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Squamous Cell Carcinoma of the Tongue After Bone Marrow Transplant and Graft-Versus-Host Disease: A Case Report and Review of the Literature

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Allogenic bone marrow transplantation (BMT) is a curative therapy for malignant and nonmalignant lymphohematopoietic diseases and other disorders. However, the development of secondary malignancies is an important complication among transplantation survivors.[1] Patients who have undergone BMT have a 2- to 8-fold higher risk of developing these cancers than the general population.[1,2] After BMT, the most common secondary malignancies, such as lymphoma or leukemia, arise in hematopoietic tissue. Moreover, these hematologic secondary malignancies develop relatively early during the post-transplantation period. However, though uncommon, secondary solid tumors, like squamous cell carcinoma (SCC), are also associated with BMT, and their incidences appear to increase with time.[2,3]

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Potential risk factors associated with the development of secondary cancers after BMT have been well described and include chronic graft-versus-host disease (GVHD), prolonged immunosuppressive therapy, pretransplantation radiation and chemotherapy, antigen stimulation arising from histocompatibility differences between recipient and donor, and other factors such as oncogenic virus infection.[1-4]

In this report, we describe a young patient with SCC of the tongue associated with chronic oral GVHD and human papillomavirus (HPV) infection after allogenic BMT.

Report of a Case

A 17-year-old woman was referred by her hematologist/oncologist for the evaluation of a tongue lesion in August 2005. She had been diagnosed as having chronic myeloid leukemia in April 2000 and received allogenic BMT in December 2000. The conditioning regimen included busulfan and cyclophosphamide, with cyclosporine and prednisolone as GVHD prophylaxis. Six months after transplantation, chronic GVHD involving the oral cavity, skin, liver, eyes, and the lungs occurred, and required treatment with cyclosporine and prednisolone. Her clinical course was characterized by recurrent episodes of oral mucositis and xerostomia.

Five years later, the patient presented at follow-up with an ulcerative lesion, 1 × 2 cm in size, involving the left lateral border of the tongue, among areas of mild mucositis (Fig 1). A biopsy of the lesion showed it to be a squamous cell carcinoma. The metastatic work-up was negative, and the tumor was classified as T2N0M0, stage II. In September 2005, she underwent ipsilateral supraomohyoid neck dissection and partial glossectomy with reconstruction using a cervical myocutaneous regional flap. Histopathologic examination of the surgical specimen showed a moderately differentiated SCC with epithelial koilocytosis (Figs 2, 3). No metastasis was found in cervical lymph nodes. The biopsy specimen was also evaluated by polymerase chain reaction (PCR) using probes for HPV and Epstein-Barr virus (EBV), and HPV-16 DNA was detected in the excised lesion (Fig 4).

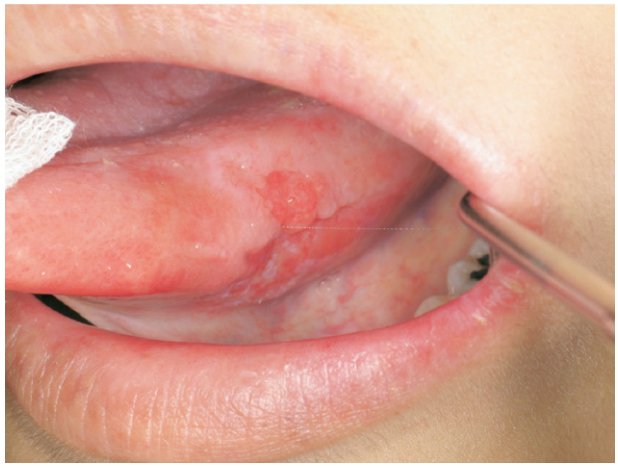

FIGURE 1. Preoperative intraoral view. The ulcerative lesion was showed in the left lateral border of the tongue.

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The patient had been followed up for 5 months without any evidence of recurrence or metastasis (Fig 5).

Discussion

Previous studies have shown that solid cancer occurrence is a later complication in BMT recipients.[2,3] Skin and mucosal neoplasm account for approximately one third of all secondary solid tumors in BMT patients, and squamous cell carcinoma accounts for 50% of these cases.[2]

Chronic GVHD is regarded as a major risk factor of secondary solid tumors in BMT patients.[1-3,5] Chronic GVHD is accompanied by chronic inflammation, and this is followed by the orchestration of the inflammatory cells involved to form a tumor microenvironment that facilitates the initial steps of carcinogenesis, or alternatively, these inflammatory cells may be coopted by neoplastic cells during tumor progression.[5,6] Prolonged immunosuppressive therapy is also a significant risk factor for SCC of skin and oral cavity in transplant recipients.[3,7] In a large cohort study, long-term chronic GVHD therapy with azathioprine, particularly when combined with cyclosporine and steroids, was identified as a major risk factor of SCC development.[3] Azathioprine, when used as treatment for chronic GVHD, appears to facilitate the develop-

