Oral Squamous Cell Carcinoma Secondary to Chronic Graft-versus-host Disease: Report of Three Cases

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Recently, the use of hematopoietic stem cell transplantation (HSCT) for the treatment of hematological malignancies has increased because of its favorable therapeutic outcomes. The most common complication of HSCT is chronic graft-versus-host disease (GVHD). GVHD is an immune response caused by donor-derived cells that recognize the recipient as a foreign body (non-self) and attack the recipient's cells. GVHD manifests as lichen planus-like mucosal lesions in the oral cavity, and there have been reports of its malignant transformation to oral squamous cell carcinoma (OSCC). Chronic GVHD-associated OSCC may exhibit more aggressive behavior and a poorer prognosis than those of OSCC in patients who did not undergo HSCT. Here, we report three cases of GVHD after HSCT that transformed into OSCC during follow-up, in which early treatment achieved favorable outcomes. It is important to explain the risk of malignant transformation in patients with chronic GVHD and oral mucosal lesions and to monitor their progression.

Key words: Chronic graft-versus-host disease, Hematopoietic stem cell transplantation, Oral squamous cell carcinoma, Secondary malignancy

INTRODUCTION

Graft-versus-host disease (GVHD) is a complication of hematopoietic stem cell transplantation (HSCT) in patients with hematological malignancies or related disorders. GVHD is an immune response caused by donor-derived cells that recognize the recipient as a foreign body (non-self) and attack the recipient's cells. Acute GVHD is defined as GVHD occurring within 100 d of HSCT. It causes characteristic symptoms in the skin, liver, and digestive system [1]. Chronic GVHD causes damage to various organs, including the skin, nails, scalp, mouth, eyes, reproductive organs, digestive system, and joints [1].

Diagnosis of chronic GVHD requires the following three criteria [2, 3]. First, a distinction from acute GVHD must be established. Second, there must be at least one diagnostic clinical sign of chronic GVHD or at least one distinctive manifestation confirmed by biopsy or other relevant tests. Finally, other possible diagnoses must be excluded. The scoring of organ manifestations requires a careful assessment of signs, symptoms, laboratory values, and other study results.

The diagnostic features of oral chronic GVHD include oral lichenoid lesions in the tongue, palate, and lips and hyperkeratotic plaques (leukoplakia). Characteristic oral symptoms of chronic GVHD include xerostomia, mucous cysts, mucosal atrophy, pseudomembranous lesions, and ulcers [4]. The oral symptoms common to both acute and chronic GVHD include gingivitis, mucositis, erythema, and pain (Table 1) [1, 2]. Oral squamous cell carcinoma (OSCC) has been reported to develop from chronic GVHD [5, 6]. In this report, we present three cases of OSCC associated with chronic GVHD and review the relevant literature.

CASE REPORT

Case 1

A 69-year-old Japanese woman presented to our hospital in 2014 with multiple white patchy lesions in the oral cavity. She was diagnosed with acute myeloid leukemia in 1996 at the age of 42 years. She received total body irradiation (TBI) (12 Gy) and cyclophosphamide as remission induction therapy and underwent HSCT. After HSCT, cyclosporine A and methotrexate were administered to prevent the development of GVHD.

Eight months after transplantation, the patient developed chronic GVHD with xerostomia, oral ulcers, diarrhea, and abdominal pain. At the initial examination, the left buccal mucosa and a white patchy lesion measuring 15 × 8 mm were noted on the left lateral border of the tongue (Fig. 1A).

During follow-up seven years after her initial consultation, ulceration and erythema developed around the leukoplakia on the right side of her tongue (Fig. 1B). A biopsy was performed, and the histopathological diagnosis was OSCC. The patient underwent a partial glossectomy. Histopathological examination of

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Table 1 Signs and symptoms of oral chronic graft-versus-host disease (GVHD)

Diagnostic (sufficient for diagnosis)	Distinctive (insufficient alone for diagnosis)	Common (seen in both acute and chronic GVHD)
	Xerostomia	Gingivitis
Lichen planus-like	Mucocele	Mucositis
Hyperkeratotic plaques	Ulcers	Erythema
	Pseudomembrane	Pain

*Table based on data reported in references [2, 3].

