

# Oral squamous cell carcinoma in coca chewers from a north region of Argentina: A case series and review of literature

Ignacio Molina-Ávila<sup>1</sup>, Andrea Arellano Rojas<sup>2</sup>, Gerardo Gilligan<sup>3</sup>, Karina Cordero-Torres<sup>4</sup>

<sup>1</sup>Stomatology Unit, Hospital Señor del Milagro, Salta, <sup>3</sup>Department of Oral Medicine, Facultad de Odontología, Universidad Nacional de Córdoba, Córdoba, Argentina, <sup>2</sup>School of Health Sciences, Universidad de Viña del Mar, Viña del Mar, <sup>4</sup>Department of Oral Pathology and Diagnosis, School of Dentistry, Universidad de Valparaíso, Valparaíso, Chile

## Abstract

Chewing coca leaves is a habit still practiced in Bolivia, Peru and Argentina. There is scarce evidence in the relationship between this habit and development of oral squamous cell carcinoma (OSCC), some authors have found oral epithelial changes in coca chewers. This study aimed to present a case series of patients with a coca chewing habit that developed OSCC, in the absence of risk factors for oral cancer. Patients were evaluated in Hospital Señor del Milagro, Salta, Argentina. None of them had a relevant morbid history and presented intraoral tumors, with an ulcerated surface on the gingivobuccal complex. Coca chewing habit was recorded in all cases. Present cases could start discussions and new lines of researches focusing on the habit of coca leaves chewing as a risk factor for OSCC. It would be very useful to know the underlying mechanisms between this habit and a possible role in oral carcinogenesis.

**Keywords:** Coca chewers, erythroxyton coca, oral cancer

**Address for correspondence:** Dr. Karina Cordero-Torres, Subida Leopoldo Carvallo, 211, Playa Ancha, Valparaíso, Chile.

E-mail: karina.cordero@uv.cl

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## INTRODUCTION

Oral cancer corresponds to 5% malignant neoplasms and 90% are oral squamous cell carcinoma (OSCC).<sup>[1]</sup> According to previous data, only 15% of cases are diagnosed in early stages.<sup>[2]</sup>

OSCC is usually associated with risk factors such as smoking, excessive alcohol consumption, aging, male gender, areca and betel nut, human papillomavirus (HPV) and chronic mechanical irritation (CMI).<sup>[3]</sup> Geographic location could influence the exposition of population to different carcinogens due to the presence of different cultural habits. A previous study had hypothesized that chewing of coca leaves could be

considered an underestimated risk factor for OSCC in South America.<sup>[4]</sup>

Coca leaves chewing is a habit that is still observed in Bolivia, Peru and northern Argentina and almost three million people chew coca leaves per year in Peru.<sup>[5]</sup> Chewing coca consists of leaving a bunch of coca leaves between the buccal pouch and molars, adding an alkaline substance as a sodium bicarbonate or tree ashes, called “*llipta*” or “*yista*,” for 2 to 3 h approximately. This habit generates systemic and local alterations, being the oral cavity the most affected.<sup>[5]</sup> The aim of this study is to present four patients who attended in the Stomatology Unit of the Hospital

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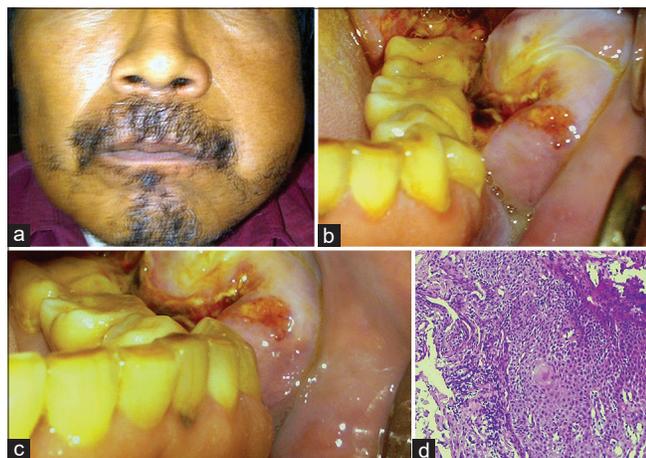
Señor del Milagro, Salta, Argentina, with an OSCC with strong coca consumption, without classic risk factors for OSCC.

