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GINGIVAL SQUAMOUS CELL CARCINOMA: A CASE REPORT. CLINICAL, RADIOLOGICAL AND HISTOLOGICAL PATTERNS CORRELATIONS

Luciana Moraes HORNOS
Department of Stomatology, School of Dentistry,
Universidade de São Paulo, São Paulo, SP, Brazil (USP)
E-mail: lucianahornos@usp.br
ORCID: http://orcid.org/0009-0007-1590-997X

Alexandre Said BUSSAD
Associação Brasileira de Odontologia (ABO)
E-mail: bussadalex@yahoo.com.br

Rodolpho Luvison Costa GUIMARÃES
Cleveland Dental Institute, Columbus (USA)
E-mail: rodolphoguimaraes@yahoo.com.br

Larissa Luvison Gomes da SILVA
Pontifícia Universidade Católica do Paraná (PUCPR)
E-mail: larissaluvison@hotmail.com

Marcelo de Gusmão Paraíso CAVALCANTI
IES: Department of Stomatology, School of Dentistry,
Universidade de São Paulo, São Paulo, SP, Brazil (USP)
E-mail: mgpcaval@usp.br
ORCID: http://orcid.org/0000-0001-8011-9623

ABSTRACT

Squamous cell carcinoma (SCC) is the most common neoplasm in the oral cavity, accounting for approximately 90% of all cases. There has been a growing increase in the number of patients with SCC without exposure to typical risk factors and associated with individuals of the female sex, with sites of greater predilection indicating the tongue and maxillary alveolus. The case reported described a SCC of the maxillary gingiva in a female patient in her fourth decade of life, with no history of exposure to typical risk factors and no previous history of potentially malignant conditions. Clinically, the tumor showed proliferative, ulcerated, and bleeding characteristics, with tooth mobility due to the total loss of bone insertion. Radiographically, an osteolytic lesion with poorly defined margins was noticed, in addition to bone infiltration. In the

histological examination, as well as in other laboratory tests, results indicated features characteristic of gingival SCC.

Keywords: Gingival neoplasms. Squamous cell carcinoma. Diagnostic imaging.

INTRODUCTION

In compliance with the International Agency for Research on Cancer - IARC (INTERNATIONAL AGENCY FOR RESEARCH ON CANCER) 390,000 new cases of oral cavity cancer have been estimated for the year 2022 alone. Among the various neoplasms, the most prevalent histological type is squamous cell carcinoma (SCC), corresponding to approximately 90% of diagnoses (International Agency For Research On Cancer; Sundermann et al, 2018).

Epidemiologically, it is much more prevalent among men, and the main risk factor is excessive alcohol and tobacco consumption, enhanced by the synergistic effect of associated consumption, with the most commonly affected anatomical sites the lateral border of the tongue and the floor of the mouth (Sundermann et al, 2018; Verma et al, 2021).

However, there is a growing number of patients who have never been exposed to predisposing factors and who have nevertheless developed SCC. Contrary to the classic pattern widely disseminated in the literature, this group is predominantly made up of middle-aged women, with a higher incidence of lesions on the tongue and jaw, whether or not preceded by potentially malignant disorders (Fiedler et al, 2023; Sundermann et al, 2018). Furthermore, in addition to distinct clinical parameters, this type of carcinoma appears to have a more immunogenic microenvironment compared to patients who consume alcohol and tobacco (Fiedler et al, 2023).

The purpose of this study was to report a case of gingival SCC in a female patient with no history of alcohol or tobacco consumption and to correlate clinical, radiographic, and histological patterns correlations.

CASE REPORT

A 45-year-old female patient, non-drinker, non-smoker, with no prior history of cancer, in good general health, and responsive, presented to a private clinic

complaining of dental mobility in the right central and lateral incisors, accompanied by ulcerated gums with spontaneous bleeding. The condition has reportedly been evolving for approximately 45 days. The intraoral examination confirmed dental mobility of teeth 11 and 12, along with gingival overgrowth of a pinkish-red color, presenting areas of ulceration and spontaneous bleeding. The growth extended orally, laterally from the mesial surface of tooth 15 to the distal surface of tooth 21, involving the cervical third of the aforementioned teeth, passing through the vestibular depth in the same region, and reaching the oral mucosa toward the lip (Figure 1).

Figure 1. Clinical presentation in frontal view depicts gingival growth, with areas of ulceration and spontaneous bleeding, extending from the upper left lateral incisor to the upper right first premolar.

