Int. J. Oral Maxillofac. Surg. 2019; 48: 488–491
https://doi.org/10.1016/j.ijom.2018.07.025, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Case Report
Oral Medicine

Drug-induced oral lichenoid reaction during nivolumab therapy

Y. Enomoto[1], H. Nakatani[2], S. Kondo[3], T. Kasai[4], Y. Tsuchiya[1]
[1]Department of Oral and Maxillofacial Surgery, Tochigi Cancer Center, Japan; [2]Department of Otolaryngology, Head and Neck Surgery, National Hospital Organization Fukuyama Medical Center, Japan; [3]Department of Oral and Maxillofacial Surgery, Faculty of Medicine, Fukuoka University, Japan; [4]Department of Medical Oncology, Division of Thoracic Oncology, Tochigi Cancer Center, Japan

Y. Enomoto, H. Nakatani, S. Kondo, T. Kasai, Y. Tsuchiya: Drug-induced oral lichenoid reaction during nivolumab therapy. Int. J. Oral Maxillofac. Surg. 2019; 48: 488–491. © 2018 International Association of Oral and Maxillofacial Surgeons. Published by Elsevier Ltd. All rights reserved.

Abstract. Oral lichenoid reaction, an immune-related adverse event of immunotherapy, has been reported in very few patients receiving anti-programmed cell death receptor-1 (anti-PD-1) therapy. Here, we describe a case of severe stomatitis (grade ≥3 by the Common Terminology Criteria for Adverse Events, version 4.0) accompanied by pharyngolaryngitis that was observed in a patient receiving nivolumab therapy. The stomatitis was diagnosed as drug-induced lichenoid reaction. Nivolumab therapy was discontinued, and the patient was administered systemic prednisolone (1 mg/kg). Most of the patient's mucosal changes in the oral cavity and pharyngolarynx resolved within approximately 3 weeks after starting the prednisolone. Clinicians should be aware that severe oral lichenoid reactions can occur in patients receiving anti-PD-1 therapy.

Key words: anti-PD-1 antibody therapy; oral lichenoid reaction; immune-related adverse event.

Accepted for publication
Available online 28 August 2018

Nivolumab, a monoclonal antibody drug targeting the programmed cell death receptor-1 (PD-1), has been shown to enhance immune responses and have great clinical efficacy in the treatment of various cancers. However, immune-related adverse events (irAEs) in multiple organ systems are a well-recognized consequence of immunotherapy.

According to the literature, cutaneous irAEs are the most common side-effects of immunotherapy. Moreover, cutaneous irAEs are observed in 8.7% of patients receiving anti-PD-1 therapy; these are usually mild and well controlled by supportive therapy[1,2]. Cutaneous irAEs of anti-PD-1 therapy include lichenoid skin reactions[1–5]. Histopathological findings have reportedly shown interface dermatitis with a lymphocytic infiltrate in the dermoepidermal junction as well as basal and suprabasal apoptotic keratinocytes.

Detailed reports of immunological and clinicopathological examinations of oral lichenoid reactions (OLRs) caused by anti-PD-1 antibody are quite scarce[1,6,7]. In particular, there are no detailed case reports of severe OLRs in patients receiving nivolumab therapy. Here, we report a case of severe OLR in a patient who was receiving nivolumab therapy for lung adenocarcinoma.

Case Description

A 52-year-old man diagnosed with advanced lung adenocarcinoma had undergone chemotherapy (six cycles of carboplatin/pemetrexed and 32 cycles of docetaxel/bevacizumab), which resulted in a complete response according to the Response Evaluation Criteria in Solid Tumors (RECICT, version 1.1). Approximately 22 months after his last treatment, a recurrence was found, at which point the patient was started on nivolumab (3 mg/kg) every 2 weeks.

Twenty-two weeks after the initial treatment with nivolumab, which was 3 days

 © 2018 International Association of Oral and Maxillofacial Surgeons. Published by Elsevier Ltd. All rights reserved.

after his 10th dose, the patient developed severe pain in his oral cavity. Haemorrhagic erosions were found along the ventral surface of the tongue (Fig. 1A), floor of the mouth, buccal mucosa and alveolar gingiva. The stomatitis was clinically estimated to be grade 3 according to the Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE V4.0)[8]. There was no involvement of the face or body surface. The patient had no relevant history of skin and mucosal disorders, autoimmune disorders or recent exposure to radiation, and he had not received any new medications of late. However, he occasionally took famotidine for more than 7 years. Because topical corticosteroid treatment was ineffective for the stomatitis and associated symptoms, the nivolumab therapy was discontinued. The patient was tested for autoantibodies, including anti-desmoglein (Dsg) 1, anti-Dsg3, and anti-bullous pemphigoid (BP)-180. Approximately 1 month after the onset of the oral symptoms, biopsies were taken from the erosions of the buccal mucosa and the internal surface of the lower lip, which seemed to be unaffected except for light erythema.

