

# Malignant and premalignant lesions of the tongue, clinical and histopathological findings for their early detection. Study of two cases

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## Article History

Received: 15 10 19

Accepted: 09 03 20

Published: 05 06 20

## ABSTRACT

**Background:** Squamous cell carcinoma affects subjects between the sixth and seventh decade of life. However, there are growing reports on the involvement of young adults. **Clinical Cases:** Two male patients aged 40 and 55, with no history of tobacco consumption and occasional alcohol consumption. They presented an exophytic ulcer and a white plaque on the lateral border of the tongue, the first diagnosed as moderately differentiated squamous cell carcinoma without HPV DNA genotypes and the second as leukoplakia without dysplasia. **Conclusions:** Risk factors commonly associated with potentially malign disorders and oral cancer, such as smoking and alcohol consumption, were not involved in the present cases. Therefore identify clinical, histopathological and molecular findings, allows the early detection of them, improving the prognosis of these patients.

**Keywords:** Carcinoma, Squamous Cell; Mouth Neoplasms; Oncovirus; Papillomaviridae; Leukoplakia, Oral; young adult.

## RESUMEN

**Introducción:** El carcinoma de células escamosas afecta a sujetos entre la sexta y séptima década de la vida. Sin embargo, hay cada vez más informes sobre la participación de los adultos jóvenes. **Casos clínicos:** Dos pacientes varones de 40 y 55 años, sin antecedentes de consumo de tabaco y consumo ocasional de alcohol. Presentaban una úlcera exofítica y una placa blanca en el borde lateral de la lengua, la primera diagnosticada como carcinoma epidermoide moderadamente diferenciado sin genotipos de ADN del VPH y la segunda como leucoplasia sin displasia. **Conclusiones:** Los factores de riesgo comúnmente asociados a enfermedades potencialmente malignas y cáncer oral, como el tabaquismo y el consumo de alcohol, no estuvieron involucrados en los casos presentes. Por tanto, identificar hallazgos clínicos, histopatológicos y moleculares, permite la detección precoz de los mismos, mejorando el pronóstico de estos pacientes.

**Palabras clave:** Carcinoma; Células escamosas; Neoplasias bucales; Oncovirus; Papillomaviridae; Leucoplasia oral; adulto joven.

## DOI

[10.17081/innosa.73](https://doi.org/10.17081/innosa.73)

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## I. INTRODUCTION

Oral cancer is the 11th most common cancer in the world; this includes cancers of the lips, tongue, gum, floor of the mouth, palate, and mouth. The squamous cell carcinoma (SCC) is the most frequent of the malignant neoplasms of the oral cavity, according to WHO corresponds to more than 90% of all malignant lesions in the mouth and the 3% of all cancers (1,2). This is a significant cause of morbidity and mortality in patients with head and neck cancer. This neoplasm is generally more frequent in male than in the female. In general, SCC affects subjects after their fifth decade of life (3). A significant increase in pathology has been reported in young adults (4), among whom patients < 30 years old are considered (5), some authors have as criteria to define young patients those under 45 years old (6). The incidence in this population ranges from 0.4% to 13% (7-9), although the data varies according to the country, in the UK it is reported 6% (10) and India between 16 and 28%(11). Its worldwide distribution is unequal, being more incident in Eastern Europe and South Asia, in the United Kingdom, it is rare cancer. In Latin America, it occurs in countries such as Uruguay, Brazil and Argentina. In Colombia, there are around 100 to 120 new cases of oral cancer for a year, mainly affecting men, patients over 60 years of age and associated with common risk factors (12). The most common sites of SCC is the lateral border of the tongue, 70% of these neoplasms involved the lateral border, followed by the floor of the mouth and a lower frequency by the soft palate, gingiva and buccal mucosa (13,14).