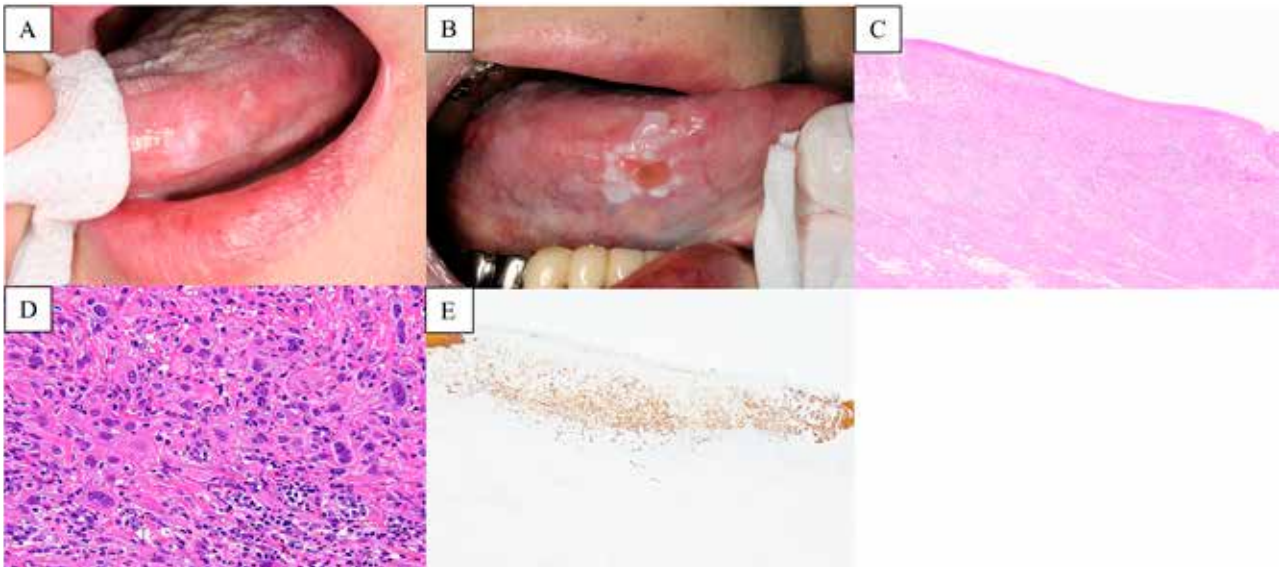

Fig. 1 Intraoral features and histopathology. (A) First visit. (B) Preoperative findings. (C and D) Hematoxylin and eosin staining of the tumor. (E) Immunohistochemical staining of the tumor. Intraoral examination revealed a well-defined white patchy lesion, approximately 15 × 8 mm in size, on the left lateral border of the tongue (A). Six years later, during outpatient follow-up, erythema and ulceration appeared around the leukoplakia on the right side of the tongue (B). Low-power field. Scale bar: 500 μm (C). High-power field. Scale bar: 50 μm (D). Tumor cells with nuclear enlargement formed trabecular structures and exhibited infiltrative proliferation (C and D). CK-AE1/AE3 positive. Scale bar: 500 μm (E).

the resected specimen revealed that the tumor cells with nuclear enlargement formed trabecular structures and exhibited infiltrative proliferation (Fig. 1C and D). Immunohistochemical analysis revealed that the tumor cells were positive for CK-AE1/AE3 (Fig. 1E). Based on these findings, the patient was diagnosed with poorly differentiated OSCC (pT1N0M0). Two years after the surgery, no evidence of recurrence or metastasis was observed.

Case 2

A 46-year-old Japanese man presented to our hospital with the chief complaint of a left tongue mass. The patient was diagnosed with chronic myeloid leukemia in 1998 at the age of 37 years. He underwent HSCT after remission induction therapy and received cyclosporine A and methotrexate as GVHD prophylaxis. Four months after HSCT, the patient developed chronic GVHD with white patchy lesions in the oral cavity. In 2008, he was referred to our department with an exophytic tumor measuring 20 × 30 mm with erythema on the left side of his tongue (Fig. 2A). No lymphadenopathy was observed in the cervical region. Biopsy revealed OSCC, and the patient underwent partial glossectomy. Histopathological examination of the resected specimen revealed that tumor cells with abundant eosinophilic cytoplasm formed a keratinized nest and infiltrated stroma (Fig. 2B and C). On the basis of these histological findings, the patient was diagnosed with well-differentiated OSCC (pT2N0M0). However, local recurrence was observed twice, and partial glossectomy was performed each time. No further evidence of recurrence or metastasis was observed.