## CASE REPORTS

Four patients attended to the Stomatology Unit of the Hospital Señor del Milagro, Salta, Argentina, between 2012 and 2014. All cases were referred with the clinical presentation of intraoral tumors, with ulcerated surface and located on the gingivobuccal sulcus, posterior buccal mucosa and retromolar pad (this subsite was previously named gingivobuccal complex). None of the patients reported relevant morbid history, they did not consume tobacco, alcohol and/or drugs. In all cases, they chewed coca leaves for more than 6 h per day for 10 years. All cases were p16 negative by immunohistochemistry. All patients gave their informed consent to have their clinical, medical and histopathological images published.

### Case 1

A 49-year-old male was referred to our institution from Tartagal (Salta, Argentina) with the presence of a tumor on the left mandibular region of 6-month-evolution. The extraoral examination showed an increased size of solid consistency, showing multiple firm and painless lymphadenopathies on the same side [Figure 1a]. An ulcerated lesion with indurated edges and necrotic areas was evidenced on the vestibular sulcus, from tooth 34 to the retromolar trigone, causing compromise and dental mobility [Figure 1b and c]. The histopathological examination revealed a moderately differentiated OSCC [Figure 1d]. The patient died 2 months after the diagnosis.



**Figure 1:** (a) Tumefaction on the left mandibular region. (b and c) An enormous ulcer with indurated margins involving the gingivobuccal left complex. (d) Histopathology. Epidermoid cells infiltrating the connective tissue are observed, with a formation of a keratin pearl. Moderately differentiated oral squamous cell carcinoma

### Case 2

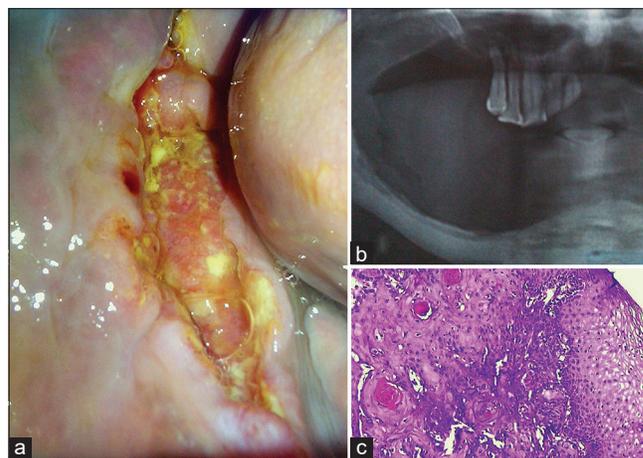
A 64-year-old male from Pichanal (Salta, Argentina) was referred with a lesion on the right mandibular alveolar ridge. The intraoral clinical examination showed a 3-month-evolution indurated ulcer [Figure 2a]. A panoramic radiography was taken, showing atrophy on the right mandibular ridge with a superficial invasion of bone cortical [Figure 2b]. In addition, a greenish pigmentation was observed on both buccal mucosae, indicating the site where coca leaves were placed when chewing. The final diagnosis was a well-differentiated OSCC [Figure 2c]. The patient died in 3 months.

### Case 3

A 48-year old male, from Tarija (Bolivia), was referred with a 9-month-evolution mandibular growth on the left side [Figure 3a]. The intraoral examination showed an indurated tumor with an ulcerated surface. The ulcer involved the vestibule sulcus from tooth 45 to the left side retromolar trigone [Figure 3b]. A huge osteolytic lesion was evidenced by cone-beam computed tomography, causing a pathological fracture and reabsorption of the mandible bone at the malignancy area [Figure 3c]. An incisional biopsy was taken which revealed a well-differentiated OSCC [Figures 3d and e]. The patient died before starting oncological treatment.

### Case 4

A 48-year-old male patient, from Oran (Salta, Argentina), was referred with a 4-months-evolution lesion on the



**Figure 2:** (a) Necrotic ulcer located on the right gingivobuccal area. A leukoedematous mucosa was observed surrounding the ulcer. It could be also observed greenish and yellowish areas indicating the presence of coca-leaves pigments. (b) Panoramic radiograph showing atrophy on the right mandibular ridge. No bone invasion (c) Histopathological findings. The specimen analysis showed an epithelium with dyskeratotic changes, loss on the basement membrane and islet cells infiltrating the underlying connective tissue. Well-differentiated oral squamous cell carcinoma

