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CASE REPORT

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## SQUAMOUS CELL CARCINOMA IN YOUNG NON-SMOKER PATIENT: CASE REPORT

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### ABSTRACT

Squamous cell carcinoma (SCC) represents approximately 90% of all oral malignant neoplasms. Oral SCC is more common in white men between the sixth and seventh decades of life, alcoholics, and smokers, and affects mainly the lateral border of the tongue. When it affects young people, it occurs predominantly in non-smoker and non-alcoholic women and the common site is the lateral border of the tongue. Its incidence in young individuals is increasing, and their mechanisms of development are still undefined. This paper aims to report a case of SCC in the lateral border of the tongue in a 25-year-old black man.

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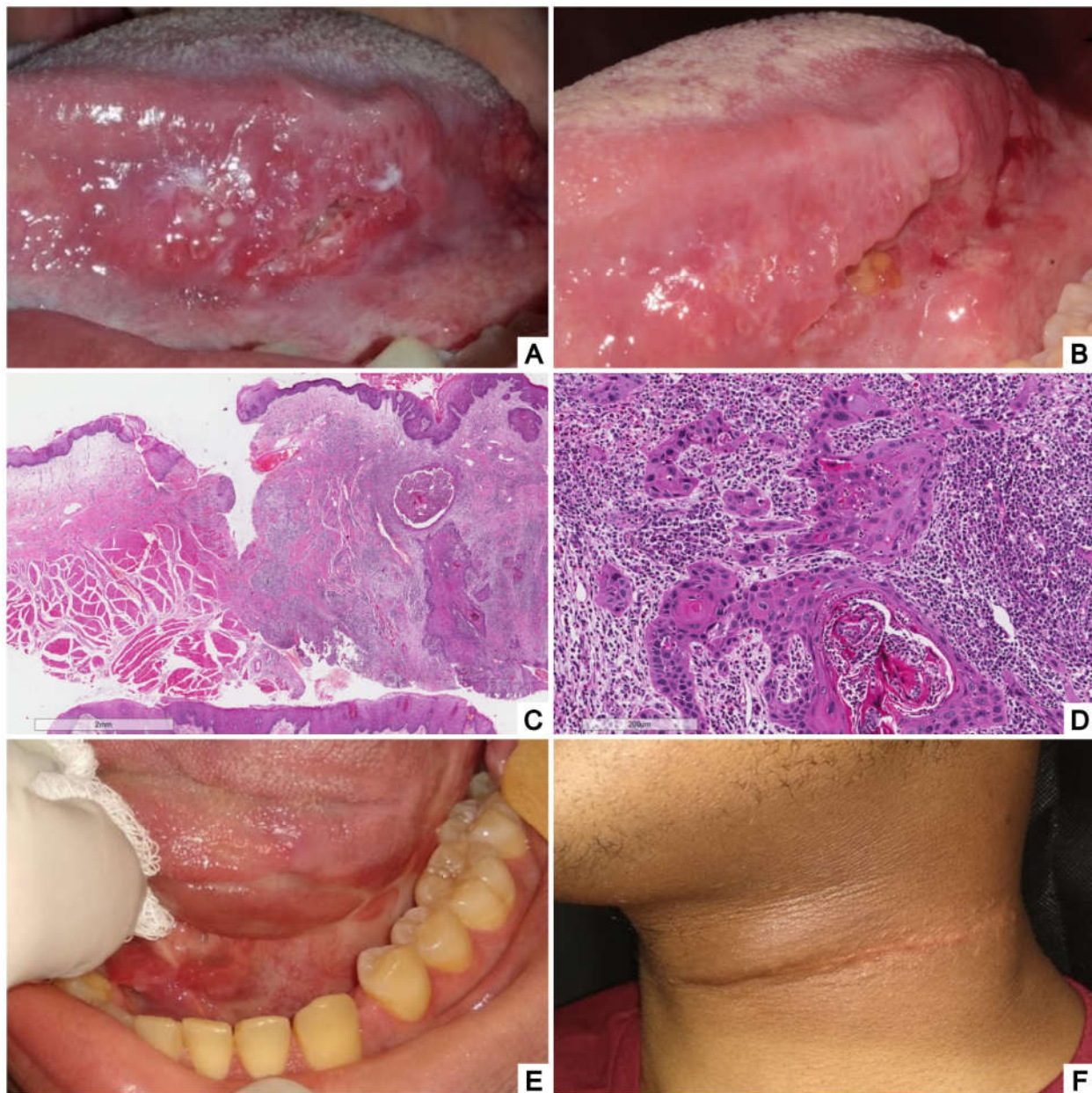
## INTRODUCTION