Case 3

A 56-year-old Japanese man presented to our hospital with the chief complaint of a left tongue mass. He was diagnosed with acute lymphoblastic leukemia at the age of 52 in 2012. The patient underwent remission induction therapy with pre-transplant chemotherapy (Japan Adult Leukemia Study Group Ph + ALL208 Imatinib protocol). After remission induction therapy, the patient underwent umbilical cord blood transplantation in 2012. Four months after transplantation, the patient developed chronic GVHD. Oral prednisone and topical medications were administered to treat chronic GVHD. In 2018, he was referred to our department because of the appearance of a 10 × 15 mm exophytic tumor on the left border of his tongue (Fig. 3A). A biopsy was performed, and the histopathological diagnosis was OSCC. No lymphadenopathy was observed in the cervical region. The patient underwent a partial glossectomy. Histopathologically, tumor cells with enlarged nuclei formed nests of various sizes and exhibited proliferative activity. Keratinization and mitosis were also observed (Fig. 3B and C). These

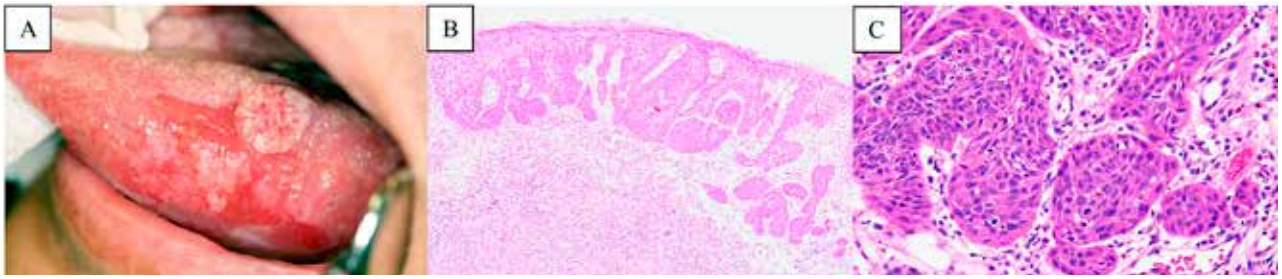

Fig. 2 Intraoral features and histopathology. (A) At the first visit. (B and C) Hematoxylin and eosin staining of the tumor. An ulcerative, exophytic tumor with erythema, approximately 20 × 30 mm in size, was observed on the left lateral border of the tongue (A). Low-power field. Scale bar: 500 μm (B). High-power field. Scale bar: 50 μm (C). Tumor cells with abundant eosinophilic cytoplasm formed nests and infiltrated stroma. Tumor nests showed keratinization (B and C).