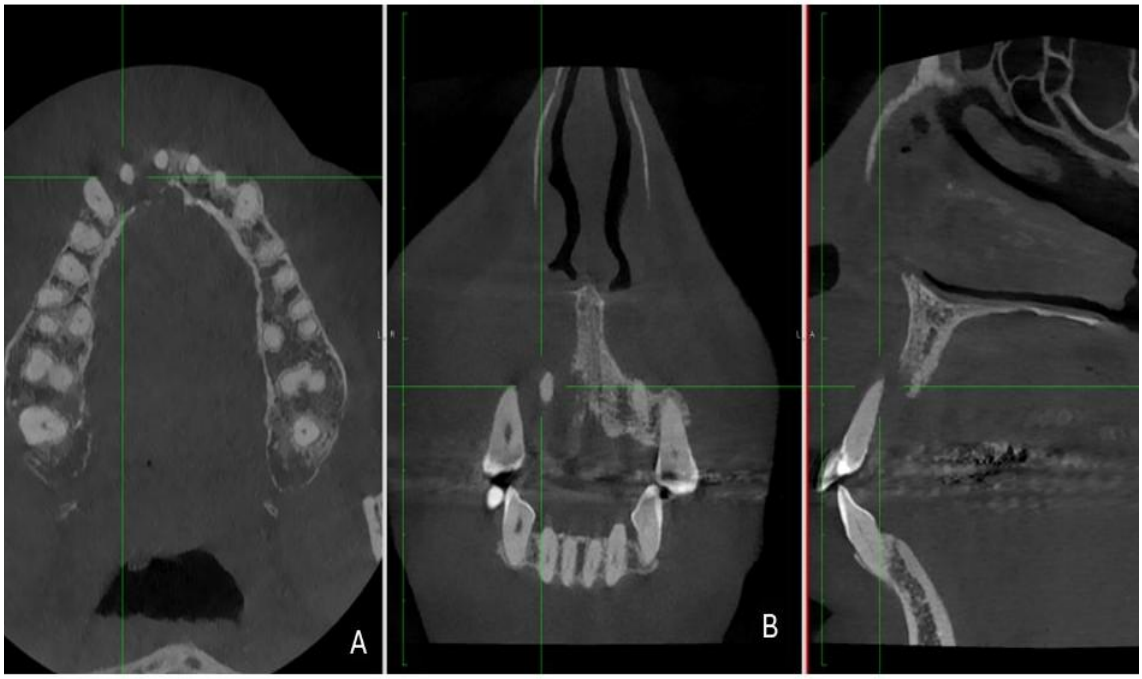
Periapical radiographic examination revealed bone loss from the middle third of the mesial side of the upper right canine (Figure 2A), loss of total bone insertion of the upper right lateral incisor, which showed a "floating tooth" appearance, extending to the apex of the upper right central incisor (Figure 2B).

Figure 2. Periapical radiographs of the upper right canine and lateral (A), and central incisors (B) respectively, demonstrate extensive bone destruction from the middle third of the mesial side of the canine to the apical region of the distal side of the right central incisor. An imaging pattern of a "floating tooth" is also noted on the right lateral incisor (A).

Given the clinical appearance combined with the radiographic characteristics, a suspicion of malignancy was raised, and the patient was then submitted to a cone-beam computed tomography (CBCT) imaging, which revealed an extensive osteolytic lesion with destruction of the buccal cortical bone, the limits of which extend from the mesial side of the canine to the midline region. There were also points of rupture of the palatal cortex, and loss of total insertion of the lateral incisor, including destruction of the alveolar bone, with no evidence of root resorption (Figure 3).