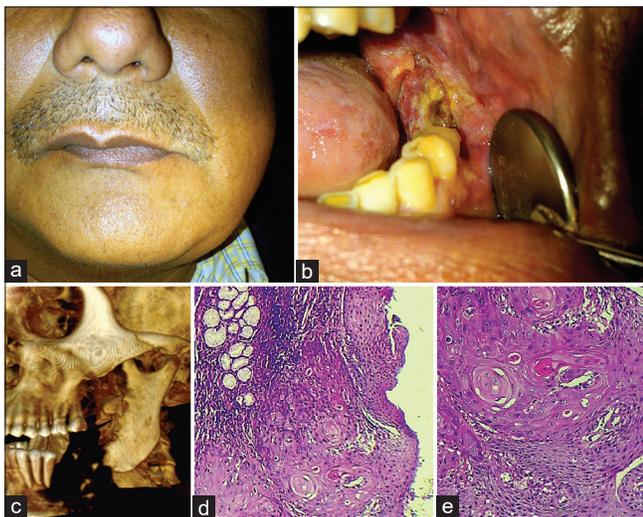
left buccal mucosa and gingivobuccal complex. The intraoral examination showed a terebrant ulcer with indurated edges accompanied by whitish zones spreading through the anterior buccal mucosa [Figure 4a]. No evidences of bone invasion were recorded by radiographic images [Figure 4b]. The final diagnosis was a poorly differentiated OSCC [Figure 4c and d].

Table 1 shows clinicopathological and immunohistochemical characteristics of these patients.

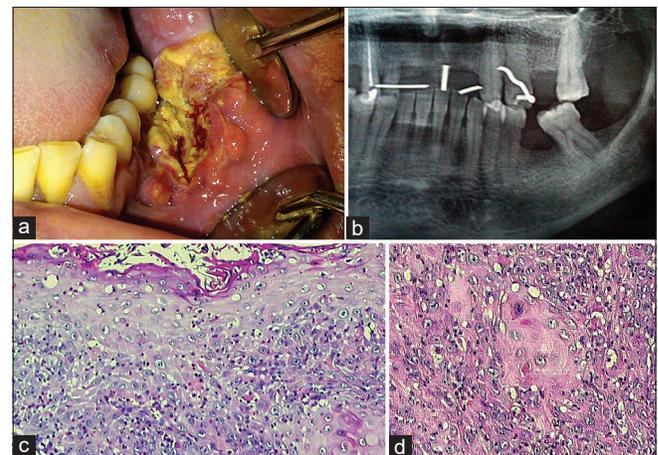
**DISCUSSION**

Oral carcinogenesis is a multistage and a multifactorial process. Regarding risk factors for OSCC, betel and areca nut chewing are well-known habits commonly found in Southeast Asia. Individuals from these regions are more likely to develop oral potentially malignant disorders such as oral submucous fibrosis.<sup>[6]</sup> Many regions of southern

Asia such as Indonesia, Singapore, Malaysia, Brunei, Cambodia, the Philippines, Vietnam, Thailand and Myanmar present the highest and alarming rates of OSCC in the world. The reasons behind this number are linked to betel chewing, a common and cultural habit from these parts of the world.<sup>[1]</sup> OSCC related to betel consumption presents different features in relation to classical OSCC related to tobacco and alcohol consumption described in Europe and America. Among them, the most involved subsites of oral mucosa are the gum and posterior buccal mucosa. The gingivobuccal complex includes the buccal mucosa, gingival sulcus, gingiva and retromolar pad.<sup>[7]</sup> Regardless of the physiopathogenic mechanisms that may link betel and coca chewing with oral carcinogenesis, it is relevant to evidence many parallelisms between the location and the clinical-pathological profile of betel OSCC with the cases reported in this study. These similar features lead to hypothesize that tumors associated with chewing plant-derived substances could present analogous physiopathogenic links, which has not been yet studied in our population. Limited scientific evidence about the



**Figure 3:** (a) Facial edema. 9-month growth on the left side. (b) Indurated tumoral lesion with an ulcerated and necrotic surface located on the left retromolar pad. (c) Tomography revealed a huge rounded osteolytic lesion which caused the jaw fracture. (d) Histopathology. Epidermoid cells invasion on the connective tissue is observed, forming keratin pearls and invading the minor salivary glands acini. (e) Cellular and nuclear pleomorphism and keratin pearls. Well-differentiated oral squamous cell carcinoma



**Figure 4:** (a) Indurated edges ulcer with whitish zones, from 34 to the posterior zone of 37, spreading through the jugal mucosa. (b) Orthopantomography. No osteolytic lesions found. (c and d) Histopathology. Presence of abundant epidermoid cells proliferation widely distributed over the connective tissue, with a clear cellular and nuclear pleomorphism, atypical mitosis and absence of keratin pearls. Diagnosis: a poorly differentiated epidermoid carcinoma