The consumption of tobacco (70%) and alcohol (36%) are the main risk factors among older patients, however in the young population, less than half of the patients consume tobacco or alcohol, which suggests the presence of other etiological factors (15). Other habits have also been associated with SCC, such as chewing betel leaves, inverted smoking, oral thrush, use of mouthwash and mate. Factors such as diet and nutrition, radiation, ethnicity, familial and genetic predisposition, immunosuppression, syphilis, dental factors, occupational risks and infectious proliferative process caused by human papillomavirus (HPV) are also considered (16,17,18,19,20). The International Agency for Research on Cancer in 2007 accepted that human papillomavirus (HPV) type 16 was a risk factor for tongue and tonsillar cancer (21). The clinical characteristics vary from the case and include the exophytic forms such as verrucous or papillary form when it starts its growth stage. In early stages, it presents as ulcerous lesions, keratotic plaques: erythroplasia, leukoplasic, or erythroleukoplakia forms. These lesions may cause painful symptoms depending on their extent and/or location, usually they are painless when they affect the ventral side and lateral edges of the tongue, so they can go unnoticed by the patient (22).

Some authors report about the changing epidemiology of tongue squamous cell carcinoma (TSCC), recent reports indicating an increasing incidence in young women. These authors reported that most areas experienced an incidence increase ranging from 0.4% to 3.3% per year and in patients under 45 years old the incidence of TSCC was higher, compare with patients over that age (23). Comparing some industrial countries such as UK, Denmark and Netherlands with USA, France, Italy, Germany and Hong Kong, the firsts one the prevalence of squamous cell carcinoma was expanded (24). The World Health Organization in 2010 reported that 2 per 100,000 people died in the Middle East, but in USA and India the rate was not that high (25). The radical primary surgery is the treatment of choice, using a free tissue transfer reconstruction where indicated. When the tumor invasion is over 3 mm, a selective neck dissection must be done, with a 0.5 cm margin of normal tissue. In elderly patients, who usually have some associated co-morbidity and even their lifestyle, based in nowadays oral cancer treatment makes difficult to have a prognosis, although those patients can die for a different reason than cancer (26,27).

## II. CLINICAL CASES

**First case.** A 40-year-old male was seen at the Stomatology Clinic, Department of Oral Medicine, University of Cartagena Dental School, for presenting a tumoral growth in the tongue. The patient reported a tumoral growth in lateral edges of the tongue for the last 6 months, without smoking habit and alcohol consumption. Sexual habits that include oral sex are reported. The patient reports a history of cancer in the family, a maternal grandmother died from cancer of the cervix as well as a paternal uncle due to gastric cancer. The patient said have noticed a white plaque, of unknown evolution, asymptomatic, on the lateral border of the tongue, which did not receive treatment. The physical examination was found a patient with a good nutritional status, oriented in person, space and time, good health condition with controlled arterial hypertension. When palpating the ganglion chains no affected lymph nodes were evident. Intraoral clinical examination showed ulcer with exophytic borders located on the left side of the tongue, which extends to ventral and dorsal surfaces, with raised and indurated edges, asymptomatic, 1.0 x 1.0 cm. Whitish plaques are observed on the ventral surface and ipsilateral mouth floor, there is evidence of vegetations in areas near the edge of the ulcerative lesion. With six months of evolution, other mucous membranes were within the normal range (**figures 1a and b**).