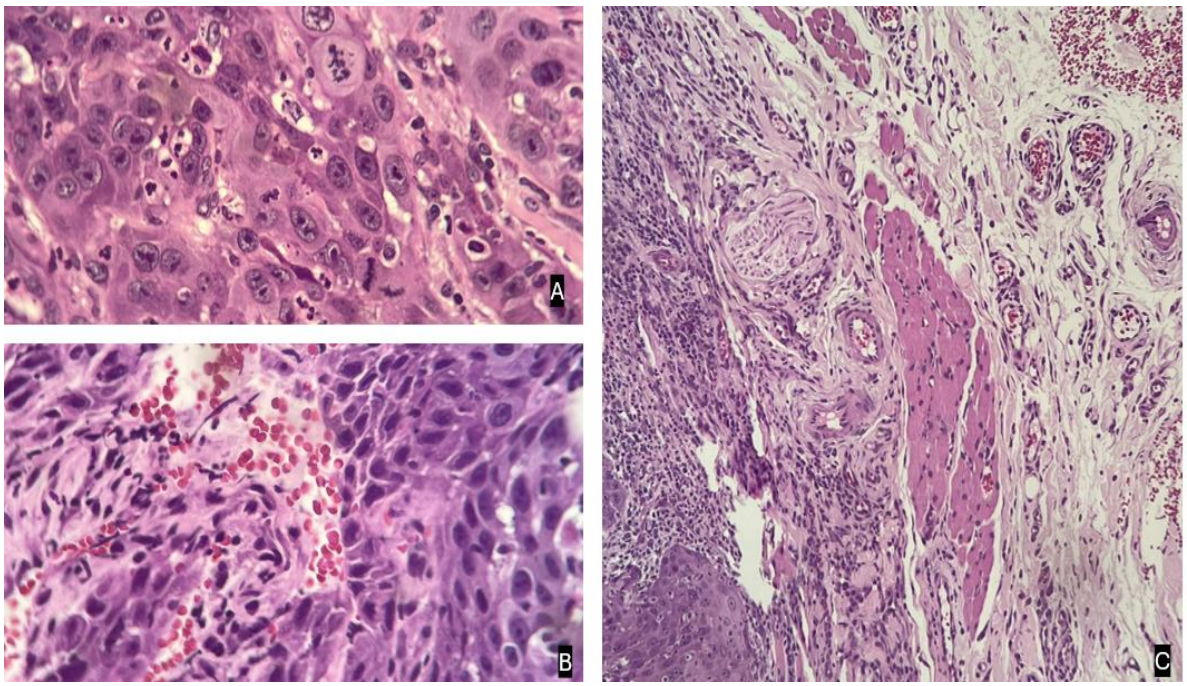
Figure.3. CBCT multiplanar reconstructed images (axial - **A**, coronal - **B**, and sagittal - **C** images) show the destruction of the buccal cortical bone from the mesial side of the right canine to the midline region, involving the right central incisor, with points of rupture in the palatal cortex. The images also demonstrate a total loss of bone insertion in the

lateral incisor, the limits of the cortical of incisive canal, and destruction of the alveolar bone.



Thus, supported by clinical and imaging examinations, the hypotheses of carcinoma, osteosarcoma, and lymphoma were considered and an incisional biopsy was performed. Histological examination showed an epithelial neoplasm made up of squamous cells, without keratinization or horny pearls, infiltrating fibro-connective tissue The tumor cells showed nuclear atypia, karyotic irregularity, hyperchromasia, and some mitosis figures (Figure 4A). Angiolymphatic (Figure 4B) and perineural invasion were also present (Figure 4C). According to the clinical, tomographic, and histological aspects, the final diagnosis was consistent with squamous cell carcinoma of the gingiva.

Figure 4. Histological examinations demonstrate cells with cellular pleomorphism, hyperchromatic nuclei and atypical mitoses (A), and the presence of vascular invasion (B). Mucosal fragment showing proliferation of atypical epithelial cells in cords and islets, with the presence of perineural invasion (C).



The patient was referred in May 2023 to the Head and Neck Oncology service in good clinical health. The negative result for metastasis was confirmed by PET-CT. A helical computed tomography (CT) imaging, as well as a magnetic resonance imaging (MRI) were also performed to aid in treatment planning and defining the safety margins. Approximately 15 days after these imaging tests, surgery to remove the tumor was performed and adjuvant chemotherapy and radiotherapy sessions were carried out. Six months after surgery, a prosthesis was installed to improve form and function, but there are still plans for plastic surgery to reconstruct the soft tissues, to be carried out in due course. In July 2024, new imaging exams were carried out for control and no recurrences were found. The patient responded to the proposed therapy and to date remains without recurrences. Her general state of health is currently stable.

DISCUSSION

Squamous cell carcinoma is considered to be the most prevalent histological type in this region of the oral cavity (Cabral et al, 2010; Sundermann et al, 2018). However, studies point to a subgroup of patients who, despite not being exposed to risk factors, such as non-smokers and non-alcohol drinkers, have developed oral cavity carcinomas (Cabral et al, 2010; Fiedler et al, 2023; KOO et al, 2013; Kruse; Bredell; Grätz, 2010). Rarer and with distinct clinicopathological characteristics, it primarily

