Oral squamous cell carcinoma after allogeneic hematopoietic stem cell transplantation: A report of 2 cases

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Abstract

Introduction

Hematopoietic stem cell transplantation (HSCT) has improved the survival rate of patients with different malignancies and other haematopoiesis disorders. However, late complications such as oral squamous carcinoma (OSCC) have been described. Chronic graft-versus-host disease (cGVHD) and long-term immunosuppression are important risk factors for the development of OSCC. This report describes two cases of secondary OSCC diagnosed early in patients with cGVHD. The clinical and histopathological findings, risk factors, and treatment are discussed.

Case report

Case 1

A non-smoking 64-year-old female patient was referred for evaluation of an asymptomatic white plaque on the ventral surface of her tongue 9 years after HSCT. The patient developed oral cGVHD after the transplant. An incisional biopsy was performed, and the histologic analysis confirmed the diagnosis of OSCC. The patient was referred to a head and neck surgeon, and the tumour was surgically excised.

Case 2

A non-smoking 55-year-old male patient was referred for evaluation of a red/white exophytic lesion, with a rugged surface, on the dorsum of the tongue that appeared 10 years after HSCT. The patient developed cGVHD with oral involvement two years after the HSCT. The microscopic exam of the incisional biopsy confirmed the diagnosis of OSCC. The patient was referred to a head and neck surgeon, and the tumour was surgically excised.

Conclusion

Oral surgeons, pathologists, and clinicians must be familiar with the clinical aspects of OSCC, especially with its differential diagnoses, including other inflammatory, infectious, and potentially malignant or malignant conditions.

Introduction

Oral squamous carcinoma (OSCC) is a common long-term complication following hematopoietic stem cell transplantation (HSCT).¹ Oral epithelial dysplasia and OSCC after HSCT are associated with chronic graft-versus-host disease (cGVHD) in 96% of cases, and this condition is considered to be a potential risk factor for the development of OSCC.²³⁴ Prolonged immunosuppressive therapy and azathioprine use are also significant risk factors for OSCC.⁴ The most frequent initial clinical presentation of OSCC is a white or red/white plaque or exophytic growth, with the tongue being the oral site most often affected.⁵ Early diagnosis and treatment of malignant lesions can provide favourable survival rates and warrant less complex treatment strategies.⁵ The purpose of the present report is to describe two cases of OSCC in patients with cGVHD and to present a review of the literature on this subject.

Case report

Case 1

A non-smoking 64-year-old female patient was previously admitted to the Hematopoietic Stem Cell Transplantation (HSCT) Unit of the Clinic Hospital of the Universidade Federal de Minas Gerais at 55 years of age to undergo an allogeneic HSCT (the donor was her brother) for chronic myeloid leukaemia in 2004. The recipient was conditioned according to standard protocols of the hospital, and 9 years after the transplantation, she was referred to the School of Dentistry for examination of an asymptomatic white plaque on the ventral surface of her tongue. Her medical history

Figure 1: Clinical appearance of the ventral surface lesion on the tongue, showing a white plaque with a rugged surface and elevated borders.
included cGVHD in the oral mucosa and skin. The only medication she was receiving was imatinib mesylate (Glivec®) (400 mg daily). Oral examination showed a predominantly white plaque measuring 10 mm in diameter with a rugged surface and elevated borders (Figure 1). The differential diagnoses included verrucous carcinoma, OSCC, verrucous leukoplakia, GVHD, and hyperplastic candidiasis. An incisional biopsy was performed, and histologic analysis revealed OSCC (Figure 2). The patient was referred to a head and neck surgeon and the lesion was surgically excised.

