

## SQUAMOUS CELL CARCINOMA OF THE LIP: A CASE SERIES OF DISTINCT CLINICAL PRESENTATIONS

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### Abstract

Typical squamous cell carcinoma of the lip generally presents as a small (<1 cm), painless, indurated ulcer that is crusted, exudative, slow-growing, and histologically well-differentiated. It most commonly occurs in fair-skinned male patients in their sixth or seventh decade of life, with primary etiological factors including UV exposure, followed by tobacco and alcohol use. This study aims to report four clinical cases of squamous cell carcinoma of the lip that exhibited presentations distinct from the classical features typically attributed to these lesions. In the first case, the carcinoma manifested as a poorly differentiated ulcer with extensive tissue destruction. The second case involved a large nodular lesion. The third case, located on the upper lip, was histologically identified as a

rare variant of squamous cell carcinoma. The fourth case appeared as an ulcerated nodule and an ulcer extending to the skin. While squamous cell carcinoma of the lip is relatively common and typically exhibits non-aggressive behavior, certain cases may present with features distinct from its classical in both clinical appearance and behavior.

**Statement of Clinical Significance:** This case series highlights atypical manifestations of lip squamous cell carcinoma, including rare upper lip involvement, basaloid variants, and aggressive lesions in uncommon patient profiles. Awareness of these unusual clinical and histopathological presentations is essential for early diagnosis, accurate differential diagnosis, and timely management.

**Key-words:** Squamous cell carcinoma; Lip cancer; Oral cancer; Lip squamous cell carcinoma; Oral oncology, Risk Factors.

## **1. Introduction**

Squamous cell carcinoma of the lip (SCCL) is one of the most common malignant lesions in the oral and maxillofacial region, accounting for 25–30% of all oral cancers and 12% of head and neck cancers [1, 2]. Exposure to UV rays is the most important etiologic factor, followed by excessive alcohol and tobacco use [3–5].

Typical clinical manifestations include leukoplastic or erythroplastic patches, fissures, or crusts on the vermilion border of the lips. The most common treatment is surgical removal with a low rate of distant metastasis and thus an excellent prognosis, with a 5-year survival rate of 90% [6–13]. In advanced cases, infiltration and severe exudative ulcers are common, often accompanied by significant pain [3, 14]. However such advanced clinical presentations are uncommon, as squamous cell carcinoma of the lip typically exhibits indolent progression, with early detection frequently achievable owing to the conspicuous nature of the lesion [3, 6, 14].

This study presents four case reports of squamous cell carcinomas of the lip with features distinct from its classical clinical manifestations. Written informed consent from the patient(s) was obtained.

## **2. Case Report**

### **2.1 Case 1**

A 48-year-old male smoker presented with a painful ulcer on the left lower lip that had persisted for four months, impairing his ability to eat and speak. The patient had previously sought care at a medical emergency department, where he was treated with acyclovir for three months for a presumed diagnosis of herpes labialis. As the lesion failed to improve, he subsequently sought care at a primary healthcare unit and was referred to our service. Clinical examination revealed a deep necrotic ulcer measuring 2 × 1 cm (Figure 1A). Differential diagnoses included orofacial gangrene and squamous cell carcinoma (SCC). Following negative tests for HIV and syphilis, an incisional biopsy was performed. Histopathological examination revealed a poorly differentiated SCC, characterized by invasive epithelial cells, marked nuclear pleomorphism, perineural invasion, and invasion of the underlying muscle tissue (Figure 1B). Immunohistochemical analysis showed positivity for p63 and CK5/6, supporting the squamous epithelial phenotype of the neoplasm. The tumor was staged as T2N1M0, corresponding to clinical stage III. The patient underwent complete tumor excision and ipsilateral neck dissection, which revealed one metastatic lymph node (Figure 1C). After completing 30 sessions of radiotherapy, he returned 11 months later with a recurrent exudative ulcer on the chin (Figure 1D). He subsequently underwent preparation for chemotherapy and palliative care and died of the disease one year after diagnosis.



