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Case Report

Successful Treatment of a Patient with anti-PD1 Antibody-Resistant Advanced Mucosal Melanoma with Nivolumab, Ipilimumab plus Denosumab Combination Therapy

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Keywords
Mucosal melanoma · Bone metastasis · Nivolumab plus ipilimumab combination therapy · Denosumab

Abstract
Since the incidence of mucosal melanoma is higher in the Japanese population compared to Caucasians, and since mucosal melanoma possesses a lower mutation burden compared to cutaneous melanoma, the efficacy of anti-PD1 antibody (Ab) monotherapy for mucosal melanoma is limited. Therefore, other targeting molecules that enhance the anti-tumor effects of immune checkpoint inhibitors are needed. In this report, we present a case with anti-PD1 Ab-resistant recurrent malignant melanoma of the nasal cavity successfully treated with nivolumab, ipilimumab plus denosumab combination therapy.

Introduction

Since the incidence of mucosal melanoma is higher in the Japanese population compared to Caucasians [1], and since mucosal melanoma possesses a lower mutation burden compared to cutaneous melanoma [2], the efficacy of anti-PD1 antibody (Ab) monotherapy for mucosal melanoma is limited [3, 4]. In addition, the efficacy of ipilimumab monotherapy in patients with nivolumab-resistant melanoma is extremely low after objective tumor progression [5].

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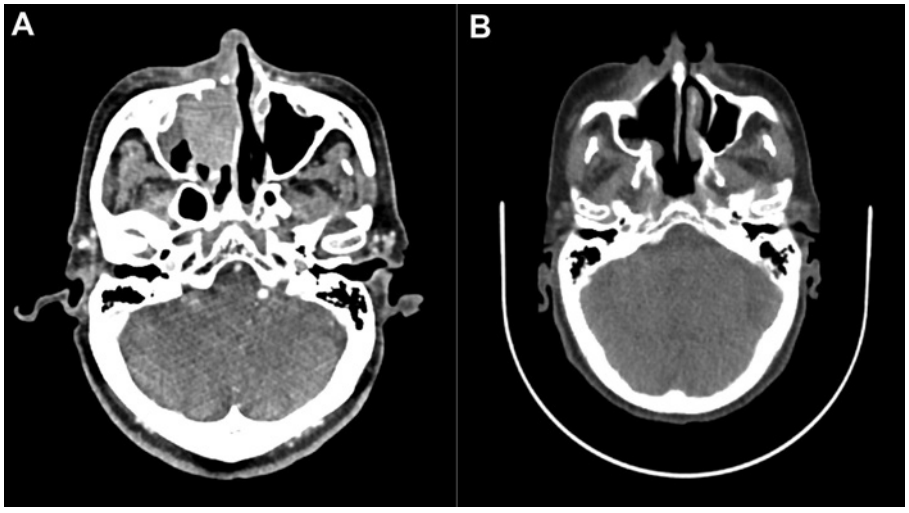

Fig. 1. CT scan before radiotherapy: local recurrence of melanoma, 36.80 × 26.78 mm in size, in the nasal cavity (**A**). MRI at 2 months after IMRT treatment: regression of the tumor (**B**).

Therefore, other targeting molecules that enhance the anti-tumor effects of immune checkpoint inhibitors (ICIs) are needed. In this report, we present a case with anti-PD1 Ab-resistant recurrent malignant melanoma of the nasal cavity successfully treated with nivolumab, ipilimumab plus denosumab combination therapy.

Case Report

The patient was an 81-year-old Japanese woman described in the *Journal of Dermatology* in 2019 [6]. Twenty-one months after the administration of pembrolizumab monotherapy, follow-up computed tomography (CT) scan revealed the local recurrence of melanoma, 36.80 × 26.78 mm in size, in the nasal cavity (Fig. 1A). Since the recurrent tumor was limited to the nasal cavity, we employed intensity-modulated radiotherapy (IMRT) using CyberKnife with 45 Gy in 9 fractions. Two months after the radiotherapy, magnetic resonance imaging (MRI) revealed regression of the tumor (Fig. 1B). However, 3 months after tumor regression, follow-up positron emission tomography (PET)-CT revealed multiple metastases in the lungs, scapula, and subcutaneous lesions (Fig. 2A). Since the melanoma was BRAFV600E mutation negative, nivolumab (80 mg/kg/every 3 weeks) was given in combination with ipilimumab (3 mg/kg/every 3 weeks) for 4 cycles without any adverse events. In addition, since this patient showed metastatic melanoma of the bone, we administered denosumab 120 mg every month. Three months after the first administration of nivolumab plus ipilimumab combination therapy, the multiple metastases in the lungs, scapula, and subcutaneous lesions had regressed (Fig. 2B). We continued to administer pembrolizumab (240 mg/kg/every 3 weeks), and there was no evidence of recurrence 6 months after achieving complete remission.