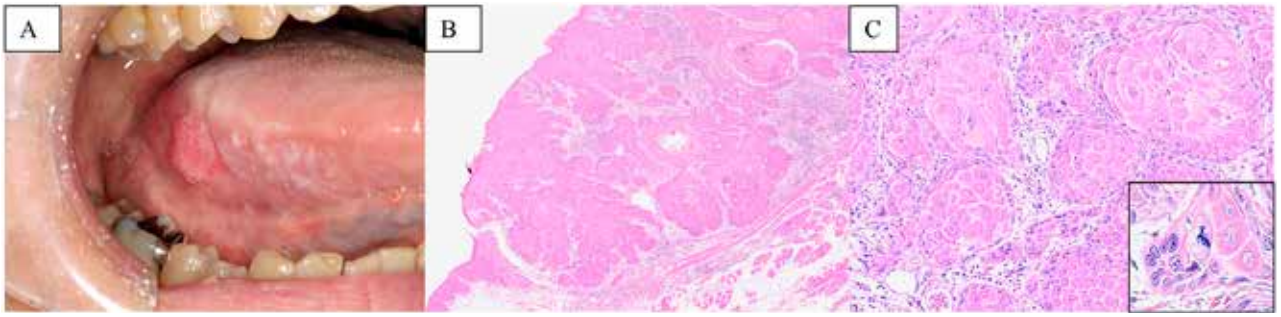

Fig. 3 Intraoral features and histopathology. (A) At the first visit. (B and C) Hematoxylin and eosin staining of the tumor. A well-defined, exophytic tumor approximately 15 × 10 mm in size was observed on the right lateral border of the tongue (A). Low-power field. Scale bar: 500 μm (B). High-power field. Scale bar: 50 μm. The inset demonstrates nuclear enlargement: 20 μm (C). Tumor cells with nuclear enlargement and eosinophilia proliferated densely and formed nests of various sizes. Keratinization, including keratin pearls, was observed (B and C).

histopathological findings indicated well-differentiated OSCC (pT1N0M0). Six years after the surgery, there was no evidence of recurrence or metastasis.

DISCUSSION

HSCT is a treatment strategy aimed at restoring hematopoietic and immunological functions in patients with hematological malignancies or other blood disorders while simultaneously eradicating residual malignant cells. Pre-transplant chemotherapy has contributed to improved long-term survival in patients undergoing HSCT [7, 8]. Risk factors for secondary solid tumors after HSCT include chronic GVHD, TBI, pre-transplant chemotherapy, and immunosuppressive therapy [4, 6, 9]. Approximately 45–80% of patients with chronic GVHD have oral symptoms and lesions, including xerostomia, oral mucosal atrophy, pain, and lichenoid lesions [10, 11]. Oral lichenoid lesions are considered to have the potential for malignant transformation [5, 12]. Chronic GVHD arises from an immune response in which donor-derived T cells attack recipient tissues, resulting in long-term immunological dysfunction [13]. Furthermore, persistent inflammatory cell infiltration associated with chronic GVHD may promote tumor formation through the release of inflammatory cytokines and chemokines [5, 13]. In Case 1, OSCC occurred at a location distant from the oral lichenoid lesions, which is inconsistent with previous reports [14]. Therefore, it is unlikely that chronic GVHD was a direct carcinogenic factor in Case 1.

Previous studies identified TBI as a major contributor [15]. However, secondary solid tumors can occur in patients without TBI [16]. Furthermore, immunosuppressive therapy may be a risk factor for secondary solid tumors [6, 9]. The use of azathioprine and cyclosporine has been associated with an increased risk of OSCC [6] and secondary solid tumors of the oral cavity [4]. Two of the patients in this report received cyclophosphamide as immunosuppressive therapy after TBI. However, the detailed mechanism of carcinogenesis in patients with GVHD remains unclear and may be due to a combination of transplantation and GVHD. Therefore, further investigation is recommended. Additionally, human papillomavirus (HPV) indicated that oropharyngeal squamous cell carcinoma has been increasing, but the role of HPV in oral squamous cell carcinoma remains unclear. We did not investigate HPV status in our study [17].

The literature search revealed 55 cases of secondary oral cancer that occurred after HSCT, including 52 cases reported in 34 papers from 1998 to 2025 and three of our own cases (Table 2). Among these cases, the sites of secondary oral cancer after HSCT were the tongue (33/55, 60%), gingiva (8/55, 14%), buccal mucosa (6/55, 10%), lips (6/55, 10%), and oral cavity (2/55, 3%), with the tongue being the most common site. The time to OSCC development after HSCT ranged from 1 to 25 years (mean 8.45 years, median 8 years) (Fig. 3). Secondary solid tumors often occur more than 5 years after HSCT, and their incidence increases with age [4, 18]. Curtis *et al.* reported a 2.2% cumulative probability of developing secondary solid tumors within 10 years after HSCT [18]. Secondary solid tumors are often oral cancers, as well as skin and esophageal cancers [4, 18]. Secondary oral cancers after HSCT occurred between 1 and 25 years (mean 8.45

Table 2 Case reports of patients who developed chronic graft-versus-host disease after hematopoietic stem cell transplantation and oral squamous cell carcinoma