Twenty-eight weeks after the initial nivolumab therapy, the patient complained of dysphagia and severe sore throat, and laryngeal endoscopy revealed severe pharyngolaryngitis (Fig. 1B). The patient was immediately administered systemic prednisolone orally (1 mg/kg). He received a tapered course of steroids without hospitalization, and most of the mucosal changes in the oral cavity and pharyngolarynx resolved within approximately 3 weeks. The treatment for lung cancer was discontinued until the mucosal changes resolved completely, which took about 3 months with steroid therapy. Nivolumab therapy was not re-challenged.

Histological Findings and Blood Examinations

Histological analysis of the biopsied lesions showed a band-like infiltration of lymphocytes in the subepithelium, accompanied by separation of the basal layer in the tissue of the erosive lesion (Fig. 2A). Another tissue specimen, taken from the internal surface of the lower lip, showed small cracks between the epithelial layer and subepithelial connective tissues in the basement membrane zone and acanthosis (Fig. 2B). Clear subepithelial blistering was not found in either of the specimens.

Immunohistochemical staining demonstrated the following immunoprofile: CD3-positive, CD4-positive, CD8-positive, and CD20-negative.

The patient was found to be negative for anti-Dsg1 and anti-Dsg3 autoantibodies, but he was found to be positive for the anti-BP180 autoantibody (titre, 44.7 U/ml) via a chemiluminescence enzyme immunoassay. Direct immunofluorescence did not show linear deposition of IgG (Fig. 2C) and C3 in the basement membrane zone.

These findings indicated nivolumab-induced OLR.

A drug-induced lymphocyte stimulation test (DLST) was performed after the systemic steroid therapy; the stimulation index for nivolumab and famotidine was 221% and 119%, respectively.

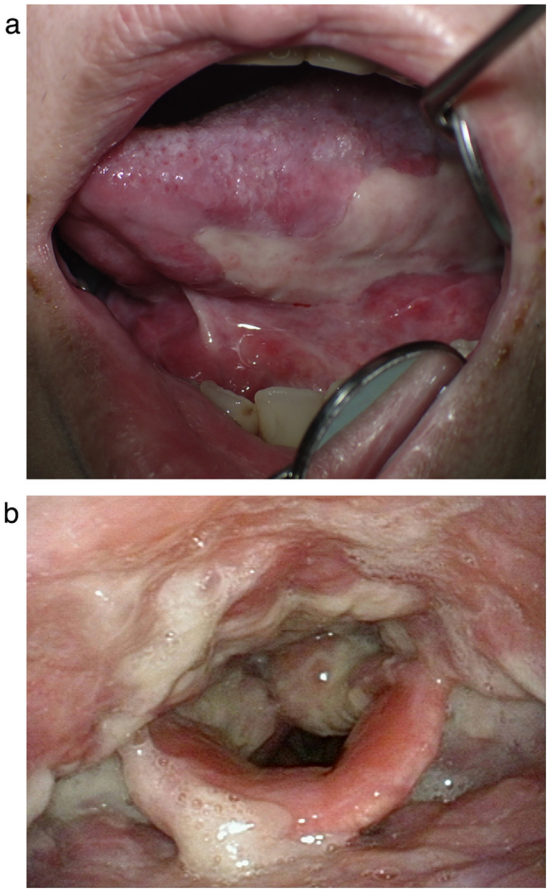

Fig. 1. Immune-related adverse events (irAEs) caused by nivolumab: (A) erosion of the tongue; (B) lesion of the pharyngolarynx.

Discussion

Oral irAEs associated with anti-PD-1 therapy have been described as less frequent and less severe than chemotherapy-induced mucositis, and most cases of oral irAEs are categorized as less than grade 3 by the CTCAE V4.0. Less severe oral irAEs can usually be managed with supportive care without discontinuation of the oncologic treatment[2,6,7]. Drug-induced lichenoid reactions may go undiagnosed, because the histopathological findings often show nonspecific oral lichenoid patterns with typical features, such as a band-like T-cell infiltration in the subepithelium, which is similar to idiopathic lichen planus.