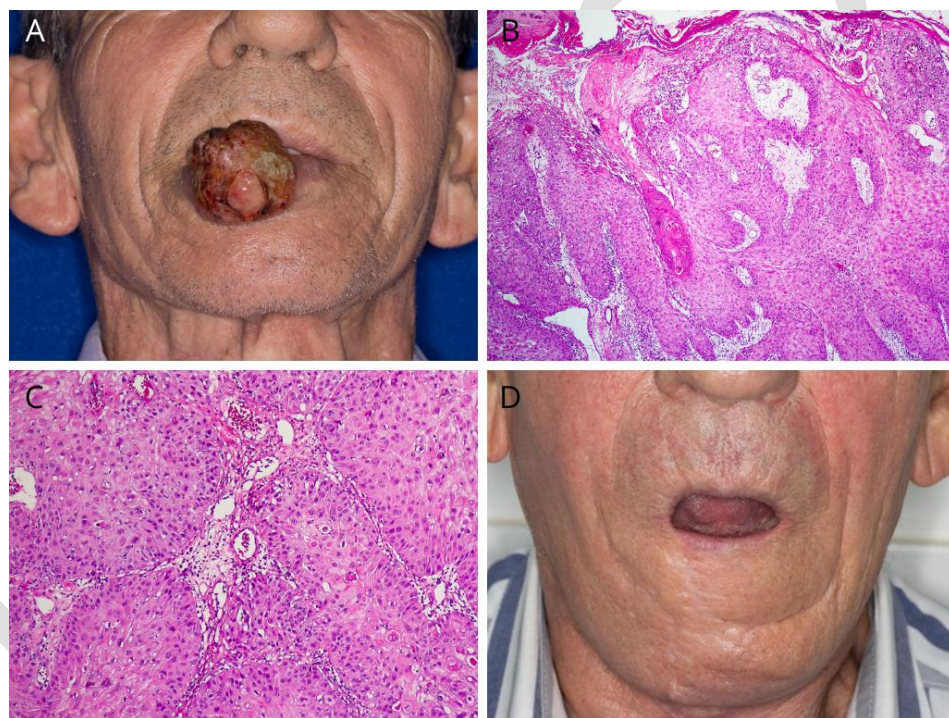
**Figure 1:** 1A) Necrotic and exudative ulcer located on the left side of the lower lip, exhibiting extensive tissue destruction, with a surface marked by crusts of varying shades, including reddish, brownish, and yellowish hues. 1B) Cells exhibiting cellular and nuclear pleomorphism, nuclear hyperchromatism, an increased nuclear-to-cytoplasmic ratio, forming islands and cords within the connective tissue, along with an absence of keratin production. 1C) Patient after surgical treatment for tumor excision, neck dissection, and radiotherapy. 1D) Recurrence of the lesion with extension to the chin region. Neoplastic cells invading and destroying skeletal muscle tissue.

## 2.2.Case 2

A 72-year-old white male, former smoker, presented with a progressively enlarging lesion on his lower right lip, first noticed after a fall . He delayed seeking treatment for nine months because he concealed the lesion by wearing a mask during the COVID-19 pandemic until it began to interfere with his eating. Clinical examination

revealed a 6 cm pedicled, exophytic nodule with an irregular surface and fibrinopurulent membrane, displaying reddish, yellowish, and brownish areas (Figure 2A). The lesion was firm, painless, and bled upon palpation, raising suspicion for squamous cell carcinoma (SCC). An incisional biopsy confirmed well-differentiated SCC, characterized by invasive squamous cells, pleomorphism, hyperchromatic nuclei, dyskeratosis, and atypical mitoses (Figure 2B and 2C).

The patient underwent full-thickness tumor excision, ipsilateral neck dissection, and 25 sessions of radiotherapy. One year and three months post-diagnosis, he remains in good health with no recurrence, reporting only xerostomia as a treatment side effect (Figure 2D).



