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Diagnosis and Clinical Management of Human Papilloma Virus–Related Gingival Squamous Cell Carcinoma in a Patient With Leukemia: A Case Report

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Abstract

Introduction—Close clinical inspection for intraoral lesions in patients with leukemia that develop chronic graft-versus-host disease (cGVHD) is critical. Additionally, neoplasias developing in bone marrow transplant patients after treatment for leukemia represent a significant obstacle for long-term patient survival, necessitating lifetime follow-up by health care providers. This case report describes the identification, diagnosis, and treatment of gingival squamous cell carcinoma (SCC) in a patient with leukemia who was treated previously with a stem cell transplant and referred for routine periodontal care.

Case Presentation—A 53-year-old male was referred to the Department of Periodontics for an assessment of tooth #10 with 2+ mobility and associated cross-bite occlusion. The patient was diagnosed with acute myeloid leukemia at age 39 years, received hematopoietic stem cell transplantation (HSCT), and later developed cGVHD followed by human papilloma virus (HPV) infections. During the periodontal evaluation, a large, non-painful, exophytic, alveolar gingival mass was identified and later diagnosed as SCC. It is unusual that oral SCC presents as an exophytic, gingival swelling. The patient received comprehensive periodontal management in coordination with his otolaryngology team before and during the diagnosis of SCC secondary to cGVHD and HPV infection.

Conclusions—Patients with a history of HSCT treatment for leukemia and subsequent cGVHD are at a high risk of developing second primary oral malignancies, including SCC. Exposure to oncogenic HPV infection may compound this risk. Therefore, it is important for dentists to be aware of special treatment concerns and to frequently screen these patients to achieve early diagnosis and treatment of these neoplasms.

Graphical abstract

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Keywords

Carcinoma; squamous cell; graft vs host disease; hematopoietic stem cell transplantation; human papillomavirus 16; leukemia; periodontal diseases

Background

Leukemia is a progressive, malignant hematologic disorder characterized by abnormal proliferation of white blood cells (WBCs). Oral manifestations of leukemia have been well documented and include gingival hyperplasia, bleeding, ulceration, and lymphadenopathy.¹

Chronic graft-versus-host disease (cGVHD) is a major complication of allogeneic hematopoietic stem cell transplant (HSCT) associated with the treatment of leukemia.² The oral cavity is affected frequently with a wide variety of signs and symptoms.^{2,3} Short- and long-term complications range from oral lichenoid lesions and mucosal sensitivity to secondary malignancies and early death.^{2,3}

Second primary malignant neoplasm formation after HSCT represents a significant obstacle for long-term survival.⁴⁻⁶ Individuals who have undergone stem cell transplantation have a four to seven times higher risk of developing second primary cancers than the average population.^{5,6} Reported risk factors for second primary neoplasms include viral infections, reduced immune function, chemotherapy agents, and radiation.⁴⁻⁸ This report describes the identification, diagnosis, and treatment of an oncogenic human papilloma virus (HPV)-related oral squamous cell carcinoma (SCC) in a patient with leukemia and cGVHD who was referred for routine periodontal care.

Clinical Presentation

A 53-year-old male patient was referred in June 2014 for periodontal assessment and evaluation within the Department of Periodontology of the University of Washington, Seattle, Washington. The patient's chief concern was related to his periodontal status and malpositioned anterior tooth. However, he was also aware of a "swelling" in the mandible that had been present for >8 weeks but was otherwise non-symptomatic. The patient provided both oral and written consent for evaluation and treatment. The patient's dental history was very sporadic because of limited finances and access to care, but teeth #18 and #19 had been removed for periodontal reasons at least 3 years before at another clinic. The patient's medical history was significant for acute myeloid leukemia diagnosed at age 39 years and treated with HSCT. Two years after transplant, the patient developed cGVHD, which affected the skin, joints, and oral cavity. cGVHD was manifested by generalized gingival, palatal, and mucosal erosions interspersed with areas of non-wipeable white

patches (Figs. 1 and 2a). Three years after the diagnosis of cGVHD, the patient developed HPV-related infections in addition to multiple white, papillary lesions on his extremities that resembled common warts (Fig. 2b). Over the next 10 years, the patient had a continued suppressed immune system subsequent to his cGVHD and was treated repeatedly for viral, cryptococcal meningitis, and fungal infections. His medical history also included multiple invasive SCCs on his legs, and his hand revealed radiation scars from basal cell carcinoma treatment (Fig. 2c).

Clinical examination of the oral cavity revealed significant gingival erythema, generalized moderate attachment loss, maxillary and mandibular probing depths ranging from 2 to 9 mm, partial edentulism, pathologic extrusion, and migration of tooth #10 with anterior cross-bite. More significantly, a large, non-painful, indurated, exophytic gingival mass without dysarthria, dysphagia, or other symptoms, was identified on the lower left edentulous area (Fig. 1).