Squamous cell carcinoma (SCC) represents approximately 90% of all oral malignant neoplasms, and the majority of cases are preceded by potentially malignant disorders (EL-NAGGAR ET AL., 2017). Generally, oral SCC affects men between the sixth and seventh decades of life, alcoholics, and smokers (CHEN et al., 2020; DOS SANTOS COSTA et al., 2018; NASSER; ST JOHN, 2020; PICKERING et al., 2014), and mainly the lateral border and ventral surface of the tongue, floor of the mouth, and soft palate (SANTOS-SILVA et al., 2014). The occurrence of oral SCC in young white female patients with no history of smoking and alcohol use has increased in recent years (ADDURI et al., 2014; BARNABÉ et al., 2019; CAMPBELL et al., 2019; CHEN et al., 2020; LLEWELLYN et al., 2004; MAHMOOD et al., 2018; MAROUN et al., 2020; MIRANDA GALVIS et al., 2018; NASSER; ST JOHN, 2020; PICKERING et al., 2014; VAN MONSJOU et al., 2013). Nevertheless, this high incidence has not yet been explained by genetic alterations, habits, or other factors, unlike oropharyngeal carcinoma in young patients, which has been strongly related to human papillomavirus (HPV) (YOSEFOF et al., 2020).

Thus, studies on oral SCC in young people are very important to elucidate the controversial aspects that involve the etiopathogenesis of the disease, contributing to an early diagnosis and reduction of high rates of morbidity and mortality. This paper aims to report a case of SCC on the lateral border of the tongue in a 25-year-old non-smoker black man.

## CASE REPORT

A 25-year-old black male was referred to the Oral Diagnostic Clinic of Antônio Pedro University Hospital (HUAP) of Universidade Federal Fluminense (UFF) for evaluation of an asymptomatic oral lesion, with a two-year evolution. During the anamnesis, the patient denied smoking and reported social drinking, with a frequency of ingestion twice a month, since he was 17 years old. The patient had no family history of cancer, and his laboratory tests were negative for syphilis (Venereal Disease Research Laboratory - VDRL), hepatitis B (Hepatitis B surface antigen - HBsAg), hepatitis C (Anti-HCV), HPV (anti-p16), and human immunodeficiency virus (Anti-HIV). In the intraoral exam, a 2.5 x 0.5 cm lesion on the left side of the tongue was identified, composed of a heterogeneous white plaque with thin



**Figure 1. Clinical and histopathological aspects. White and non-homogenous plaque, with thin and thick areas with approximately 2.5 x 0.5 cm, exhibiting ulceration with indurated border on the left lateral border of the tongue (A). Clinical aspects after one week of the biopsy (B). Histopathology demonstrated mucosal tongue with ulceration and invasion of the connective tissue with epithelial nests depicting hyperchromatic nuclei and pleomorphic cells and nuclei, mitosis and atypical keratin pearls were seen, and a diagnosis of moderately differentiated squamous cell carcinoma was confirmed (C and D). Surgical scar on the left lateral border of the tongue (E). Surgical scar on the cervical area after lymph nodes removal (F).**

and thick areas, as well as red areas and ulcer. The edges of the lesion were hard (Fig 1 A and B). Fixed and hard lymph nodes of sudden appearance were palpable on the left side of the submandibular area. The clinical diagnostic hypothesis was SCC. An incisional biopsy was performed and the histopathological exam showed an ulcerated lesion, with invasion of the epithelium into the underlying connective tissue. The nests of epithelial cells showed keratinocytes with hyperchromatic nuclei, cellular and nuclear pleomorphism, and numerous figures of mitosis, including atypical ones. Keratin pearls were also seen in the nests of epithelial cells. The diagnosis was moderately differentiated squamous cell carcinoma (Fig. 1 C and D).

The patient was referred to the National Cancer Institute (INCA) for treatment, where was submitted to surgical removal of the tumor with free surgical margins, as well as ganglionic emptying (pathological classification pT3 pN2a and clinic III). Adjuvant radiotherapy and immunotherapy protocols were performed. Radiotherapy comprised 33 sessions, a dose of 60 GY in 30 sessions, and reinforcement of a dose of 6 GY in three applications.