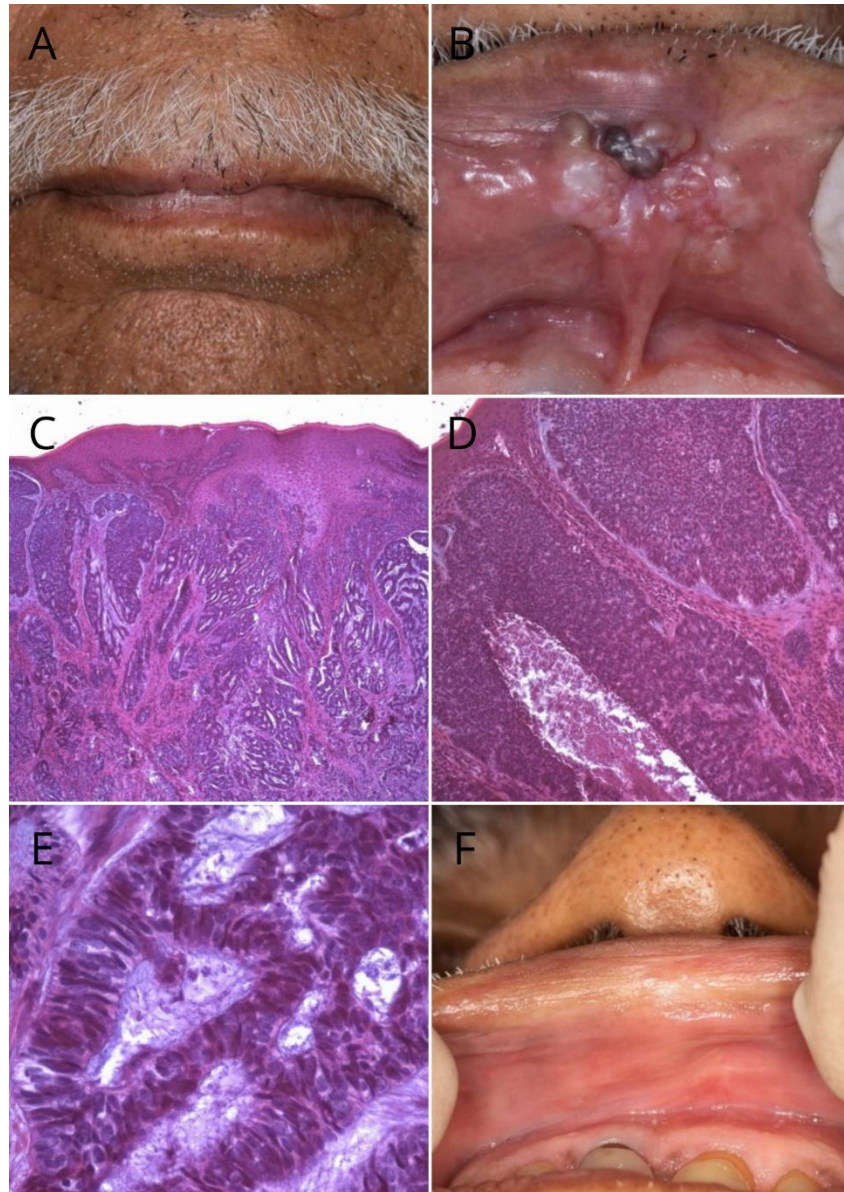
**Figure 2:** 2A) Clinical appearance of the lesion observed on frontal physical examination: presence of a large pedunculated nodule with a crusted and ulcerated surface. 2B) Proliferation of squamous epithelial cells with invasion into the underlying connective tissue (H&E staining, 40x magnification). 2C) Cellular atypia, including nuclear hyperchromatism, nuclear and cellular pleomorphism, and the presence of some dyskeratotic cells (H&E staining, 100x magnification). 2D) Patient after treatment with surgery and radiotherapy.

### 2.3.Case 3

An 81-year-old Black Brazilian man, a non-smoker and non-drinker, sought medical evaluation for persistent pain from a lesion that had not healed for two years after a dental impression for dentures.

Extraoral examination revealed loss of the nasolabial fold, with no involvement of the overlying skin (Figure 3A), while intraoral examination identified a 2 cm sessile, indurated nodule in the upper labial mucosa, with an irregular, lobulated surface, areas of ulceration, and variegated coloration (black, white, and red). (Figure 3B).