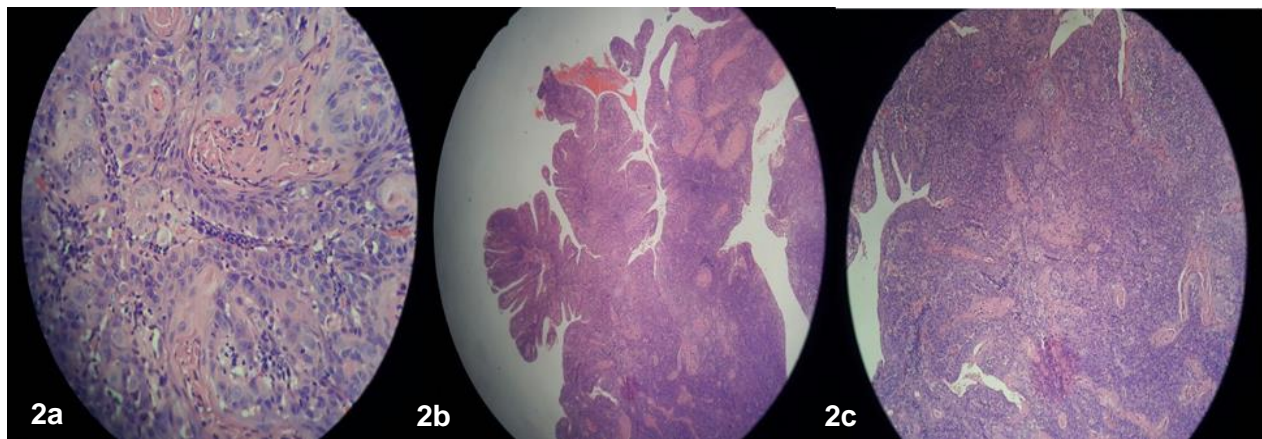


**Figure 1a:** A localized ulcer is observed on the lateral border of the tongue, left side, with extends to the ventral surface and the dorsal surface, with raised and indurated edges, asymptomatic, of 1.0 x 1.0 cms. Note the white plaques in the tongue ventral face and the ipsilateral mouth floor, there is evidence of vegetations near the edge of the ulcerative lesion. **1b:** On the tongue ventral side adjacent to the ulcer, white and asymptomatic plaques are observed, with do not detach from shaving and from unknown evolution. In the exophytic edge of ulcerative lesion, vegetation is observed, in the form of cauliflower, white, asymptomatic with a rough surface.

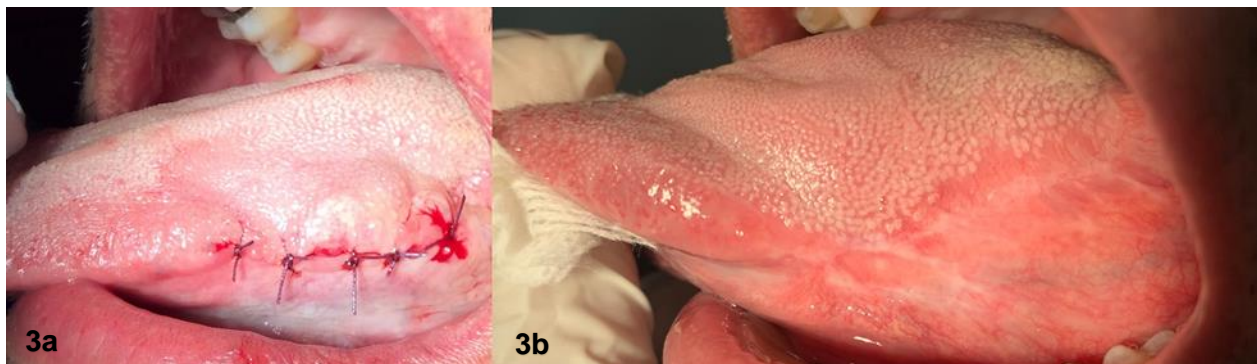
No presence of palpable ganglion chains in the neck and submaxillary and submental region. An incisional biopsy of the lesion is performed, including in the sample apparently healthy margins. A part of the sample is sent for detection of HPV genotypes by real-time PCR and another part for anatomopathological study. The histopathological result reveals ulcerated oral mucosa with tumor lesion of epithelial lineage characterized by a proliferation of large cells of hyperchromatic nuclei that are arranged in solid and infiltrating nests, with individual

keratinization, surrounded by a fibrous stroma with chronic inflammatory infiltrate. The histopathological diagnosis was squamous cell carcinoma of large cells, moderately differentiated, infiltrating and ulcerated (**figure 4**). The pathological study reported cellular changes compatible with dysplasia, nuclear hyperchromatism, pleomorphism and atypical mitosis (**figures 2 a, b and c**).

The real-time PCR evaluated the presence of 29 genotypes in the sample sent, 19 of high risk, among which genotypes 16 and 18 were evaluated and nine of low risk (genotypes 6,11,42,54), were not identified HPV genotypes in the sample sent. The patient is referred to oncological surgery of head and neck who performs partial hemiglossectomy with superficial ipsilateral neck emptying. The patient in the six months control after the surgical procedure is without clinical signs of recurrence of the neoplasm, the figures 5a and b show the immediate and six months postoperative (**figure 3 a and b**).