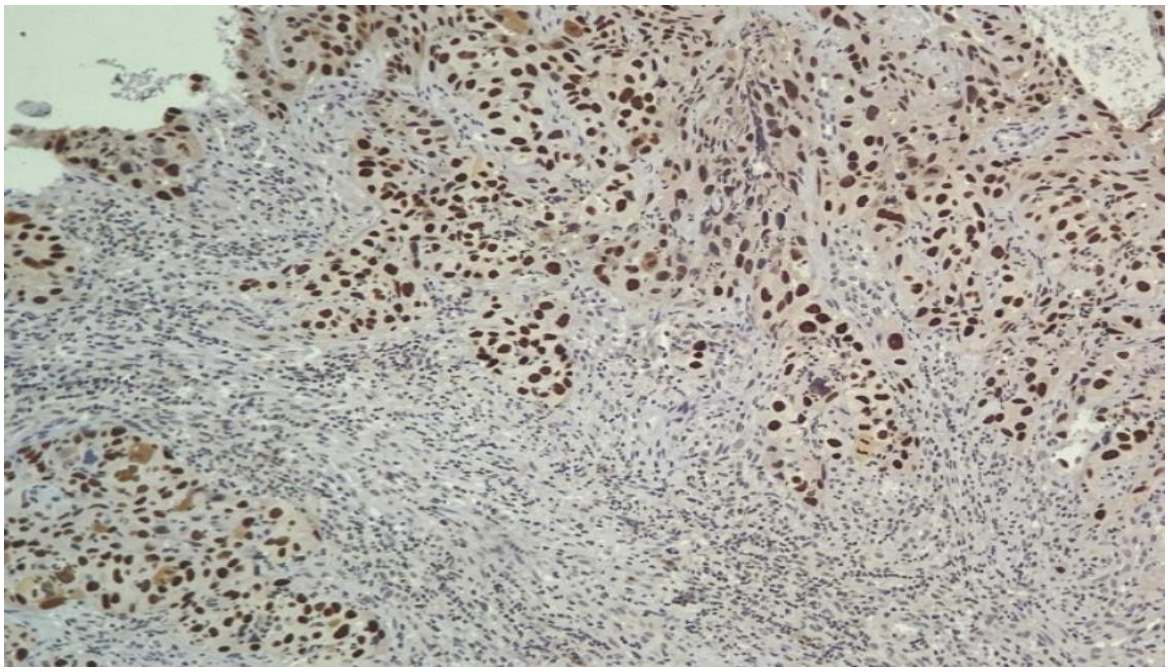
differs in location and sex, meaning it is much more common in women than in men, with the most preferred anatomical sites being the tongue and maxillary alveolus (KOO et al, 2013). The age of the patient at the time of diagnosis is still controversial in the literature when compared to patients who are traditional smokers and drinkers, i.e. some studies suggest that the vast majority of patients are around the 7th decade of life (Fiedler et al, 2023; Kruse; Bredell; Grätz, 2010) while others point to a growing increase in cases of gingival carcinomas in both older patients and younger patients aged between 18 and 44 (Uddin et al, 2022).

Studies have investigated the hypothesis of an association between the possible increase in cases in this age group and the presence of the HPV virus in p16-positive tumors, although the etiology is not very well established. However, the oncogenic potential of HPV is much more associated with oropharyngeal carcinoma and its contribution to the development of squamous cell carcinoma of the oral cavity is low, thus requiring further discussion (Uddin et al, 2022; Zafereo et al, 2016). This case report showed a young female patient with maxillary gingival carcinoma who was not exposed to risk factors. In order to verify a possible association with HPV-16 positivity, we additionally conducted an investigation, the immunoexpression of which was negative for p16, indicating the absence of expression for high-risk HPV. However, studies point to the fact that p16 immunohistochemical staining has little relevance for detecting HPV, given its low specificity for oral tissues (Magalhaes et al, 2016; Zafereo et al, 2016). However, analyses of gene expression profiles were not carried out.

Pseudepitheliomatous hyperplasia, as well as amelanotic melanoma, were also considered as differential diagnoses. However, the presence of atypical mitoses, infiltration into the connective tissue, and cellular polymorphism ruled out the hypothesis of pseudepitheliomatous hyperplasia, and the positive p63 test (Figure 5) excluded the possibility of amelanotic melanoma. Nevertheless, Foy *et al* (Foy et al, 2017) hypothesized that if oral squamous cell carcinoma (OSCC) in non-smokers and non-drinkers is epidemiologically distinct from OSCC seen in traditional smokers and alcoholics, it is therefore plausible to assume that the tumor microenvironment is also distinct. From this same perspective, Fiedler et al (Fiedler et al, 2023) conducted a study which consisted of a comparative analysis of the clinical, histopathological and immunological characteristics of patients exposed and not exposed to risk factors.

