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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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 kaiocytosis (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).
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 co-opted 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-
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. Many investigators strongly suggest that patients who have undergone radiation-based pretransplantation conditioning have an increased risk of cancer development. In fact, the risk of cancer in transplant recipients that underwent irradiation has been reported to be elevated 18.4-fold. Moreover, oncogenic viruses, such as HPV and EBV, appear to play an etiologic role in many post-transplant solid cancers. A large cohort study found that HPV-16 was the most common type among HPV-positive oral and genital cancers, and Hermann et al reported a case of oral SCC coinfect 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. In this context, it remains unanswered as to whether carcinoma is caused by BMT factors, the nature of Fanconi’s anemia, or by both. In the pre-

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age at Diagnosis (yrs/gender)</th>
<th>Location</th>
<th>Oral Chronic GVHD</th>
<th>Interval Between BMT and Oral Cancer (yrs)</th>
<th>Medication for Chronic GVHD</th>
<th>Oncogenic Virus Detection</th>
<th>Reason for BMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lishner et al.</td>
<td>1990</td>
<td>41/M</td>
<td>Buccal mucosa</td>
<td>Yes</td>
<td>6</td>
<td>P, A</td>
<td>Negative</td>
</tr>
<tr>
<td>Bradford et al.</td>
<td>1990</td>
<td>29/F</td>
<td>Tongue</td>
<td>Yes</td>
<td>10</td>
<td>Steroids</td>
<td>HPV</td>
</tr>
<tr>
<td>Socie et al.</td>
<td>1991</td>
<td>29/M</td>
<td>Oral cavity</td>
<td>Yes</td>
<td>5</td>
<td>Cs</td>
<td>NA</td>
</tr>
<tr>
<td>Flowers et al.</td>
<td>1992</td>
<td>30/F</td>
<td>Tongue</td>
<td>Yes</td>
<td>10</td>
<td>P, A</td>
<td>NA</td>
</tr>
<tr>
<td>Lowsky et al.</td>
<td>1994</td>
<td>31/F</td>
<td>Tongue</td>
<td>Yes</td>
<td>11</td>
<td>Cy, Cs, P</td>
<td>NA</td>
</tr>
<tr>
<td>Otsubo et al.</td>
<td>1997</td>
<td>20/F</td>
<td>Gingival</td>
<td>Yes</td>
<td>6</td>
<td>P, A</td>
<td>NA</td>
</tr>
<tr>
<td>Millen et al.</td>
<td>1997</td>
<td>18/F</td>
<td>Buccal mucosa</td>
<td>Yes</td>
<td>9</td>
<td>Cs, A</td>
<td>NA</td>
</tr>
<tr>
<td>Jansisyanont et al.</td>
<td>2000</td>
<td>24/F</td>
<td>Tongue</td>
<td>Yes</td>
<td>15</td>
<td>None</td>
<td>NA</td>
</tr>
<tr>
<td>Abdelwahab et al.</td>
<td>2002</td>
<td>24/M</td>
<td>Buccal mucosa</td>
<td>Yes</td>
<td>2</td>
<td>NA</td>
<td>Negative</td>
</tr>
<tr>
<td>Zhang et al.</td>
<td>2002</td>
<td>35/M</td>
<td>Tongue</td>
<td>Yes</td>
<td>8</td>
<td>NA</td>
<td>Negative</td>
</tr>
<tr>
<td>Szeto et al.</td>
<td>2004</td>
<td>45/M</td>
<td>Tongue</td>
<td>Yes</td>
<td>6</td>
<td>Steroid, Thal, A</td>
<td>Negative</td>
</tr>
<tr>
<td>Demarosi et al.</td>
<td>2005</td>
<td>53/F</td>
<td>Gingiva</td>
<td>Yes</td>
<td>5</td>
<td>Cs, P</td>
<td>Negative</td>
</tr>
<tr>
<td>Current case</td>
<td></td>
<td>17/F</td>
<td>Tongue</td>
<td>Yes</td>
<td>5</td>
<td>Cs, P</td>
<td>HPV16</td>
</tr>
</tbody>
</table>

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.

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.\textsuperscript{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.

References