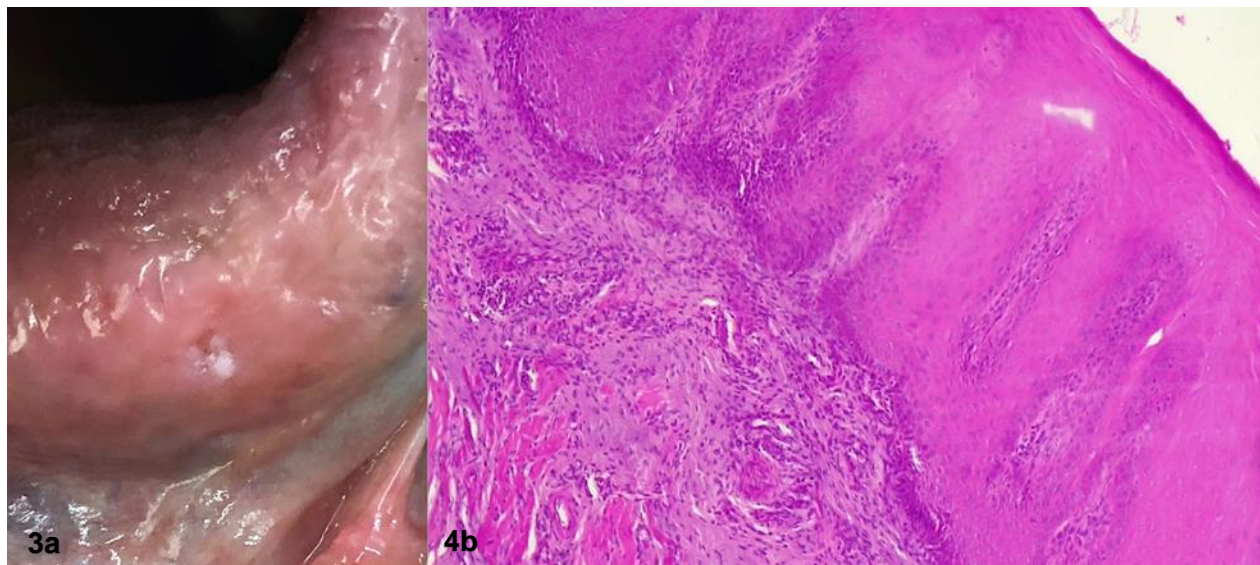
**Figures 2:** **2a.** The histopathological section shows the cellular characteristics of the malignancy: nuclear hyperchromatism, pleomorphism and atypical mitosis. **2b.** Observe the loss of the normal architecture of the oral epithelium. **2c.** The invasion of the epithelial cells within the connective, with zones of keratinization around these, is visible in this section.



**Figure 3:** **3a.** Immediate postoperative, of incisional biopsy, showing adequate opposition of tissues in the intervened area. **3b.** 6-month control. Observe the adequate healing of the intervened tissue. It is evident the plaque of whitish border, center hypochromic, asymptomatic, with no induration, compatible with leukoplakia.

**Second case.** A 55-year-old male was seen at the Stomatology Clinic, Department of Oral Medicine, University of Cartagena Dental School, for presenting a white plaque in tongue. The patient reported a tumoral growth in lateral edges of the tongue for the last six months, without smoking habit and alcohol consumption. The physical examination was found a patient with a good nutritional status, oriented in person, space and time, good health condition without any clinical background. When palpating the ganglion chains no affected lymph nodes were evident. Intraoral clinical examination showed ulcer with exophytic borders located on the right ventral surface side of the tongue, with raised and indurated edges, asymptomatic, 3 mm x 3 mm. There is evidence of white plaque in areas near the edge of the ulcerative lesion, with 6 months of evolution, other mucous membranes were within the normal range (**figure 4a**).

An incisional biopsy of the lesion was performed, including in the sample apparently healthy margins for an anatomopathological study. The histopathological result reveals oral mucosa with an intraepithelial lesion with gout shaped epithelial ridges, hyperplasia and hypercellularity in the basal stratum, without dysplasia, and with hyperkeratosis and papillomatosis. The own sheet shows chronic inflammation. The histopathological diagnosis was leukoplakia without dysplasia (**figure 4b**). A surgical excision was practiced, keeping the patient in controls for 1 year without showing recurrence.



**Figure 4:** **4a.** localized ulcer is observed on the ventral surface of the tongue, right side, with raised and indurated edges, asymptomatic, of 3 x 3 mm. Note the white plaque in areas near the edge of the ulcerative lesion. **4b.** The histopathological section does not show the cellular characteristics of the malignancy: Intraepithelial lesion with gout shaped epithelial ridges, hyperplasia and hypercellularity in the basal stratum, without dysplasia, and with hyperkeratosis and papillomatosis.