However, the patient described in this report experienced severe stomatitis (grade 3 by the CTCAE V4.0) accompanied by pharyngolaryngitis, which can cause respiratory stenosis. Due to the severity of his reaction, the patient required systemic steroid therapy. Topical corticosteroid treatment was ineffective in ameliorating the stomatitis or providing pain relief. The histopathological aspects of the OLRs included destructive change in the basal layer. Full-thickness necrosis of the epithelium with a CD8-positive lymphocytic infiltrate in the spinous cell layer was also found. Sibaud et al.[6] speculated that PD-1/PD-1 ligand (PD-L1) pathway inhibition triggers epithelial cell apoptosis and

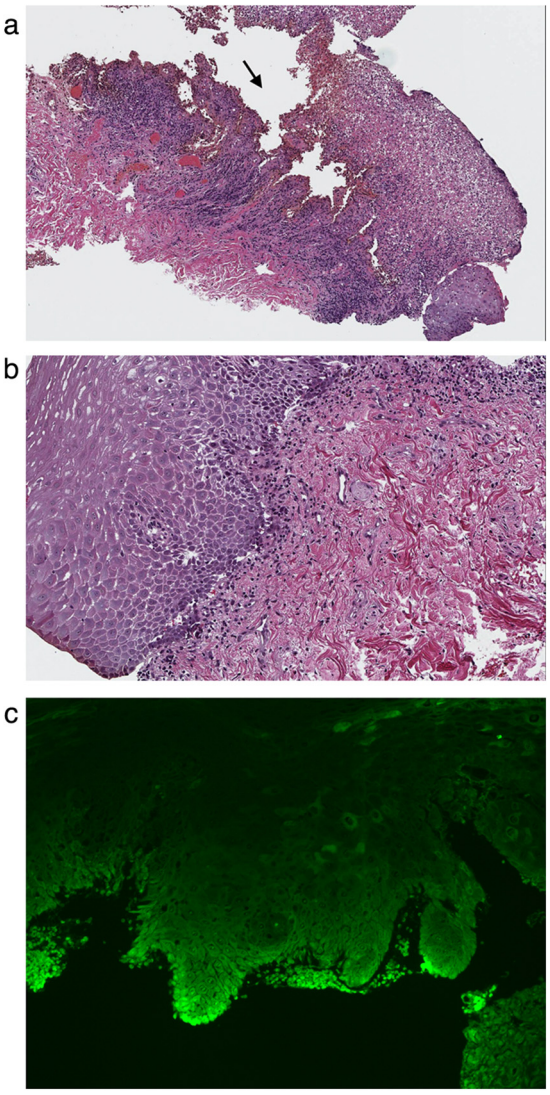

Fig. 2. Haematoxylin–eosin staining of biopsied lesions, original magnification ×8 (A), ×20 (B). Subepithelial lymphocyte infiltrations and separation of the basal layer (black arrow) are seen. Direct immunofluorescence reveals no linear deposition of immunoglobulin G in the basement membrane zone (C).

alterations of the basement membrane zone in susceptible individuals.

Bullous disorders, including bullous pemphigoid, have also been reported as cutaneous irAEs of anti-PD-1 therapy[1,2,9]. In the current case, we could not find features associated with bullous disorders, such as subepidermal blistering, even though the patient tested positive for the anti-BP180 autoantibody. We also performed direct immunofluorescence (DIF) to rule out bullous pemphigoid. Despite the presence of small cracks in the basement membrane zone, immunoglobulin G (IgG) and C3 were detected in very small quantities in a limited section of the specimen, with no definitive linear immunoreactivity in the basement membrane zone (Fig. 2C). DIF confirmed that the primary mechanism underlying the oral mucosal lesions was a cell-mediated immune response. The pathogenicity of the detected anti-BP180 antibody remains unclear. According to Naidoo et al.[9], BP180 is an antigen that can be expressed on the surface of melanocytic tumor and non-small-cell lung carcinomas cells and in the basement membrane of the skin. Blockade of the PD-1/PD-L1 pathway may increase autoantibody production against the hemidesmosomal protein BP180 on tumor cells and in the basement membrane of the skin via a process that is mediated by both T-cells and B-cells. Another possibility is that the life-threatening pharyngolaryngeal lesion, which could not be biopsied, was related to a bullous disorder as one of the irAEs or represented the beginning of blister formation as another irAE.

The patient in this case had progressively worse pharyngolaryngitis, which resulted in severe sore throat and dysphagia. Despite the fact that the pharyngolaryngeal symptoms developed before the oral mucositis, we could not definitively conclude whether the pharyngolaryngeal lesions were related to the oral irAE. This is because we were hesitant to perform a biopsy of the pharyngolaryngeal lesions due to the risk of airway compromise.