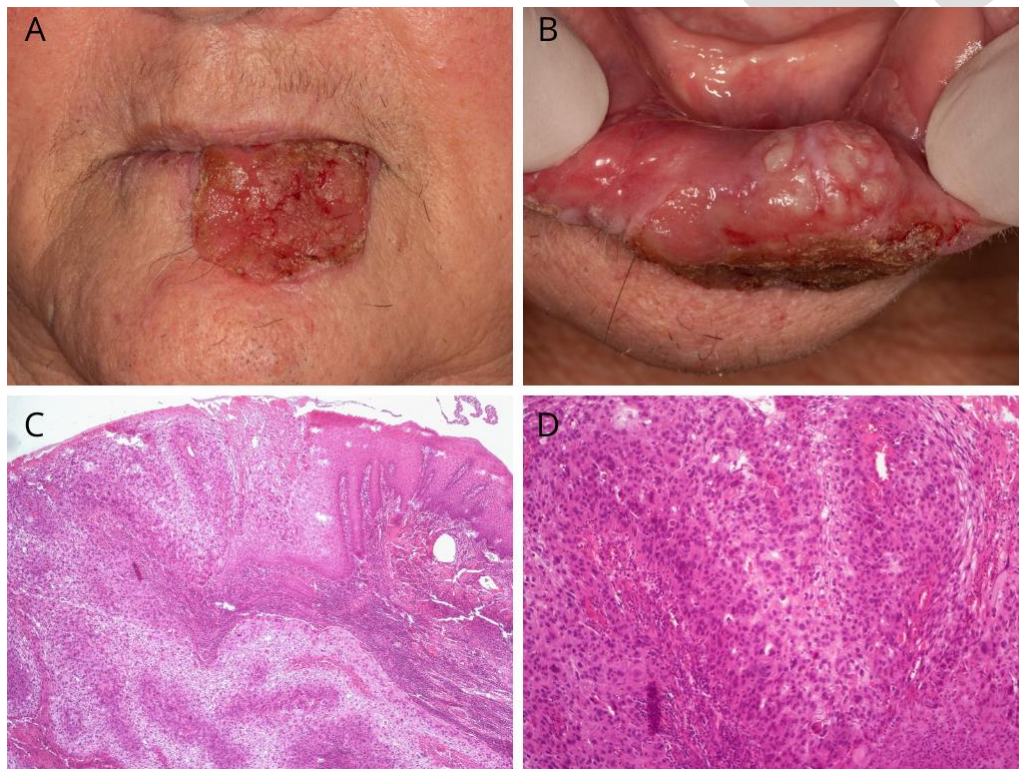
Differential diagnoses included squamous cell carcinoma (SCC), melanoma, and scar fibrosis. An incisional biopsy revealed a poorly differentiated malignant neoplasm with basaloid areas and pigmentation suggestive of melanin (Figure 3C–E). Immunohistochemical analysis was subsequently performed and showed positivity for p63, supporting the epithelial origin of the neoplasm. Based on the combined clinical, histopathological, and immunohistochemical findings, a final diagnosis of basaloid SCC was established. The patient was referred for treatment, which involved full-thickness tumor excision, two lip reconstruction surgeries, and 30 sessions of radiotherapy. One year after diagnosis, he remains well, with no signs of recurrence (Figure 3F).



**Figure 3:** 3A) Extraoral examination showing loss of the nasolabial fold, with no involvement of the overlying skin by the lesion. 3B) Clinical appearance of the lesion observed on intraoral physical examination: a nodule with blackened, whitish, and reddish areas, an irregular and slightly lobulated surface, and ulcerated regions. 3C) Proliferation of cells with predominantly squamous differentiation, largely composed of a proliferation of basaloid-appearing cells (H&E staining, 40x magnification). 3D) Proliferation of basaloid-appearing cells, forming islands with solid and lobulated appearances, as well as areas resembling cords (H&E staining, 40x magnification). 3E) Cords of basaloid cells (H&E staining, 400x magnification). 3F) Intraoral examination after surgical excision of the lesion and radiotherapy.

## 2.4. Case 4

A 68-year-old white woman, a non-smoker and non-drinker, presented with an itchy mouth sore that had developed over the past year. Physical examination revealed a very extent ulcerated nodule and multiple small ulcers on the lower labial mucosa, with a significant ulcer extending from the vermilion border to the skin, measuring 2 cm in diameter and 2.5 cm in height, characterized by a crusted surface and reddish-brown coloration (Figure 4A and 4B). A differential diagnosis of SCC prompted an incisional biopsy, which confirmed a malignant neoplasm with atypical epithelial cells invading connective tissue, along with pleomorphism and hyperchromatism (Figure 4C and 4D). The diagnosis was well-differentiated squamous cell carcinoma. The patient was referred for tumor staging and treatment at a specialized hospital.



**Figure 4:** 4A) Extraoral aspect of the lesion, showing an ulcer extending to the skin with a crusted surface. 4B) Intraoral aspect of the lesion showing an ulcerated nodule, smaller ulcers, and whitish plaques in the region of the lower labial mucosa. 4C) Connective tissue being invaded by atypical epithelial cells (H&E staining, 40x magnification). 4D) Cells exhibiting cellular and nuclear pleomorphism, hyperchromatism, and an increased nuclear-to-cytoplasmic ratio (H&E staining, 100x magnification).

## DISCUSSION

Among the types of cancer that manifest on the lips, squamous cell carcinoma is the most common [1, 13–15]. Its clinical presentations typically include asymptomatic, indurated ulcers or crusts, predominantly located on the lower lip [4, 9, 16, 17]. These lesions generally measure around 1 cm in width and approximately 6 mm in depth [8, 18, 19]. In our series, the clinical presentation was the main aspect in which atypical features were observed. Case 1 exhibited a more aggressive clinical presentation, characterized by a deep, destructive, and necrotic lesion resulting in significant tissue loss in the affected region. Case 3 presented in an atypical location, the upper labial mucosa, and with a rare histological subtype. Cases 2, and 4 exhibited ulcers larger than the average sizes reported in the literature.