### III. DISCUSSION

Oral squamous cell carcinoma corresponds to more than 90% of oral cancer diagnoses, is commonly associated with risk factors such as smoking and alcohol, without ignoring the hereditary factor. The tongue cancer nowadays has increased, significantly between 1973 and

2012 (0.6% annual increase), more specifically in young white women even though the use of tobacco decreased in the USA. (28). Regarding the age group, squamous cell carcinoma is a rare disease in patients under 45 years of age, mainly affecting subjects between the fifth and sixth decade of life. However, there are reports of cases of oral carcinomas in young adults, without the risk factors commonly associated with neoplasia (29-30). Adorno-Farías et al (31), report a case of verrucous carcinoma in the tongue in a 60-year-old patient without known risk factors, just like in the present report. These authors also conducted a review of cases in the period between January 1984 and October 2010, reporting 20 cases of warty carcinoma in patients with an average age of 70.7 years, verrucous carcinoma with clinical and histological particular characteristics, affects primarily the male sex between the fifth and seventh decade of life, with is why it differs from the present report. In young adults relationship between malignancy and HPV infection associated with sexual contact pathway (orogenital) has been reported, without conclusive data considering the virus as an etiological factor (32,33). Many studies show that HPV DNA is present in a considerable number of squamous cell carcinomas but it represents a distinct entity with many doubts to be solved regarding the casual relationship between the virus and carcinoma (34). Chen X et al, recommend the use of makers such as P16 and HPV genotypes as test for the detection of HPV in patients with squamous cell carcinoma. The human papillomavirus is considered an etiological factor of this pathology an even for oral premalignant disorders (34). Kouketsu A et al, reported and expression in 24 subjects of the P16 protein of 174 subjects evaluated with squamous cell carcinoma, with the most prevalent subtypes being 16 and 18. This authors conclude that HPV has a minor role in oral oncogenesis in patients Japanese in this report, HPV genotypes associated with neoplasia were not found (35). Falaki F et al. in 2011 published a retrospective study of patients diagnosed with squamous cell carcinoma, received in the last 13 years in a health care center in Iran. of the 158 cases of squamous cell carcinoma diagnosed, 21 patients were young adults under 40 years of age, 12 of them males. In the group of patients studied there were no significant risk factors associated, the tongue was the most common site of presentation, with exophytic ulcer being the most common clinical lesion. HPV DNA was not detected in these patients. All the data of the studied population are coincident with the case in this report, highlighting the non-presence of common risk factors and the non-detection of HPV DNA (12) (36).

#### IV. CONCLUSIONS

Associated findings at the white plaques or erosive lesions in the lateral borders of the tongue, must caught the attention of the clinical professional when are present in young patients without the habits that are commonly associated with oral squamous cell carcinoma.

It is important a well detailed clinical history that reveal data of the background of this lesions, how they have been treated and how often do they show up, furthermore it has to be considered the biopsy to determinate the presence of dysplasia changes in the evaluated tissue, not forgetting the immunohistochemical studies to determinate oncogenesis such as P16 and established a prognosis of the lesions evaluated. The best prognosis of oral cancer it is given by the early diagnosis.

**Ethical revelation.** The authors declare that no experiments were performed in humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article.

**Authors contribution:** "Conceptualization, Adel Martínez-Martínez. Antonio Diaz-Caballero.; methodology, Adel Martínez-Martínez. Antonio Diaz-Caballero.; software, Antonio Diaz-Caballero.; validation, Adel Martínez-Martínez.; formal analysis, Adel Martínez-Martínez. Antonio Diaz-Caballero. Natalia Quintero-Echenique.; research, Adel Martínez-Martínez. Antonio Diaz-Caballero.; resources, Antonio Diaz-Caballero.; data healing, Antonio Diaz-Caballero.; writing: preparation of original draft, Adel Martínez-Martínez.; writing: review and editing, Adel Martínez-Martínez. Natalia Quintero-Echenique.; viewing, Adel Martínez-Martínez. Natalia Quintero-Echenique.; supervision, Adel Martínez-Martínez project management, Antonio Diaz-Caballero.; fund acquisition, Antonio Diaz-Caballero. All authors have read and accepted the published version of the manuscript."Yes"

**Acknowledgements.** To our patient who today allows us to learn from her case.

**Conflicts of interest.** The authors declare no conflict of interest.

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