During the initial examination, radiographs revealed a soft tissue mass over the edentulous area with an ill-defined radiolucent lesion contained within the left mandible (Fig. 3). Because of the patient's medical history and risk factors, he was immediately referred to the Department of Otolaryngology for consultation and evaluation, and it was determined that an excisional biopsy was warranted.

Case Management

In preparation for the excisional biopsy and projected radiotherapy, the patient's primary care physician recommended 2 g prophylactic amoxicillin 60 minutes before periodontal therapy. Blood work showed normal components with slightly decreased red blood cell (RBC) count and hemoglobin (Hb) values (Table 1). Supragingival and subgingival debridement was performed by mechanical, ultrasonic, and air abrasive methods. After scaling and root planing (SRP) on tooth #10, a provisional fixed splint was fabricated using annealed, multistrand orthodontic wire on the lingual surfaces of teeth #6 through #11 to stabilize tooth #10. This facilitated proper hygiene efforts, improved patient comfort, reduced tooth migration, and mitigated the effects of traumatic forces applied to the anterior teeth.⁹ A minor occlusal adjustment was performed to keep tooth #10 out of occlusion and in proper alignment. After consultation with the surgical team, preventive treatment included extraction of the hopeless tooth #30 and the fabrication and delivery of a provisional vacuum-formed appliance to maintain arch integrity while undergoing additional treatments (Fig. 4). Approximately 4 weeks later, excisional surgery was performed within the Department of Otolaryngology with segmental alveolar bone resection, and the specimen was sent for histopathologic evaluation (Fig. 5).

Clinical Outcomes

After initial periodontal treatment, reevaluation revealed that all clinical parameters stabilized. Tooth #10 remained in proper alignment, and the site of tooth #30 healed uneventfully (Fig. 6). Microscopic examination revealed a papillary neoplastic proliferation of the surface epithelium invading the stromal connective tissue (CT) (Figs. 7a through 7c).

The immunohistochemistry stain revealed that the tumor was strongly positive for expression of p16, a surrogate marker for high-risk (oncogenic) HPV types (Fig. 7d). A diagnosis of papillary SCC associated with oncogenic HPV was rendered. The case was referred to an oncologist for tumor staging, and surgical/radiation treatment was planned. Consultation with the surgical team recommended continued oral care follow-up during the healing phase. The patient was placed on a strict 4- to 6-week recall program with splint maintenance and periodontal, dental, and oral mucosal maintenance in preparation for additional surgical procedures and radiotherapy.

As of June 2015, the patient underwent additional hemimandibulectomy and radiotherapy during the prior year, and his response to treatment was extremely favorable.

Discussion

This case report addresses a multilayered problem starting with leukemia, treatment with HSCT, infection with HPV, and the development of multiple skin and mucosal SCC carcinomas. Treatment with HSCT is reported to be associated with 2.2% solid cancer formation over 10 years, increasing to 6.7% over 15 years with second primary cancer formation in the oral cavity being highly prevalent.⁷ Generally, the recipients of bone marrow transplants have two to six times higher risk of developing second primary malignancies than the general population.⁵

The extent of GVHD after HSCT is considered to be another high-risk factor for second primary neoplasias.^{7,8,10} It has been suggested that immunologic injury to the oral mucosa by donor T-lymphocytes may be an etiologic factor transforming lichenoid- or leukoplakia-type lesions into malignancies.^{3,11} The patient in this case report displayed numerous non-wipeable, white oral lesions (Fig. 1a), as well as wart-like lesions on his hands, further necessitating close observation and follow-up with a multispecialty team.¹²

HPV-associated oral SCCs are by far more common in the posterior-most aspect of the mouth (i.e., tonsillar and oropharyngeal areas), not the gingiva as is the case in this patient. In recent years, the incidence of HPV-induced oropharyngeal SCC has nearly doubled, which has been attributed to increasing incidence of infection with oncogenic HPV.^{13,14} Despite the unusual site, this patient fits the clinical profile of HPV-associated SCCs in that they usually occur in white males younger than 50 years with a history of no or little tobacco or alcohol use.¹⁵

This report emphasizes the importance of careful examination of a patient's medical record, especially those with history of leukemia combined with HSCT treatment and viral infections. Given the significantly increased risk of developing oral SCC, these patients require comprehensive extraoral/intraoral examination three to four times per year combined with regularly scheduled multidisciplinary consultations.²

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Summary

Why is this case new information?