Case 2

A non-smoking 55-year-old male patient underwent an allogeneic HSCT (the donor was his sister) for the treatment of chronic myeloid leukaemia in 2000. The patient developed cGVHD with oral involvement two years after the HSCT. In 2010, the patient was referred to the School of Dentistry for assessment of the oral involvement of cGVHD. His medical history included bronchitis, which had been treated with Alenia® (formoterol fumarate dihydrate, 6 mcg, and budesonide, 100 mcg, twice daily inhalation) and Bactrim® (trimethoprim, 80 mg, and sulfamethoxazole, 400 mg). Oral examination showed a red/white exophytic lesion > 30 mm in the largest diameter, with a rugged surface, on the dorsum of the tongue (Figure 3). The patient reported symptoms of pain and dysgeusia. Fluconazole, 150 mg weekly, was prescribed for the treatment of overlying oral candidiasis. After two weeks, the patient reported an improvement in the candidiasis symptoms, and an incisional biopsy was performed with the main diagnostic hypothesis of verrucous carcinoma and OSCC. Histologic analysis revealed OSCC (Figure 4). The patient was referred to a head and neck surgeon, and the tumour was surgically excised.

Discussion

The incidence of solid cancer after HSCT is 4.2% at 10 years, which has increased with improved survival rates obtained through advancements in therapeutic options. These lesions are considered a late complication in long-term survivors. OSCC has an incidence rate of 1.9% at 10 years following HSCT, corresponding to 37% of all solid tumours, with the tongue being the most commonly affected oral site. The risk of secondary OSCC seems to increase with time, with a median time to diagnosis of 8 years following HSCT. Prolonged duration of GVHD therapy and cGVHD are important risk factors for OSCC. GVHD is characterized by alloreactivity, which implicates immunosuppression treatment.

The median age at transplantation is 34 years and oral dysplasia or OSCC is diagnosed at a median age of 49 years. The age of OSCC diagnosis ranges from 15 to 68 years, with a median age of 31 years. Men are more affected than women, with a male to female ratio ranging from 1.36 to 3:1. Well-documented risk factors for primary OSCC include alcohol consumption, smoking, and human papillomavirus (HPV) infection. However, the influence of HPV infection in OSCC development following allogeneic HSCT is not consistent. Chen et al. recently reported that none of the five OSCC patients in their study were infected with HPV. The donor source is also a possible risk factor, as Janin et al. demonstrated that OSCC in 50% of the patients analysed in their study was attributable to the engrafted allogeneic donor.

Figure 2: A) Histopathological view of the lesion showing invasive islands of malignant epithelial cells (haematoxylin and eosin staining; magnification, 100X). B) Keratin pearl formation (arrow), cells with hyperchromatic nuclei and pleomorphism (haematoxylin and eosin staining; magnification, 400X).

Figure 3: Clinical appearance of the tumour on the dorsum of the tongue showing red/white colouring and a rugged surface.
bone marrow. The possible fusion of bone marrow stem cells to OSCC cancer stem cells or to epithelial stem cells is one theoretical interpretation for this finding.

The prevalence of the stem cells in the OSCC may be understood as an effect of chronic tissue injury and as the replacement of the epithelial stem cells by cells derived from the bone marrow. Keratinocytes isolated from areas of cGVHD and from biopsy sites showed greater numbers of tetraploid cells than normal tissue. Haploinsufficiency for p53 due to the loss of chromosome 17 was reported in keratinocytes co-cultured with HLA-mismatched allogeneic lymphocytes or inflammatory cytokines.

Information about the treatment of OSCC following HSCT is scarce. Extensive and inoperable lesions are treated with radiotherapy. However, the first choice of treatment is surgical excision of the tumour that can be combined with radiotherapy, especially when tumour margins are compromised. The rate of OSCC recurrence following HSCT can reach 45%, and multifocal OSCCs are not uncommon, being found in 28% of cases.

Conclusion
Transplant patients should periodically undergo a careful clinical evaluation for the early diagnosis of malignant and potentially malignant lesions in an effort to achieve longer survival and reduced morbidity and mortality. Oral surgeons, pathologists, and clinicians must be familiar with the clinical aspects of OSCC, especially with its differential diagnoses, including other inflammatory, infectious, and potentially malignant or malignant conditions.

Consent
Written informed consent was obtained from the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

References