*Case Report*

**SAGE Open Medical Case Reports**

SAGE Open Medical Case Reports
Volume 10: 1–4

DOI: 10.1177/2050313X221118203
journals.sagepub.com/home/sco
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# Multiple oral squamous cell carcinoma 6 years after allogeneic stem cell transplantation complicated with chronic graft-versus-host disease: A case report

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**Abstract**

Oral squamous cell carcinoma is a potential long-term complication after hematopoietic stem cell transplantation. This may be related to mechanisms including radiation and chemotherapy regimens, chronic graft-versus-host disease, inflammation, and prolonged immunosuppression. The current case describes the development of multiple oral white thick keratotic lesions in the floor of the mouth and the tongue 6 years after hematopoietic stem cell transplantation complicated with chronic graft-versus-host disease. A biopsy performed with histopathological analysis revealed a well-differentiated squamous cell carcinoma. The patient was treated by subtotal glossectomy, bilateral neck dissection, and flap reconstruction. This report highlights the significance of the routine oral examination of long-term surveillance post hematopoietic stem cell transplantation to ensure early detection of these tumors at potentially treatable stage.

**Keywords**

Hematopoietic stem cell transplantation, chronic graft-versus-host disease, oral squamous cell carcinoma

Date received: 29 April 2022; accepted: 20 July 2022

## Introduction

Hematopoietic stem cell transplantation (HSCT) is widely used as a treatment modality for patients with hematological malignancies and improves their survival rates.[1] Advances in the field of HSCT over the past two decades have resulted in a significant increase in number of HSCT survivors.[2] This success has brought the recognition of long-term complications of HSCT including secondary cancers.[3]

Secondary solid tumors are considered a significant cause of late mortality in allogeneic HSCT recipients. The risk of developing secondary malignant tumors in patients receiving HSCT is approximately 3.5% at 10 years and 11.5% at 15 years.[4,5]

Oral squamous cell carcinoma (OSCC) is one the most common secondary tumors following allogenic HSCT and can appear 5–10 years after HSCT.[6] Potential risk factors associated with the development of secondary oral cancer after HSCT include regimens with high-dose chemotherapy, total body irradiation, chronic graft-versus-host disease (cGVHD), prolonged immunosuppressive therapy, male sex, and advanced age of patients.[3,7] Of these, cGVHD is a major complication of HSCT with an incidence in more than 30% in long-term HSCT survivors.[8]

Recently, cGVHD was included in the category of an oral potentially malignant disorder, with oral mucosa malignant transformation being approximately 2.5 times more likely to happen in cGVHD patients than those in the general population.[9]

This report describes a case of development of multiple squamous cell carcinoma in the floor of the mouth and different surfaces of the tongue 6 years after HSCT. This

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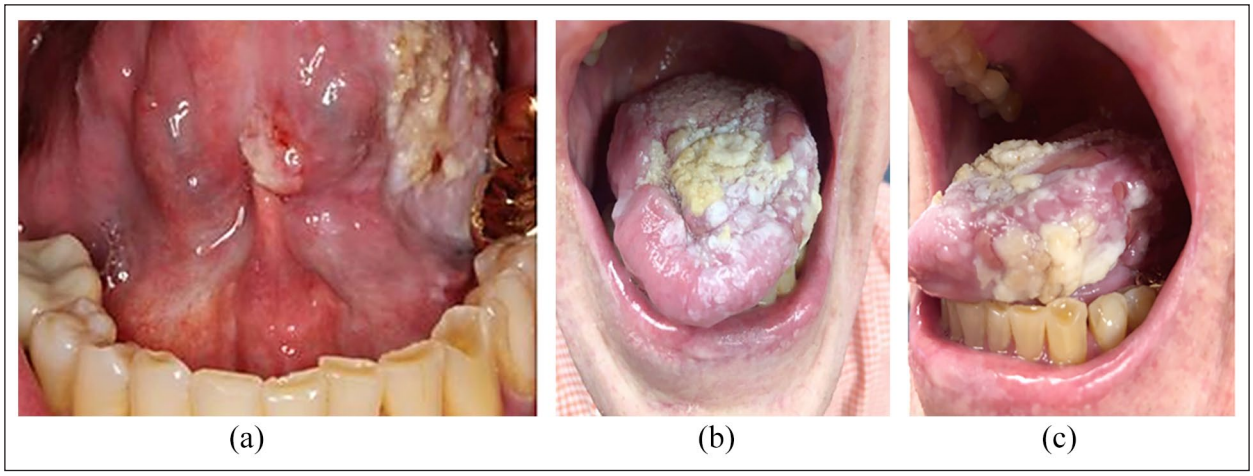


**Figure 1.** Clinical photograph showing diffuse white lesions on ventral (a), dorsal (b), and lateral (c) surfaces of the tongue arising in a patient diagnosed with history of stem cell transplantation.

reinforces the importance of routine oral examination of long-term surveillance post HSCT to ensure early detection of these tumors at potentially curable stage.