Among the manifestations of LSCC, a higher prevalence is observed among male patients with fair skin, primarily due to greater sun exposure [14,18,20–23]. In the cases presented, two patients (Cases 2 and 4) reported a history of intense sun exposure, as both had worked as agricultural workers. However, at least two of the cases did not fully align with these typical characteristics. In Case 1, the patient worked as a motorcycle courier on the night shift, with limited occupational sun exposure. In Case 3, the patient had dark skin.

According to authors such as Oliveira Silva et al. (2020)[16] the progression of these lesions is typically slow, exhibiting a much lower degree of aggressiveness compared to intraoral squamous cell carcinomas, with a better prognostic. Furthermore, most studies indicate that these lesions are generally asymptomatic in their early stages [2, 3, 16, 20]. Despite being asymptomatic, these lesions are often diagnosed early, mainly because they are easily visible to healthcare professionals and even to the patients themselves [4, 10, 11, 14, 21, 22]. Contrary to what is reported in the literature, in Clinical Cases 1 and 2, we observed a much more rapid progression, with both patients reporting pain from the onset of the lesion. Additionally, Clinical Case 1 exhibited a particularly poor prognosis, ultimately leading to the patient's death. In Clinical Case 2, there was a significant delay in diagnosis and subsequent lesion growth, as the patient concealed the lesion from family members and healthcare professionals due to the COVID-19 pandemic and the use of face masks.

Regarding the histological differentiation of these lesions, following the WHO classification, studies indicate that 39.2% to 64.2% of cases are histologically classified as well-differentiated, while only 2.1% to 6.9% are poorly differentiated [7, 8, 18, 23, 24]. Clinical Case 1, after histopathological analysis, was classified as poorly differentiated, thus falling within the minority of cases.

In Clinical Case 3, the histopathological diagnosis was basaloid squamous cell carcinoma. This subtype is classified by the WHO as a rare, aggressive, and high-grade variant of squamous cell carcinoma, characterized by basaloid and squamous components [25]. Clinically, it presents as an ulcerated, firm, and exophytic mass [26, 27]. Several studies in the literature report that the most common sites for this lesion are the pharynx, hypopharynx, oropharynx, larynx, epiglottis, and the base of the tongue [26, 28, 29]. Other locations, particularly intraoral, are considered rarer but have been reported in the palate, floor of the mouth, tonsil, and maxillary tuberosity [26, 27, 30]. In the reported case, the lesion was located intraorally on the upper labial mucosa, a site rarely described in the literature for this rare variant, as well as for conventional squamous cell carcinomas, since 95% of these occur on the lower lip [16, 18, 31]. One of the most frequently reported etiological factors for basaloid SCC is tobacco and alcohol abuse [26], whereas, in Clinical Case 3, the patient reported no use of either substance.

Taken together, the cases presented in this series illustrate clinical and histopathological features that differ from the classical presentation of LSCC described in the literature. These include unusual lesion characteristics, such as greater size, deep and destructive growth, symptomatic and rapid progression, poor histological differentiation, and an uncommon histological subtype and anatomical location. In addition, some patients did not present the demographic or behavioral characteristics commonly associated with LSCC, such as fair skin, substantial sun exposure, tobacco use, or alcohol consumption. These findings highlight the clinical heterogeneity of LSCC and reinforce the importance of maintaining clinical suspicion even when lesions do not conform to their typical presentation.

## CONCLUSION

Although squamous cell carcinoma of the lip is relatively common and typically exhibits a non-aggressive behavior, some cases may present with features distinct from its classical in terms of clinical appearance, histopathological characteristics, or clinical behavior. Therefore, it is crucial for dentists and all healthcare

professionals to be familiar with these lesions, as this knowledge can facilitate early diagnosis and appropriate management.

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Brenda Corrêa Santos contributed to the writing of the manuscript and was responsible for the patient care involved in this study. Fábio Augusto Ito performed the photography, provided patient care, and assisted in the revision of the manuscript. Ademar Takahama Junior was involved in patient care, provided supervision, and contributed to the revision and correction of the manuscript.

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### **Competing interests:**

None of the authors have conflict of interest.

### **Ethics approval:**

Written informed consent from the patient(s) was obtained.

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