They collected clinical data from 131 patients and then performed immunohistochemical staining for the main immune cells that infiltrate tumors. Regarding clinical characteristics (such as tumor location, sex, and age), the findings of this study were in line with the literature for non-smokers and non-alcohol drinkers patients. However, they also found that the expression of infiltrating lymphocyte cells is higher in non-smokers and non-alcohol drinkers, giving this group a less aggressive tumor subtype with a better prognosis, given the fact that, according to the authors, they promoted less perineural invasion. However, this last statement was not unanimous. For example, Tran *et al* (Tran et al, 2023) clarify that there was no consensus regarding the prognosis between patients exposed and not exposed to risk factors. They further added that some studies tend to state that the disease course is more aggressive in young patients, while others claim that tumor aggressiveness is more prevalent in older patients, always comparing alcohol and tobacco users versus non-smokers and non-alcohol drinkers.

Figure 5. Positive nuclear staining for p63 shows squamous epithelial differentiation of the neoplasia.



From this same perspective, immunohistochemical staining for TCD4+ and TCD8+ was also carried out on our patient. However, a greater expression of tumor

lymphocyte infiltration was not confirmed. It was worth mentioning that a more immunogenic profile could be the target of immunotherapy, which could make up a promising therapeutic strategy for these patients (Fiedler et al, 2023; Foy et al, 2017; Uddin et al, 2022). Thus, it is more accurate to say that prognosis depends on clinical, radiological, and histopathological characteristics or the sum of them. Histological differentiation, perineural and angiolymphatic invasion, bone infiltration, depth of invasion into adjacent tissues, positive surgical margins, and the use of postoperative adjuvant therapy (chemotherapy and/or radiotherapy) are generally factors that indicate an unfavorable prognosis (Hong et al, 2024; Slieker; De Bree; Van Cann, 2020).

Regarding the diagnostic contribution of imaging exams, Morice *et al.* (Morice et al, 2016) concluded that bone infiltration observed on CT scans of the nasal fossa, maxillary sinus, and orbital floor of a maxillary gingival squamous cell carcinoma were also significantly associated with lower overall patient survival, since were factors suggestive of recurrence, even if histologically negative margins were found. This means that imaging exams have proved to be good predictors of prognosis. Furthermore, in the event of suspected bone infiltration, radiographic examination was essential to aid diagnosis, location, and information on the extent of the lesion. Radiographically, bone infiltration was interpreted as an osteolytic lesion with irregular edges, with rupture of the bone cortex, which can lead to total loss of tooth insertion (Slieker et al, 2022), thus exhibiting an appearance of “floating teeth”, which corroborates the initial findings of the periapical radiographs, and which was later confirmed in the CBCT of our case.

Computed tomography (CT) and magnetic resonance imaging (MRI) are widely used exams for preoperative tumor classification and are therefore necessary for surgical planning and defining safety margins[17]. In a comparative study between CT and MRI, no statistically significant difference was found regarding the detection of bone invasion by maxillary squamous cell carcinoma. Therefore, the choice between one or the other can be determined by greater accessibility, greater or lesser presence of bodies that could produce artifacts or even exposure to radiation (Slieker et al, 2020). Nevertheless, cone-beam computed tomography (CBCT) can be an useful imaging modality, given the low radiation dose compared to helical computed tomography, and is also appropriated for evaluating the maxillary bones (Slieker et al.,

2020). Similarly, both CT and MRI images were acquired from our patient and contributed to surgical planning, as well as defining safety margins.

Periapical and panoramic radiographs are used in the clinical practice of the dental surgeon, and can provide parameters for a suspected malignancy to be included in the diagnostic hypothesis. However, imaging exams such as computed tomography (cone-beam or helical), magnetic resonance imaging, and PET-CT allowed visualization of the lesion's behavior regarding its extent, depth, invasion, metabolic activity, degree of destruction, as well as involvement and impairment of adjacent structures. These imaging exams are valuable not only for diagnosis but also for treatment planning and monitoring the lesion's progression.

The case report showed a maxillary gingival squamous cell carcinoma in a young female patient, with no exposure to predisposing risk factors, not preceded by potentially malignant disorders and therefore uncommon. It has a proliferative, ulcerated, and bleeding clinical appearance, with marked tooth mobility due to the total loss of bone insertion, with classic radiographic features such as floating teeth and an osteolytic lesion with ill-defined edges and bone infiltration. Histologically, the findings included perineural and angiolymphatic invasion as well as the presence of positive margins.

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