Cases		55
Age		17–75
	Average	48.4
	Median	48.0
Sex	Men	37 (67%)
	Women	18 (32%)
Primary	Tongue	33 (60%)
	Gingiva	8 (14%)
	Buccal mucosa	6 (10%)
	Low lip	6 (10%)
	Oral floor	2 (3%)
Primary disease	Acute Myelogenous Leukemia	14 (17%)
	Chronic Myelogenous Leukemia	13 (31%)
	Malignant Lymphoma	13 (31%)
	Acute lymphoblastic leukemia	8 (17%)
	Myelodysplastic syndrome	7 (11%)
Recurrence	Yes	30 (54%)
	No	19 (34%)
	Unknown	6 (10%)

Fifty-five cases were reported in 34 references between 1998 and 2025, including those examined at our institution.
This study included 37 men and 18 women. Patient ages ranged from 17 to 75 years, with a mean age of 48.4 years and median age of 48.0 years.

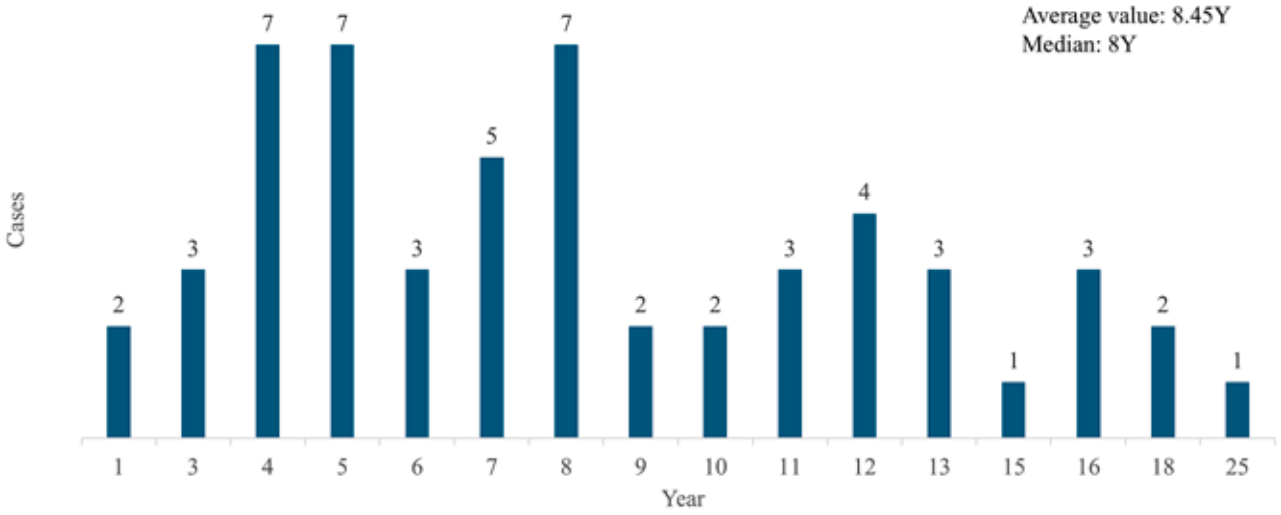

Fig. 4 As reported, the mean and median time from transplantation to oral squamous cell carcinoma development was 8.4 and 8 years, respectively, with a range of 1 to 25 years. In our cases, the time to development of oral squamous cell carcinoma after hematopoietic stem cell transplantation (HSCT) was 6, 9, and 25 years, with 25 years being the longest among all patients.

years, median 8 years) (Fig. 4).

Furthermore, it has been reported that DNA damage caused by TBI does not immediately lead to tumor formation, with secondary solid tumors developing after the long-term accumulation of multiple genetic abnormalities [19]. Accordingly, given the risk of secondary solid tumors, careful long-term follow-up is required.

CONCLUSION

We reviewed three cases of OSCC that occurred in patients with chronic GVHD after HSCT. One patient had two local recurrences, but all three patients are currently doing well with no recurrence or metastasis. In cases of chronic GVHD with oral lesions after HSCT, patients should be advised of the possibility of malignant transformation, and long-term follow-up should be performed.

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