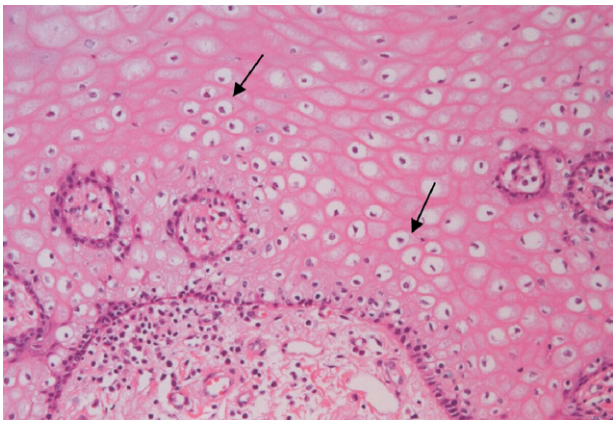

FIGURE 3. Histopathologic examination showed features of koilocytosis in the epithelial surface adjacent to the neoplasm (*arrows*) (hematoxylin and eosin, original magnification x200).

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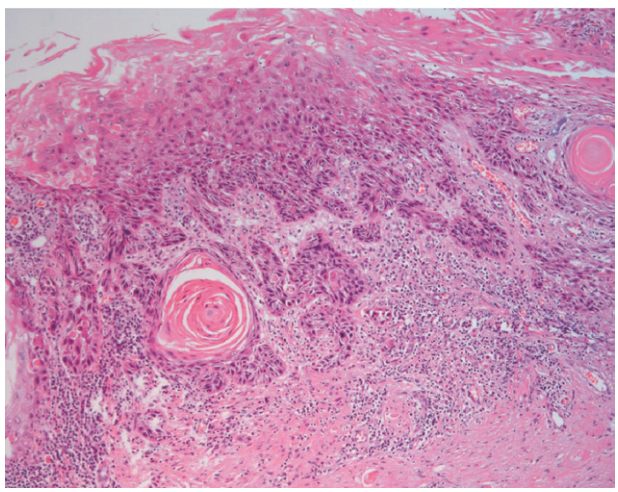

FIGURE 2. Histologic section showing a moderately differentiated squamous cell carcinoma (hematoxylin and eosin, original magnification x100).

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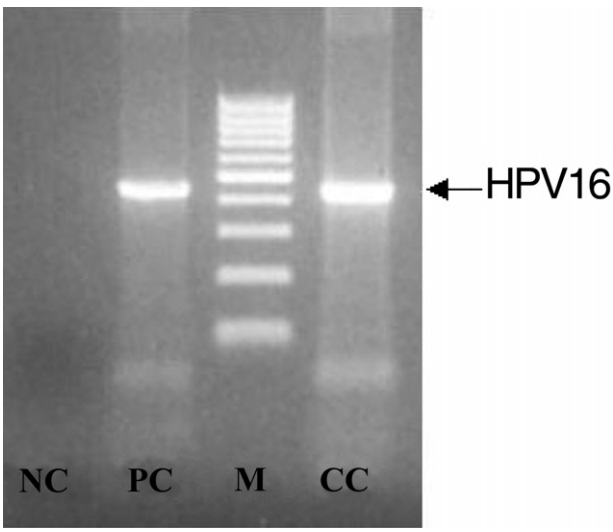

FIGURE 4. Human papillomavirus-16 DNA was detected in the tongue lesion by PCR (*NC*, negative control; *PC*, positive control; *M*, 100 bp ladder; *CC*, current case).

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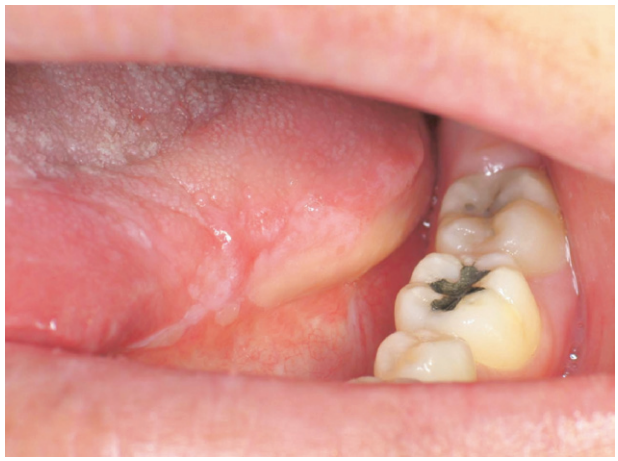

FIGURE 5. Five months postoperatively, the lateral border of the tongue was reconstructed using a cervical myocutaneous regional flap.

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ment of secondary neoplasm, and cyclosporine may promote cancer progression via a direct cellular effect that is quite independent of its effect on the host's immune cells.[7] Many investigators strongly suggest that patients who have undergone radiation-based pretransplantation conditioning have an increased risk of cancer development.[1-3,5,7] In fact, the risk of cancer in transplant recipients that underwent irradiation has been reported to be elevated 18.4-fold.[2] Moreover, oncogenic viruses, such as HPV and EBV, appear to play an etiologic role in many post-transplant solid cancers.[2,4,8-10] A large cohort study found that HPV-16 was the most common type among HPV-positive oral and genital cancers,[4] and Hermann et al[10] reported a case of oral SCC coinfected with HPV-18 and EBV.