DLST for our patient showed that famotidine was not responsible for the mucosal lesions. However, DLST should be based on normal lymphocyte function, and nivolumab had irreversibly changed the patient's lymphocyte function before DLST was performed. For precise evaluation of the results, further research on DLST in the setting of nivolumab-induced reactions is necessary[10].

In conclusion, clinicians should be aware that severe OLRs can occur in patients receiving anti-PD-1 therapy. Early recognition and appropriate management of this complication are required.

Acknowledgements. The authors thank Dr. Nobuo Hoshi (Pathology Department, Tochigi Cancer Center) for his insights on the histopathological findings and Dr. Yohichi Nakamura (Department of Medical Oncology, Division of Thoracic Oncology, Tochigi Cancer Center) for reviewing and approving this manuscript. The authors also appreciate KYODO BYORI for their technical support of pathology and Editage for English language editing.

Funding. None.

Competing interests. None.

Ethical approval. Not relevant.

Patient consent. Written informed consent to publish this report was obtained from the patient.

References

1. Hofmann L, Forschner A, Loquai C, Goldinger SM, Zimmer L, Ugurel S, Schmidgen MI, Gutzmer R, Utikal JS, Göppner D, Hassel JC, Meier F, Tietze JK, Thomas I, Weishaupt C, Leverkus M, Wahl R, Dietrich

U, Garbe C, Kirchberger MC, Eigentler T, Berking C, Gesierich A, Krackhardt AM, Schadendorf D, Schuler G, Dummer R, Heinzerling LM. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. *Eur J Cancer* 2016;**60**:190–209.

2. Naidoo J, Page DB, Li BT, Connell LC, Schindler K, Lacouture ME, Postow MA, Wolchok JD. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol* 2015;**26**:2375–91.
3. Shi VJ, Rodic N, Gettinger S, Leventhal JS, Neckman JP, Girardi M, Bosenberg M, Choi JN. Clinical and histologic features of lichenoid mucocutaneous eruptions due to anti-programmed cell death 1 and anti-programmed cell death ligand 1 immunotherapy. *JAMA Dermatol* 2016;**152**:1128–36.
4. Hwang SJ, Carlos G, Wakade D, Byth K, Kong BY, Chou S, Carlino MS, Kefford R, Fernandez-Penas P. Cutaneous adverse events (AEs) of anti-programmed cell death (PD)-1 therapy in patients with metastatic melanoma: A single-institution cohort. *J Am Acad Dermatol* 2016;**74**. 455–461.e1.
5. Goldinger SM, Stieger P, Meier B, Micaletto S, Contassot E, French LE, Dummer R. Cytotoxic cutaneous adverse drug reactions during anti-PD-1 therapy. *Clin Cancer Res* 2016;**22**:4023–9.
6. Sibaud V, Eid C, Belum VR, Combemale P, Barres B, Lamant L, Mourey L, Gomez-Roca C, Estilo CL, Motzer R, Vigarios E, Lacouture ME. Oral lichenoid reactions associated with anti-PD-1/PD-L1 therapies: clinicopathological findings. *J Eur Acad Dermatol Venereol* 2017;**31**:e464–9.
7. Vigarios E, Epstein JB, Sibaud V. Oral mucosal changes induced by anticancer targeted therapies and immune checkpoint inhibitors. *Support Care Cancer* 2017;**25**:1713–39.
8. National Institutes of Health NCI. Common Terminology Criteria for Adverse Events v4.0 (CTCAE). 2010. https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf [Accessibility verified Apr 21, 2018].
9. Naidoo J, Schindler K, Querfeld C, Busam K, Cunningham J, Page DB, Postow MA, Weinstein A, Lucas AS, Ciccolini KT, Quigley EA, Lesokhin AM, Paik PK, Chaft JE, Segal NH, D'Angelo SP, Dickson MA, Wolchok JD, Lacouture ME. Autoimmune bullous skin disorders with immune checkpoint inhibitors targeting PD-1 and PD-L1. *Cancer Immunol Res* 2016;**4**:383–9.
10. Koda R, Watanabe H, Tsuchida M, Iino N, Suzuki K, Hasegawa G, Imai N, Narita I. Immune checkpoint inhibitor (nivolumab)-associated kidney injury and the importance of recognizing concomitant medications known to cause acute tubulointerstitial nephritis: a case report. *BMC Nephrol* 2018;**19**:48. http://dx.doi.org/10.1186/s12882-018-0848-y.

Address:
Yasuharu Enomoto
Department of Oral and Maxillofacial Surgery
Tochigi Cancer Center
4-9-13 Yohnan
Utsunomiya
Tochigi 320-0834
Japan
Tel.: +81 28 658 5151
Fax: +81 28 658 5488
E-mail: yenomoto@tochigi-cc.jp