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Squamous cell carcinoma associated with chronic graft versus host disease-like/lichen planus-like lesion of the oral cavity in a patient managed for metastatic melanoma with a PD-1 inhibitor pembrolizumab

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This is a 61-year old male with a history of *KRAS* Q61R-mutant, *BRAF*, *NRAS* and *C-KIT* wild type (WT) acral melanoma originating from his left sole. The melanoma metastasized to bilateral lungs and pelvic region in early 2013. The metastatic melanoma to the pelvic region was treated with intensity-modulated radiation therapy, 24 Gy in 4 fractions completed in February, 2013 and at about the same time he was started on ipilimumab at 3 mg/kg intravenous every 3 weeks for 4 cycles. However, due to grade 3 hepatotoxicity and

Conflict of interest statement

All authors declare that there are no financial conflicts associated with this study and that the funding source has no role in conceiving and performing the study.

pruritic maculopapular rash covering 60% of his body, ipilimumab treatment had to be interrupted/postponed and finally discontinued after the patient received only 3 cycles. At this time no oral symptoms or oral lesions were identified.

Four months later, follow-up scans showed complete resolution of lung metastases, shrinkage and decreased FDG-avidity of the pelvic tumors. New scans done 10 months later (June, 2014), showed recurrence and hypermetabolic activity in the left inguinal lymph nodes. Due to a history of previous surgery and radiation, the patient was deemed non-resectable. After a discussion with the patient on the risks and benefits of an expanded access of MK-3475 (pembrolizumab), that targets the programmed death receptor 1 (PD-1), prior to commercially availability, he was started on pembrolizumab 2 mg/kg every 3 weeks.

After the sixth cycle of pembrolizumab (November, 2014), the patient reported his first complaint of oral pain and sores on bilateral buccal mucosa, at which time was considered mild. During the course of his dosing, the lesions persisted and became severe requiring interruptions in dosing and steroid prescription.

After 24 cycles of pembrolizumab (March, 2016), the patient was seen by the dental service for evaluation of persistent mucositis. On examination, the lesions were characterized by mucosal lichenoid-keratotic changes, erythematous areas and pseudomembranous ulcerations involving the left buccal mucosa (Fig. 1A), palatal mucosa (Fig. 1B), right buccal mucosa (Fig. 1C), ventral tongue (Fig. 1D) and gingiva. An oral care regimen of steroid, antifungals, and chlorhexidine rinses was prescribed and pembrolizumab treatment was withheld. Over the course of the next few weeks, there was an initial improvement in the patient's symptoms, but the lesions in the oral cavity persisted. Two additional cycles of pembrolizumab were given. An incisional biopsy was recommended for a worrisome area at the left retromolar trigone (Fig. 2A). The biopsy was performed (July, 2016) and histopathologically diagnosed as an invasive squamous cell carcinoma, keratinizing, moderately differentiated (Fig. 2B). Other complications reported during the course of pembrolizumab medication were hypopigmentation of facial hair, pneumonitis and fever. The patient's social history is negative for smoking and alcohol use.

Pembrolizumab was approved by the United States, Food and Drug Administration in September, 2014, as the first PD-1 inhibitor to be used for the management of advanced (unresectable or metastatic) melanoma following disease progression after ipilimumab, and for *BRAF*V600-mutant melanoma, a *BRAF* inhibitor. FDA later expanded the treatment indication of pembrolizumab to include the initial treatment of unresectable or metastatic melanoma in December, 2015. Pembrolizumab is a highly-discriminatory IgG4- κ monoclonal antibody against PD-1. PD-1 is a member of the B7/CD28 superfamily [1]. It is broadly expressed on activated T-cells, B-cells, natural killer cells, myeloid cells and antigen presenting cells [2,3]. It regulates T-cells activity by binding to its ligands (PD-L1 and PD-L2) [3]. These interactions adversely affect the activity of T and B-cells, constraining anti-tumor, anti-infectious and autoimmunity activities [4]. Blocking/inhibiting PD-1 increases the anti-tumor response by activated systemic T-cells. Pembrolizumab has demonstrated clinical benefits in the management of advanced melanoma (as evidenced by our case) and metastatic non-small cell lung cancer [5,6]. Other PD-1 pathway inhibitors are nivolumab

(FDA approved for the management of advanced melanoma and metastatic non-small cell lung cancer), pidilizumab, durvalumab and atezolizumab, currently in different phases of clinical trials [7].

The adverse toxicities of pembrolizumab are attributed to immune-reactivity against normal tissue. The most prevalent adverse toxicities are pneumonitis, colitis, hepatitis and endocrinopathies [8]. Xerostomia was the only reported oral adverse toxicity during clinical trials in patients treated with MK-3475; pembrolizumab [5,9]. However, oral graft versus host disease (GVHD)-like or lichen planus-like lesions has been suggested to be possible potential adverse toxicities with the use of immune checkpoint inhibitors (cytotoxic T lymphocyte antigen-4 and PD-1 pathway inhibitors) [10,11]. GVHD is a multisystem immunologic T-cell activation caused by activated donor T-cells attacking various immunosuppressed receipt tissues. Similar phenomenon does occur in patients on immune checkpoint inhibitors; increasing systemic activated T-cells with more likelihood of an immune-reactivity against normal tissue (autoimmunity), which may induce or accelerate adverse toxicities similar to oral GVHD-like or lichen planus-like lesions (another T-cell mediated condition) [10,12,13].

Several authors have reported on the association between chronic GVHD and the development of mucocutaneous carcinomas [14–16]. Although rare, solid malignancies have evolved from anatomic sites previously involved by GVHD [14–17]. The role of chronic inflammation in oncogenesis is well recognized [18]. Chronic GVHD of the oral mucosa leads to prolonged mucosal inflammation predisposing to carcinogenesis. Oral lichen planus is considered a premalignant condition. Patients with oral lichen planus are at an increased risk of developing oral squamous cell carcinoma [19,20]. A recent systemic review and meta-analysis showed that the overall mean rate of malignant transformation of oral lichen planus and oral lichenoid lesion is 1.09% [21].

To our knowledge, this is the first report of an oral GVHD-like or lichen planus-like lesion in a patient treated with an immune checkpoint inhibitor PD-1 inhibitor pembrolizumab. This however appears to be a rare complication as patients have been treated with pembrolizumab with great clinical promise for the management of advanced melanoma and other advanced-stage malignancies. Oncologists involved in the care of patients managed with these relatively new immune checkpoint inhibitors should be aware of this complication and the possibility of such persistent oral GVHD-like or lichen planus-like lesions potentially giving rise to squamous cell carcinoma.

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Fig. 1. Clinical pictures of the oral cavity shows painful, mucosal lichenoid-keratotic changes, erythematous areas and pseudomembranous ulcers after 24 cycles of pembrolizumab, initially observed 17 months earlier. Left buccal mucosa (A), palatal mucosa (B), right buccal mucosa (C) and ventral tongue (D). The white lesions could not be wiped off with cotton gauze.

Fig. 2. Shows the clinical picture of the biopsied site and photomicrograph of the biopsied specimen. Lesion at the left retromolar trigone (A) and photomicrograph depicting an invasive squamous cell carcinoma, H&E $\times 200$ (B).