J Infect Chemother 23 (2017) 774–777

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Case Report

Uveitis induced by programmed cell death protein 1 inhibitor therapy with nivolumab in metastatic melanoma patient

Hiroaki Kanno [a], Kyoko Ishida [a, b, *], Wataru Yamada [a], Takashi Nishida [a], Nobumichi Takahashi [a], Kiyofumi Mochizuki [a], Yuki Mizuno [c], Kanako Matsuyama [c], Tomoko Takahashi [c], Mariko Seishima [c]

[a] Department of Ophthalmology, Gifu University Graduate School of Medicine, Gifu, Japan
[b] Department of Ophthalmology, Toho University Ohashi Medical Center, Tokyo, Japan
[c] Department of Dermatology, Gifu University Graduate School of Medicine, Gifu, Japan

ARTICLE INFO

Article history:
Received 4 March 2017
Received in revised form
2 April 2017
Accepted 10 April 2017
Available online 18 May 2017

Keywords:
Immune checkpoint inhibitors
Programmed cell death-protein 1
Nivolumab
Uveitis
Melanoma

ABSTRACT

Nivolumab, a new immune checkpoint inhibitor, binds to programmed cell death-protein 1 receptors on T cell, blockades binding of its ligands, and augments the immunologic reaction against tumor cells. Augmented immune response, however, may lead to immune-related adverse events. Herein we describe a rare case of bilateral anterior uveitis induced by nivolumab treatment for metastatic melanoma. A 54-year-old woman presented with mild conjunctival redness and blurred vision two months after initiating nivolumab treatment. Ophthalmological examination revealed bilateral non-granulomatous anterior uveitis. The flare values in the anterior chamber were monitored as an objective inflammatory index during nivolumab therapy and clinical time course was reported in this paper.

1. Introduction

A new immune checkpoint inhibitor, nivolumab was recently approved for the treatment of metastatic melanoma and other refractory cancer. Nivolumab, is a fully human monoclonal IgG4 antibody, and it binds to programmed cell death-protein 1 (PD-1) receptors on T cell and inhibits binding of its ligands (PD-L1 and PD-L2) to restore the host's immune response to tumors [1]. Tumor cell sometimes express PD-1 receptors and PD-1 receptor expression is a potential mechanism by which tumor cells inhibit the immune system. Therefore, PD-1 inhibition may have two potential benefits by activating T-cell proliferation and by inhibiting PD-1 expressing tumor cells [1]. As a consequence of impaired self-tolerance from loss of T-cell inhibition, however, immune-related adverse events from immune checkpoint inhibitors occurs [2]. They can potentially involve every organ system. The clinical studies suggest that the main adverse events associated with the use of nivolumab are diarrhea, skin toxicities, endocrinopathies, hepatitis, pneumonitis, and colitis [1–4]. Ocular toxicity with nivolumab is uncommon. Herein we report on a case that developed bilateral anterior uveitis secondary to treatment with nivolumab.

2. Case report

A 54-year-old woman with metastatic melanoma whose primary site was not known was referred to ophthalmologic evaluation. Before an ophthalmic examination, the diagnosis of metastatic malignant melanoma was made by stomach and dorsum skin lesions (Fig. 1A). Local excisions of the skin showed metastatic malignant melanoma (Fig. 1B and C). Immune phenotype was Melan-A+, HMB45+, and S100+. Chest and abdominal computed tomographic images showed mesenteric and para-aortic lymphadenopathy with multiple retroperitoneum, lung, and liver metastases.

On ophthalmic exams, her best-corrected visual acuity (VA) was 24/20 OU, and the intraocular pressure (IOP) was 12 mmHg OU. Slit-lamp and fundus examinations showed no sign of ocular disease. The flare value measured by a laser flare meter (Aqueous flare cell

* Corresponding author. Department of Ophthalmology, Toho University Ohashi Medical Center, 2-17-6 Ohashi, Meguro-ku, Tokyo 153-8515, Japan. Fax: +81 3 3468 2926.
E-mail address: kyoko.ish@gmail.com (K. Ishida).