Two cycles of immunotherapy with Atezolizumab (1200 mg) were conducted. Moreover, recovering from the surgery, the patient performed five speech therapy sessions, with no difficulties in the mobility of the tongue. The patient is being followed up for approximately two years at the Oral Diagnosis Clinic of the UFF HUAP, without signs and symptoms of recurrence. Clinically, there is a surgical scar on the tongue and left cervical region (Fig. 1 E and F).

## DISCUSSION

SCC in young people became a more serious problem after the 2000s when epidemiological evidence showed a significant increase in cases (CHOI *et al.*, 2019). The disease appears clinically and biologically distinct from that in older age (LLEWELLYN *et al.*, 2004; MAROUN *et al.*, 2020; VAN MONSJOU *et al.*, 2013; YOSEFOF *et al.*, 2020). Its etiology and pathogenesis are still not well understood and recently, attention has been given to the genetic

factors research in developing of oral SCC in young people (MAHMOOD *et al.*, 2018). It is known that genetic changes are determined by two main parameters: level of exposure to mutagenic factors and inherent ability to repair DNA damage efficiently (BODNER *et al.*, 2014). The broad exposure to mutagens, on average, is higher in older patients, therefore, young patients seem to harbor a significantly lower number of mutations than older individuals (BODNER *et al.*, 2014; MAROUN *et al.*, 2020). Oral SCC among individuals with diseases or syndromes that predispose to cancer development is probably related to genetic instability (BODNER *et al.*, 2014). People with genetic syndromes, such as Fanconi anemia, xeroderma pigmentosus, congenital dyskeratosis, and the graft-versus-host disease, are at increased risk for the development of SCC in the first two decades of life (BODNER *et al.*, 2014). Immunohistochemical analyzes have shown that different molecular markers are involved in the development of oral SCC and the reported proteins are related to the cell cycle, local invasion, lymphatic growth, cell proliferation, and activation of cancer products (DOS SANTOS COSTA *et al.*, 2018). The tumor suppressor gene *TP53* is the most frequently mutated gene in human cancers and the p53 protein expression has been used as a marker for mutation in SCC (DOS SANTOS COSTA *et al.*, 2018; PICKERING *et al.*, 2014). Although tobacco and alcohol are known to increase the frequency of *TP53* mutations in head and neck cancers (BRENNAN *et al.*, 2007), a study by Pickering *et al.* (2014) of tongue cancer in nonsmoking patients over and under 45 years old observed a trend towards a higher rate of *TP53* mutation among younger patients. However, this difference was not statistically significant (PICKERING *et al.*, 2014). Other studies have identified a high proportion of p53 immunorexpression in younger patients (ADDURI *et al.*, 2014; DE PAULA *et al.*, 2009). In contrast, Choi *et al.* (2019) showed that p53 expression was not statistically different when comparing the different age groups. Therefore there is a divergence in the literature regarding *TP53* mutations in oral SCC in young people.

Regarding immunological responses, it has been reported that younger patients with oral SCC appear to have an attenuated immune response, which may be related to a higher frequency of immunogenic mutations in *ATM*, *BRCA1*, *E2F1*, and *FHIT* genes (KNOPF *et al.*, 2015). Other studies compared the expression of other biomarkers between young and elderly and found a greater expression of p16 (BARNABÉ *et al.*, 2019), cyclin D1 (KAMINAGAKURA *et al.*, 2011), EGFR, VEGF-C3 (DOS SANTOS COSTA *et al.*, 2018), C-ErbB2 (MIRANDA GALVIS *et al.*, 2018), CYP1B1 (KAMINAGAKURA *et al.*, 2011), MMP-9 (DOS SANTOS COSTA *et al.*, 2018), SMAm (MIRANDA GALVIS *et al.*, 2018), and podoplanin in young patients (DOS SANTOS COSTA *et al.*, 2018). However, the different expression patterns deserve a better investigation to understand the role of these molecules in the development of oral SCC in young people. Tongue SCC can be considered a subtype of head and neck cancer, which affects mainly young patients, with a significant proportion not associated with classic risk factors (CAMPBELL *et al.*, 2019). A study by Campbell *et al.* (2019) analyzed location distribution with regard age and found that the lower the age of the individual with oral SCC had a greater association with cases located on the tongue. The case described agrees with this study representing a young man, who was non-smoker and with a low alcohol consumption habit, with a SCC located on the tongue. Commonly, the main risk factors for SCC development include smoking and alcohol consumption, which are strongly synergistic (VAN MONSJOU *et al.*, 2013). However, despite the increasing use of smokeless tobacco products, such as chewing tobacco, in young people, no associations were observed between smoking (chewing tobacco, cigarettes, cigars, or pipes) and the development of tongue SCC under the age of 50 (CAMPBELL *et al.*, 2019). Moreover, studies suggest that exposure of young people to these carcinogenic agents does not last long enough to justify its malignant transformation (LLEWELLYN *et al.*, 2004; NASSER; ST JOHN, 2020). However, the difficulty in determining the type, quantity, and frequency of the habit can be considered an important obstacle when interpreting the results (DOS SANTOS COSTA *et al.*, 2018).