- Rarity of one patient developing multiple malignancies (leukemia, multiple skin SCCs, an oral SCC, and a basal cell carcinoma)
- Uncommon occurrence of a patient with leukemia developing HPV-associated oral SCC and gingival SCC being associated with HPV (HPV-associated cancers being by far more common in the tonsillar/oropharyngeal area)
- Unusual presentation of oral SCC as an exophytic gingival swelling

What are the keys to successful management of this case?

- Proper and frequent oral cancer screening of patients with leukemia (especially those that receive bone marrow transplant)
- Understanding the potential and frequent complications associated with leukemia and its treatment
- Proper coordination of dental professionals with multidisciplinary medical teams
- Early diagnosis and treatment of oral lesions to improve the quality of life

What are the primary limitations to success in this case?

- Lack of coordination between medical and dental professionals
- Lack of access to care or patient compliance
- Detecting disease, especially SCC, at a late stage

FIGURE 1.

Initial presentation. **1a** Labial view showing the anterior lateral incisor cross-bite and red and white, non-wipeable lesions along the maxillary labial marginal gingiva between teeth #8 and #9, as well as between teeth #11 and #12 (arrows). A portion of the oral SCC is also seen on the left mandibular posterior alveolar ridge. **1b** Occlusal view of the mandible showing an exophytic sessile reddish-pink swelling of the left posterior mandibular alveolar ridge. **1c** Lateral view showing extension of lesion posteriorly from the second premolar to the posterior retromolar area, measuring $4.0 \times 3.5 \times 2.0$ cm.

FIGURE 2.

Oral features of cGVHD and skin lesions of basal cell carcinoma. **2a** The hard palate showing diffuse superficial red lesions interspersed with white spots consistent with plaque or lichenoid-like reactions that have been associated with cGVHD. **2b** Fingers displaying multiple warty white lesions that may indicate reduced immune function and previous viral exposure as indicated by the patient's medical history. **2c** Well-demarcated brown scars of an excised basal cell carcinoma and radiation-induced scarring of the skin and the nails.

FIGURE 3.

Preoperative radiographs. **3a** Panoramic radiograph showing an ill-defined radiolucency in the left posterior mandible. This radiolucency was associated with the exophytic gingival swelling overlying the area. Also note the severe periodontal changes around tooth #30. **3b** Periapical image revealing vertical bony defects around tooth #10. **3c** Axial computed tomography scan showing bony breakdown of the body of the mandible with a lingual plate perforation.

FIGURE 4.

Initial periodontal management. **4a** SRP of tooth #10. **4b** Provisional fixed splint fabricated using an annealed, multistrand orthodontic wire luted to the lingual surfaces of teeth #6 through #11 to stabilize tooth #10. **4c** Hopeless tooth #30 was extracted and replaced with a provisional vacuum-formed appliance.

FIGURE 5.

Intraoral biopsy. **5a** Intraoral view of enucleated lesion site and extent of intrabony invasion.

5b The mass after the excision. The tumor (3.5×2.0 cm) was papillary and vascular and generated significant bleeding on removal. **5c** Primary wound closure achieved with 3-0 chromic gut sutures.

FIGURE 6.

Three-week postoperative assessment. **6a** Occlusal view showing the healing result after the mass was excised. Also present is the provisional vacuum-formed appliance restoring teeth #29 and #30. Oral hygiene was well controlled. **6b** Panoramic radiograph showing successful splinting of tooth #10 and the healing extraction site of tooth #30. The radiolucency of the left posterior mandible is slightly enlarged as expected in response to tumor resection.

FIGURE 7.

Histopathology study. **7a** Section demonstrating papillary and confluent neoplastic epithelial cells cut tangentially. The neoplastic cells superficially invaded the CT in the form of nests and islands (hematoxylin and eosin [H&E]; original magnification $\times 40$). **7b** Section demonstrating neoplastic cells invading the CT in the form of nests and islands with central necrosis (H&E; original magnification $\times 40$). **7c** Section demonstrating neoplastic epithelial cells exhibiting high mitotic activity, nuclear hyperchromatism, and focal nuclear pleomorphism (H&E; original magnification $\times 200$). **7d** Immunohistochemistry stain for p16, a surrogate antibody to oncogenic HPV. The stain is 100% uniformly positive, highlighting the papillary configuration and invasion of the neoplastic cells (original magnification $\times 40$).

TABLE 1

Laboratory Blood Test Results

Blood Test	Result	Normal Value
WBCs (billion/L)	8.00	3.5 to 10.5
Neutrophils (%)	62	40 to 70
Lymphocytes (%)	28	25 to 45
Monocytes (%)	10	2 to 8
Eosinophils (%)	1	1 to 5
Basophils (%)	0	0 to 1
RBCs (trillion/L)	3.84	4.3 to 5.7
Hb (g/dL)	11.7	13 to 17
Hematocrit (%)	37	37 to 52
Platelets (billion/L)	262	150 to 450