## Case report

A 68-year-old White male was referred to the Oral and Maxillofacial Surgery Department, College of Dentistry, University of Florida, for further evaluation of diffuse white lesions on the dorsal, lateral, and ventral surfaces of the tongue as well as the floor of the mouth.

The patient had no history of alcohol or smoking habits, he had a significant medical history of cutaneous T-cell lymphoma diagnosed 9 years ago, for which he was treated with chemotherapy Bexarotene followed by Pralatrexate and focal electron beam radiation therapy to skin lesions.

Patient eventually underwent HSCT from a human leukocyte antigen matched sibling (sister) 3 years after initial diagnosis. The patient received myeloablative fludarabine (30 mg/m$^2$/day on days −6, −5, −4, −3) and intravenous busulfan (0.8 mg/kg/day on days −6, −5, −4, −3) conditioning regimen and Tacrolimus was administered by mouth at 0.05 mg/kg/day starting with a target serum concentration of 5–10 ng/mL. Sirolimus was administered as a 12 mg oral loading dose, followed by a 4 mg/day single dose for GVHD prophylaxis which was continued for 13 days. Oral evaluation prior to HSCT was unremarkable. His transplant course was complicated by oral, skin, ocular, and lung (biopsy proven) cGVHD. The cGVHD was characterized by moderate severity, treated with systemic steroids and sirolimus and continued for 6 months.

The oral lesions involved both the tongue and the buccal mucosa. White plaque lesions on the dorsal surface and the left lateral border of the tongue as well as white lesions on the buccal mucosa were noted. Whitish color oral lesions were present under the patient's tongue for approximately 6 years which were thought to be associated with oral cGVHD. As a treatment for possible flare of oral cGVHD, the patient was started on systemic steroids without significant improvement of symptoms. Therefore, due to worsening of symptoms interfering with oral intake, the patient was referred to Oral Medicine department, College of Dentistry, University of Florida, for further evaluation (Figure 1). The patient was referred to the clinic of oral and maxillofacial surgery, and biopsies of the tongue and the floor of the mouth were obtained.

On intra-oral examination, white thick keratotic and elevated lesions on the dorsal, lateral, and ventral surfaces of the tongue were noted. The lesions could not be wiped off. The lesion on the dorsal surface measured roughly $2.5 \times 3$ cm$^2$ in size while the left lateral surface of the tongue was $2 \times 3$ cm. The floor of the mouth showed mixed red and white lesions with an average size about 1 cm (Figure 1).

Microscopic examination of the tongue lesions revealed islands of malignant epithelial neoplastic proliferation scattered within a fibromyxoid connective tissue stroma surrounded by skeletal muscle tissue and neurovascular bundles as well as a salivary duct. The neoplastic tissue exhibited squamous cell deformation and cytologic alterations including basilar hyperplasia, nuclear hyperchromasia, increased nuclear/cytoplasmic ratios, abnormal and atypical mitoses with dyskeratosis, and surrounding nuclear pleomorphism. A fragment of surface epithelium was noted in one corner of the specimen. A significant dysplasia with atypical arborization of the rete ridges and islands of keratinizing invasive epithelium distributed randomly within connective tissue stroma was present, and it was diagnosed as invasive squamous cell carcinoma (Figure 2).

The patient was referred for treatment to the Head and Neck Surgery team. The patient then underwent subtotal glossectomy, bilateral neck dissection, and flap reconstruction. The final pathology report showed a well-differentiated