In the present case reported, the patient denied smoking and reported social drinking, with low frequency and dose. We believe that the short duration of exposure to the risk factor could not be sufficient for the malignancy development. In the last 15 years, it has been an increase in SCC incidence induced by HPV, especially subtypes 16 and 18, with a high frequency in young, non-smoking, and non-alcoholic individuals (SANTOS-SILVA *et al.*, 2014). Although HPV infection has been well established as a factor in the development of oropharyngeal SCC, the possible involvement of HPV in the etiology of oral SCC is controversial (DOS SANTOS COSTA *et al.*, 2018; NASSER; ST JOHN, 2020; SANTOS-SILVA *et al.*, 2014). Regardless some authors consider that the increase in oral SCC in young people may be associated with HPV, most studies describe a low presence of this virus in oral SCC in young individuals (less than 11%) (MELO *et al.*, 2020). Interestingly, Kaminagakura *et al.* (2012) found a greater incidence of HPV16 in oral SCC in Brazilian young patients (68.2%). This discrepancy in results may be related to the location of the tumor, geographic heterogeneity, and the different methods used for the detection of HPV (DOS SANTOS COSTA *et al.*, 2018). In the present case, the investigation of HPV 16 was negative. The SCC treatment depends on the age, location, extension, and presence of metastasis, and consists mainly of surgical excision followed by radiotherapy (SANTOS-SILVA *et al.*, 2014). In the present case, removal of the tumor with free surgical margins, lymphnode emptying, in addition to radiotherapy and immunotherapy was performed.

Immunotherapy is a biological therapy capable of inducing and/or regulating anti-tumor immune responses, representing a complementary approach to conventional treatments of cancer, with greater applicability in a minimal residual disease and reducing distant metastases after other therapeutic interventions (DAVIDSON *et al.*, 2009). Emerging forms of immunotherapy in the treatment of SCC involve both the use of monoclonal antibodies (mAb), as well as various forms of vaccine strategies that activate and target cell immunity of the patient against the tumor (DAVIDSON *et al.*, 2009). In the present case, immunotherapy with mAb (atezolizumab) was performed. Considering the prognosis, there is still no consensus about oral SCC in young patients (BODNER *et al.*, 2014; DOS SANTOS COSTA *et al.*, 2018). Studies suggest that oral SCC in young patients tends to be more aggressive, with less time for cancer development and regional metastases, quickly reaching advanced stages of the disease (ADDURI *et al.*, 2014; DAVIDSON *et al.*, 2009; DOS SANTOS COSTA *et al.*, 2018). According to Saggi *et al.*, (2018) SCC in elderly patients has greater recurrence and shorter survival, probably due to the presence of common comorbidities in this age group, which can influence overall survival rates (MIRANDA GALVIS *et al.*, 2018). So far, the patient is in clinical control and without signs of the disease. The lack of consensus in determining the age groups considered young and elderly was another obstacle for comparing the studies. The standardization of this criterion is fundamental for comparisons and to understand differences between the groups.

## CONCLUSION

The etiology and pathogenesis of SCC in young patients are still uncertain and need further clarification and investigation. Although there are some differences about the profile predominantly described in the literature, the present report contributes to understanding the SCC in young people. This occurrence in young patients with no smoking habit and low frequency of alcohol consumption suggests that genetic factors are involved in its development.

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