg/day PSL. In the future, we need to prospectively investigate the risk factors for AID flare-ups in patients receiving ICI treatment.

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

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