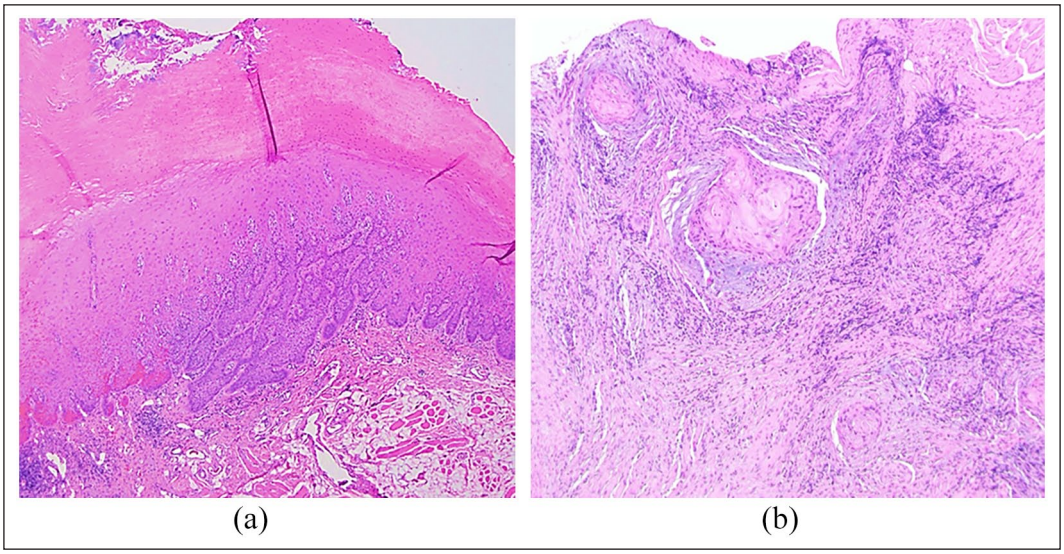


**Figure 2.** Photomicrograph of biopsy specimen revealed severely thickened abnormal appearing epithelium with disturbed maturation pattern. (a) Severely thickened and keratotic epithelium exhibiting significant dysplasia with atypical arborization of the rete ridges (magnification 4×). The keratin layer is twice the thickness of the rest of the epithelium. (b) Islands of keratinizing invasive epithelium distributed randomly within connective tissue stroma (magnification 10×).

squamous cell carcinoma that was 13 mm thick. There was a perineural invasion. There was no positive lymph node involvement. Adjuvant radiotherapy was indicated because of perineural invasion. Subsequently, the patient received postoperative radiotherapy with a total of 55 cGy.

## Discussion

In the present case, we described a patient with history of cutaneous T-cell lymphoma treated with HSCT, followed by cGVHD of the lung, eye, and oral mucosa. The oral cavity presented white keratotic lesions at the floor of the mouth as well as the dorsal, lateral, and ventral surfaces of the tongue that eventually turned to well-differentiated OSCC.

The diagnosis of OSCC occurred 6 years after HSCT, in contrast to other study by Montebugnoli et al., who reported development of multiple OSCC 17 years after the hematopoietic stem cell transplant.[10] Myoken et al.[11] reported a case of OSCC 11 years after HSCT. Tsushima et al.[12] reported a case of OSCC that developed 22 years after the patient received allogeneic HSCT from his human leukocyte antigen-identical sister as a treatment for acute myelocytic leukemia. Our patients developed cGVHD and received chemotherapy, radiotherapy, and prolonged immunosuppressive treatment which may act as predisposing factors for secondary oral cancer after HSCT.[7]

Secondary oral cancers could be diagnosed in a short- or in long-term periods of follow-up after HSCT. The malignant transformation of oral lesions after HSCT was reported in the duration of 1 year to more than 20 years.[7] cGVHD is a major complication in recipients of HSCT seen in 60%–80% of HSCT survivors.[13] Based on prior literatures, patients with cGVHD have a 35 times higher risk for developing OSCC than the general population.[5] The usually presented oral lesion in association with cGVHD shows lichen-like appearance;[14] however, this is not the presentation in our case in which there are tender, multiple raised nodular and discolored white-yellow areas over the floor of the mouth, dorsal, ventral, and left lateral surfaces of the tongue.

The long-term immunosuppressive therapy using steroids and sirolimus in our patient as well as cGVHD is a potential risk factor of OSCC after HSCT. In addition, it was reported that the long-term immunosuppressive therapy may increase the risk of oral cancer through decreasing the tissue repairability of the oral mucosa as well as increasing the risk of oncogenic viruses.[3,10] We screened our OSCC case for HPV (human papillomavirus) infection by running p16 immunohistochemistry, but it showed no positive nuclear or cytoplasmic staining.

Multiple factors should be considered in the management of long-term HSCT survivors. Effective strategies are needed to prevent cGVHD to diminish the development of OSCC. Therapeutic decisions of patients who received HSCT should include a comprehensive follow-up protocol to enhance earlier detection of dysplastic changes or the oral epithelium. Thorough oral examination of HSCT recipients should be performed at 6 months, 1 year, and yearly thereafter[14] with a special attention to individuals who manifest cGVHD requiring prolonged immunosuppression.

In conclusion, the current case report highlights the apparent vulnerability of patients with cGVHD to the development of oral cancer. These cases required the short-term and long-term follow-up for the early detection and management.

## Author contributions

**Joseph Katz:** Writing – original draft.
**Wafaa Saleh:** Writing and Editing – original draft.
**Hamad Alharbi:** Writing and Editing – original draft.
**Nosha Farhadfar:** Writing – review & editing.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

## Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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