

LETTER TO THE EDITOR

Association of squamous cell carcinoma of the oral cavity in allogeneic hematopoietic stem cell transplant recipients

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Selected hematological malignancies can be cured by allogeneic hematopoietic stem cell transplant (allo-HSCT). Allo-HSCT conditioning regimens consist of various chemotherapeutic agents with or without radiation therapy, and may cause varying degrees of extra-medullary toxicity, specifically graft-versus-host disease (GvHD) and oral cavity mucositis. An important long-term complication following allo-HSCT has been secondary malignancies.¹ We report a case series of allo-HSCT patients developing oral cancers after cure of their primary disease. We hypothesize that secondary oral-cavity squamous cell carcinomas can occur without oral chronic GvHD (cGvHD).

We retrospectively studied patients who initially underwent allo-SCT and developed secondary malignancies, focusing on patients who developed oral squamous cell carcinomas. Three cases are presented (Table 1).

Case I was a 65-year-old female diagnosed with acute myeloid leukemia (French American British (FAB) subtype M1), in October 2003. She was treated with daunorubicin, cytosine arabinoside and etoposide induction chemotherapy, attaining complete remission. She underwent non-myeloablative allo-HSCT in complete remission from a human leukocyte antigen-matched sibling donor in February of 2004, with a conditioning regimen of fludarabine and cyclophosphamide. She had a 10-pack year history of smoking and no history of alcohol use. GvHD prophylaxis included, tacrolimus, mycophenolate and methotrexate. The patient received immunosuppression for 9 months post allo-HSCT, due to extensive, mild, cutaneous cGvHD without evidence of oral cGvHD. A year post allo-HSCT, she presented with an ulcerated lower lip lesion. Biopsy was diagnostic of invasive, well-differentiated squamous cell carcinoma. She underwent Mohs micrographic surgery. She also received antiviral therapy for Herpes Simplex virus oral infection. She has had no recurrence of the oral cancer or acute myeloid leukemia.

The second case was a 46-year-old male diagnosed with acute myeloid leukemia (FAB subtype M1) in June 1996. He received induction chemotherapy with cytosine arabinoside and idarubicin and attained complete remission; receiving a human leukocyte antigen-matched sibling Allo HSCT in October 1996 with a conditioning regimen of etoposide, cyclophosphamide and total body irradiation, 1000 cGy. GvHD prophylaxis included cyclosporine and methotrexate. He developed liver cGvHD and was treated

with cyclosporine and steroids for 2 years, with resolution. At 6.8 years post transplant, at age 53, he developed a leukoplakic lesion on the right lateral border of the tongue without evidence of oral cGvHD. Biopsy of this lesion revealed squamous mucosa with acanthosis and parakeratosis. He was monitored until August 2004, when he developed a new erythematous area at the same site. Biopsy of this lesion revealed micro-invasive squamous cell carcinoma. He underwent right hemiglossectomy and has remained without evidence of recurrent squamous cell carcinoma or acute myeloid leukemia.

The third case was an 11-year-old female diagnosed with Hodgkin Disease in 1975. She achieved a complete remission after chemotherapy and mantle field radiation. At age 18, she developed chronic myeloid leukemia and underwent human leukocyte antigen-matched sibling allo-SCT in 1982, with a conditioning regimen of cytosine arabinoside, cyclophosphamide and total body irradiation (500 cGy). GvHD prophylaxis consisted of methotrexate. The patient developed cutaneous acute GvHD (aGvHD), and was treated with azathioprine and prednisone. She also developed cutaneous cGvHD, as manifested by fibrosis as well as oral cGvHD that remained stable (Figure 1). At age 33, 15 years post transplant, in 1997, a left retro-molar trigone lesion was identified and biopsy revealed invasive squamous cell carcinoma. She underwent left segmental mandibulectomy with neck dissection and reconstructive surgery. Eighteen years post transplant, she had local recurrence in the left hard palate and underwent left partial maxillectomy. Nineteen years post transplant, she had disease recurrence in the pterygoid plate. She declined further intervention and died a few months later.

We describe three allo-HSCT patients presenting with oral cavity squamous cell carcinoma at one, 6 and 15 years post transplant. Two patients did not have any contributing risk factors, specifically no smoking history, alcohol or tobacco use. All three patients received various conditioning regimens, including total body irradiation. One patient developed mild cutaneous cGvHD and oral Herpes Simplex virus infection. One patient experienced liver cGvHD and one patient had cutaneous acute and chronic GvHD as well as oral cGvHD.

We demonstrate that oral squamous cell carcinoma develops in allo-SCT patients who develop mild or severe forms of acute and chronic GvHD, and that oral cGvHD does not need to be present.

Allogeneic hematopoietic stem cell transplant is associated with early post transplant lymphoproliferative malignancies and long-term survivors are at an increased risk of developing solid tumor malignancies.^{2,3} There are 17

Table 1 Patient demographics

Reference	Age at diagnosis/sex	Location of tumor	Histology	Interval between BMT and oral malignancy	GvHD (oral)
Case 1	65/female	Lip	Well-differentiated, invasive SCC	16 months	No
Case 2	46/male	Tongue	Microinvasive SCC	7 years	No
Case 3	18/female	Mandible/ palate	Well-differentiated SCC	15 years	Yes

Abbreviations: BMT = blood or marrow transplant; GvHD = graft-versus-host disease; SCC = squamous cell carcinoma.



Figure 1 Painful ulcerative lesions of labia, buccal cavity and palate of the 18-year-old patient with a severe form of chronic GvHD of the oral cavity. GVHD = graft-versus-host disease.

reported cases of oral epidermoid/squamous cell carcinomas developing after allo-HSCT. The interval between transplant and oral-cavity cancer development ranged from 2 to >10 years,²⁻⁹ and our patients had a similar range, with patient 1 developing oral squamous cell carcinoma at 16 months post allo-HSCT. Immunologic alterations may predispose patients to squamous-cell cancers of the oral cavity, particularly in view of the association between oral mucositis and chronic GvHD. In a recent report on aplastic anemia patients undergoing allo-HSCT, the incidence of solid tumors, predominantly buccal cavity and cutaneous squamous cell carcinoma, was significantly increased after azathioprine therapy for cGvHD. In addition, the major risk factors non-oral cavity squamous cell carcinomas were severe cGvHD and azathioprine therapy combined with cyclosporine and glucocorticoids. Length of treatment for cGvHD was also an independent risk factor.¹⁰ Patients undergoing allo-HSCT have an increased long-term risk of solid tumor cancers. The peak incidence occurs at 7 years following allo-HSCT.¹ In a recent review, almost all patients who developed oral squamous cell carcinoma had evidence of cGvHD. Interestingly, in our patient series, contrasting with prior reports and earlier hypotheses, oral squamous cell carcinomas developed in two patients without evidence of cGvHD. In the patient with active oral cGvHD, a more aggressive cancer with recurrence was observed.

The risk of developing oral cancers after allo-HSCT is definitely higher. It is likely that several factors contribute to this increased risk independent of oral cGvHD. With

improved therapies and prolonged survival, effective management of these patients is by universal screening. Long-term allo-HSCT survivors optimally, should be evaluated annually in a comprehensive transplant clinic, with special dental evaluation of the oral cavity. Primary care physicians and patients should be educated regarding the importance of annual dental visits and the risk of oral secondary malignancies following allo-HSCT.

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