Discussion

The combination or sequential administration of nivolumab and ipilimumab with a planned switch is among the most effective chemotherapies against advanced melanoma [7, 8], but the efficacy of ipilimumab monotherapy in patients with nivolumab-resistant cuta-

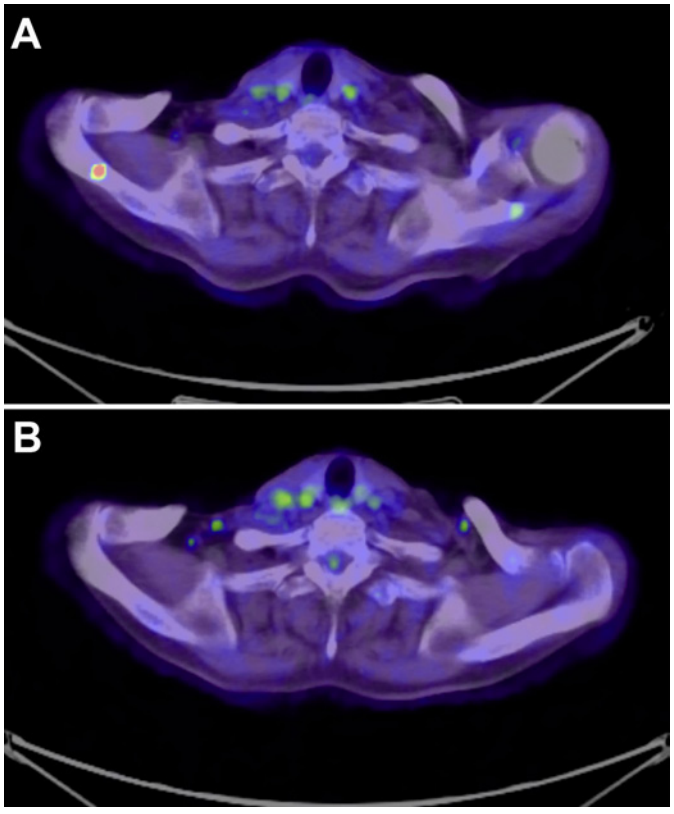

Fig. 2. PET-CT image: metastasis at the scapula before (**A**) and after (**B**) combination therapy.

neous and mucosal melanoma is low after objective tumor progression compared to its efficacy in patients with planned-switched treatment [5, 9]. These reports suggested that the efficacy of nivolumab plus ipilimumab combination therapy in anti-PD1 Ab therapy-resistant patients is lower than that in anti-PD1 Ab therapy-naïve patients. In addition, recently, Hamid et al. [4] has reported the results of a case series with mucosal melanoma treated with pembrolizumab monotherapy. The objective response rate to pembrolizumab for ipilimumab therapy-naïve mucosal melanoma patients was 22%, suggesting a poor prognosis for mucosal melanoma compared to cutaneous melanoma patients [10]. Therefore, additional methods to enhance the anti-tumor effects of ICIs in patients with mucosal melanomas are needed.

To enhance the anti-tumor effects of anti-PD1 Abs, not only the induction of CD8+ T cells in the tumor lesion [11, 12], but also other targeting molecules that enhance the anti-tumor effects of ICIs should be taken into account [13]. Recently, Ahern et al. [14, 15] have highlighted the therapeutic effects of co-administration of anti-RANKL Abs with ICIs, such as anti-PD1 Abs and anti-CTLA4 Abs, against melanoma by the suppression of $RANKL^{+}$ $PD1^{high}CD8$ T cells in a B16F10 mouse melanoma model. They concluded that anti-RANKL Abs could enhance the anti-melanoma effects of ICIs. Indeed, in clinics, anti-RANKL Abs enhanced the therapeutic effects of ipilimumab in patients with terminal-stage metastatic melanoma [16, 17]. These reports suggested that denosumab might improve the therapeutic effects of nivolumab plus ipilimumab combination therapy against advanced anti-PD1 Ab-resistant mucosal melanoma.

In this report, we described a case of anti-PD1 Ab-resistant advanced mucosal melanoma treated with nivolumab, ipilimumab plus denosumab combination therapy. Our present case suggested that nivolumab, ipilimumab plus denosumab combination therapy is not only useful for conventional cutaneous melanoma as we previously reported [17], but also useful for recurrent anti-PD1 Ab-resistant mucosal melanoma as a second-line therapy.

Statement of Ethics

The patient gave written informed consent.

Disclosure Statement

The authors have no conflicting interests to declare.

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Author Contributions

Taku Fujimura designed the research study. Taku Fujimura, Yumi Kambayashi, Ohuchi Kentaro, Ryo Amagai, Sato Yota, Tanita Kayo, and Akira Hashimoto treated the patient and acquired the clinical data. Taku Fujimura wrote the manuscript. Taku Fujimura and Setsuya Aiba supervised the study.

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