http://dx.doi.org/10.1016/j.jiac.2017.04.007
1341-321X/

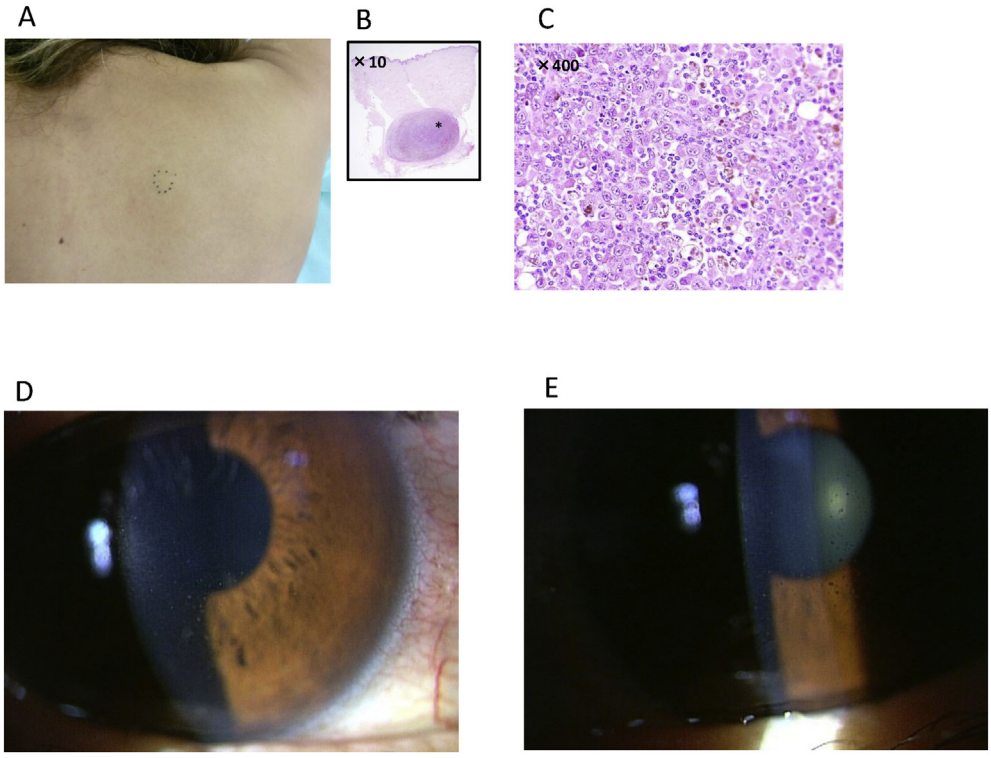

Fig. 1. A: Dorsum skin photograph showing subcutaneous tumor. An elastic hard tumor of the 4 mm size is located in black dots circle. B: Histopathologic sample obtained from the dorsum skin (Hematoxylin and Eosin, 10×). *Nodular lesion with clear borderline is present in subcutaneous adipose tissue. C: Histopathologic findings of malignant melanoma (Hematoxylin and Eosin, 400×). Large atypical cells with marked nucleus proliferate diffusely. Melanin granular in cytoplasm and divisions of the nucleus are observed. D and E: Photographs of the anterior segment of a patient with malignant melanoma treated by nivolumab. D: Slit-lamp image of the right eye shows conjunctival injection and small, non-granulomatous keratic precipitates. E: Slit-lamp image of the left eye shows non-granulomatous keratic precipitates. The inflammation developed after the fourth treatment of nivolumab.

analyzer FM-600, Kowa, Tokyo, Japan) was 4.6 photons/msec OD and 8.0 photons/msec OS.

She was diagnosed with stage IV (T × N3M1c) melanoma without the V600 *BRAF* mutation. The treatment with intravenous dacarbazine (190 mg/day), alkylating agents once a day for 5 days was initiated. One month later, nivolumab intravenous infusion 2 mg/kg every 3 weeks was started.

After the 4th treatment of nivolumab (Total dose; 480 mg), she noticed mild conjunctival redness of her eyes and the binocular blurred vision. Her VA was 20/20 OU, and IOP was 15 mmHg OD and 13 mmHg OS. Slit-lamp examination revealed bilateral ciliary injection, +1 anterior chamber cells (by Standardization of Uveitis Nomenclature, SUN, criterion [5]), and mild non-granulomatous keratic precipitates on the posterior surface of the cornea (Fig. 1D and E). The flare value in the anterior chamber was elevated to 129.3 photons/msec OD and 110.3 photons/msec OS (Fig. 2). There was no ocular metastasis of melanoma. Funduscopic examination, fluorescein angiography, optical coherence tomography, ultrasound biomicroscopy, and electrophysiological examination revealed no abnormal findings. A complete laboratory work-up to rule out infectious or autoimmune causes of uveitis was performed, however, the results were negative for any associated disease. A diagnosis of bilateral anterior grade 2 uveitis (The CTCAE classification [6]) induced by nivolumab was made. Because nivolumab therapy had the potential to prolong the patient's lifetime [7,8], it was continued. The patient was treated topically with 0.1% betamethasone eye drops and the follow-up visit showed progressive reduction of inflammation (Fig. 2). The nivolumab therapy was repeated 2 more times (Total dose; 780 mg) and an improvement of the metastatic melanoma was detected. However, she developed acute interstitial nephritis and was treated with tapered prednisone after a starting dose of 30 mg/day orally. Four and half months after the last administration of nivolumab, anterior uveitis resolved completely and topical steroid was tapered off.

3. Discussion

Harnessing the immune system is an effective strategy for treating melanoma and other cancers [8]. Activation of the PD-1 receptor inhibits T-cell response; inhibiting the PD-1 receptors with nivolumab increases T-cell activation and anticancer activity [7]. However, adverse immunologic reaction, such as immune-mediated pneumonitis, hepatitis, acute renal failure, colitis, hypothyroidism, and hyperthyroidism, have been reported with PD-1 inhibitors [1–4,7]. According to the package insert of nivolumab, uveitis occurred in less than 1% of 1887 patients treated in clinical trial [8].

A case with uveitis as an ocular adverse event from nivolumab was first reported in 2016 [9]. A 60-year old man with metastatic renal cell carcinoma showed arthropathy after 4 doses of nivolumab therapy (10 mg/kg once every 3 weeks) and grade 2 uveitis with cystoid macula edema at 28 cycle (month 14). Laterality was not mentioned. The second case was a 66-year-old woman with grade 2 bilateral anterior uveitis occurred after 4 doses of nivolumab therapy (3 mg/kg every 2 weeks) for lung carcinoma [8]. The third case was a 55-year-old man with malignant melanoma. Bilateral acute anterior uveitis with Vogt–Koyanagi–Harada-like eruptions was induced two weeks after initiation of nivolumab therapy (The treatment dose was not clarified) [10]. Although these authors reported recoveries from uveitis with intraocular steroid