In addition to the present case, a review of the literature showed 20 other oral SCC cases that developed in patients who had undergone allogenic BMT (Table 1). The tongue was the most commonly affected site (11 cases), and the great majority of cases (18 cases) had chronic GVHD, which was being treated mostly with cyclosporine, prednisolone, and azathioprine. Reasons for BMT (including the present case) were leukemia (8 cases), aplastic anemia (6 cases), Fanconi's anemia (6 cases), and non-Hodgkin's lymphoma (1 case). However, several studies have reported that SCC develops in Fanconi's anemia patients before the administration of any treatment for anemia.[16,17] In this context, it remains unanswered as to whether carcinoma is caused by BMT factors, the nature of Fanconi's anemia, or by both.[17] In the pre-

Table 1. ORAL SQUAMOUS CELL CARCINOMAS IN BONE MARROW TRANSPLANTATION PATIENTS

Reference	Age at Diagnosis (yrs/gender)	Location	Oral Chronic GVHD	Interval Between BMT and Oral Cancer (yrs)	Medication for Chronic GVHD	Oncogenic Virus Detection	Reason for BMT
Lishner et al,[11] 1990	41/M	Buccal mucosa	Yes	6	P, A	Negative	AA
Bradford et al,[9] 1990	29/F	Tongue	Yes	10	Steroids	HPV	A
Socie et al,[12] 1991	29/M	Oral cavity	Yes	5	Cs	NA	AA
	20/M	Lip	Yes	8	MTX	NA	AA
	12/M	Tongue	No	6	Cs	NA	FA
Flowers et al,[13] 1992	30/F	Tongue	Yes	10	P, A	NA	FA
	25/F	Tongue	No	12	None	NA	FA
Lowsky et al,[14] 1994	31/F	Tongue	Yes	11	Cy, Cs, P, A	NA	AA
	27/F	Mouth	Yes	6	P, A	NA	AA
Otsubo et al,[15] 1997	20/F	Gingival	Yes	4	Cs, P	NA	AA
Millen et al,[16] 1997	18/F	Buccal mucosa	Yes	9	Cs, A	NA	FA
Jansisyanont et al,[17] 2000	24/F	Tongue	Yes	15	None	NA	FA
Abdelsayed et al,[18] 2002	24/M	Buccal mucosa	Yes	2	NA	Negative	ALL
	14/M	Tongue	Yes	8	NA	Negative	ALL
Zhang et al,[8] 2002	35/M	Tongue	Yes	8	None	Negative	CML
	47/M	Lower lip	Yes	7	Cs, P	HPV18	CML
	54/M	Lower lip	Yes	5	None	HPV16, 18	AML
Szeto et al,[5] 2004	45/M	Tongue	Yes	6	Steroid, Thal, A	Negative	AML
	50/M	Tongue	Yes	2	Steroid, Thal, A	Negative	AML
Demarosi et al,[7] 2005	53/F	Gingiva	Yes	5	Cs, P	Negative	NHL
Current case	17/F	Tongue	Yes	5	Cs, P	HPV16	CML

Abbreviations: P, prednisolone; A, azathioprine; Cy, cyclophosphamide; Cs, cyclosporine; MTX, methotrexate; Thal, thalidomide; NA, not available; HPV, human papillomavirus; AA, aplastic anemia; FA, Fanconi's anemia; ALL, acute lymphoblastic/lymphocytic leukemia; AML, acute myeloid leukemia, CML, chronic myeloid leukemia; NHL, non-Hodgkin's lymphoma.

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viously mentioned 21 cases of oral SCCs after BMT, oncogenic virus infection was evaluated in 11 cases (including the present case), HPV was detected in 4 cases, but no EBV-positive case has been reported to date.

Our patient did not undergo pretransplant radiation, and chronic GVHD developed 6 months after BMT. Moreover, chronic oral mucositis had persisted in an intermittent manner until the tongue SCC occurred. Histopathologically, the tumor showed features of koilocytosis throughout the epithelial surface adjacent to neoplasm, which concurs with another report that presented histological features of koilocytosis, hyperkeratosis, and parakeratosis, considered pathognomonic of papillomavirus infection.[9] In the present case, HPV-16 DNA was detected by PCR, and the tumor histological features were characteristic of epithelial koilocytosis. HPV-16 is the most common form of HPV among HPV-positive oral and genital cancers. In the present case, chronic inflammation due to chronic GVHD, prolonged immunosuppressive therapy, and HPV infection are suspected to be causally associated with the development of tongue SCC. We recommend that BMT recipients should be closely followed to ensure the early detection of oral cancer, particularly in those with a chronic GVHD and/or HPV infection.

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