**Table 1: Clinicopathological data registered of cases of oral squamous cell carcinoma related to coca chewers**

Case	Age	Gender	Pattern of coca-chewing	Tobacco and alcohol consumption	Location	Diagnosis - Degree of differentiation	Follow-up	IHC P16
1	49	Male	Unilateral	None	Left buccogingival complex	Moderate, differentiated OSCC	Died (2 months from diagnosis)	-
2	64	Male	Bilateral	None	Right buccogingival complex	Well-differentiated OSCC	Died (3 months from diagnosis)	-
3	48	Male	Unilateral	None	Left buccogingival complex	Well-differentiated OSCC	Died (2 months from diagnosis)	-
4	48	Male	Unilateral	None	Left buccogingival complex	Poor-differentiated OSCC	No data	-

OSCC: Oral squamous cell carcinoma, IHC: Immunohistochemical

carcinogenic effect of coca chewing habit in South America emphasizes the need of epidemiologic and biomolecular studies to clarify this issue. These parallelisms between both the habits (coca and betel consumption) were also addressed by Panta.<sup>[8]</sup>

Several studies have described the carcinogenic, mutagenic and genotoxic effects of the betel quid ingredients, especially tobacco and areca nut. Betel quid is usually made of betel leaf (piper betel vine), areca nut, slaked lime and tobacco. Other spices are added too, such as cardamom and cloves.<sup>[9]</sup> The microtrauma generated by friction of the fibers not only generates mechanical damage to itself but also enables the alkaloids and flavonoids spread within the connective tissue.<sup>[6]</sup> Any other external factor which may generate tissue injury may also result in an inflammatory process. Furthermore, some authors have proposed that this habit-related microtrauma could facilitate the entry of HPV infection due to the exposition of basal keratinocytes through a superficial break.<sup>[10]</sup>

Nersesyan *et al.* observed that coca leaves chewing does not induce cellular anomalies with genetic damage like the presence of micronucleus in a group of heavy coca users. Nevertheless, high levels of other changes were found, such as karyorrhexis and karyolysis. In addition, the observed changes were correlated to the diary intake and addiction to other substances that allow to increase the coca alkaloids. The authors concluded that, in contrasts to other chewing habits as betel, tobacco or khat, coca leaves intake might induce toxic effects but not genetic changes.<sup>[11]</sup> In a previous review, Petti described no association between this coca chewing and oral cancer. However, these studies included healthy patients with oral health favorable conditions.<sup>[12]</sup> Our case series showed that patients presented severe periodontal disease, multiple dental loss and sharp edges, associated with CMI. Thus, further studies should be performed including patients with oral conditions that could be representative of the population of coca chewers. It should not be forgotten that the development of OSCC is a multifactorial process. Although Nersesyan *et al.* study demonstrated the absence of cellular genomic effects of coca on the oral mucosa, in presence of a previously initiated mucosa (by exposition to other genotoxic like arsenic water contamination, agrochemicals or random mutations),<sup>[11]</sup> coca chewing could have a promoting and progressive effect on oral carcinogenesis.

Several studies performed in coca-chewing populations have previously described dental and periodontal lesions related to this habit. Ayala *et al.* found periodontal lesions possibly related to a high alkalinity microenvironment

caused by the lime used among coca chewers. This alkaline status could irritate oral mucosa generating chronic lesions with a possible long-term carcinogenic effect.<sup>[13]</sup> In our case series, it was observed defective teeth with severe periodontal disease and poor oral hygiene. Furthermore, all patients reported a history of previous oral irritations related to the habit.

In an Argentine study carried out in a coca-chewer population (Humahuaca, a northern region of the country), the presence of leukoedema was found in a 65.2%.<sup>[14]</sup> In addition, other Peruvian study described that coca chewing may generate hyperkeratotic lesions in gingival mucosa associated to a chronic chemical and mechanical irritation generated during the habit. In accordance with Indian findings in patients with OSF, it could be hypothesized that coca leaves chewing habit could generate a similar disorder of the collagen fibers, leading to fibrosis. Finally, a dose-dependent cause–effect relation was also evidenced.<sup>[15]</sup> Figures 1-4 show clinical features of coca-chewer patients with areas of oral mucosa with leukoedematous lesions next to the ulcerated lesions. Thereby, in accordance with the aforementioned studies, leukoedema is a common lesion found in coca chewers. However, its presence next to OSCC could indicate a clinical sign that should not be underestimated. White plaques and leukoedema in the context of a strong coca-chewer individual could represent an aware finding for dentists or clinicians. These patients should be closely monitored.

## CONCLUSIONS

The case series and review literature could evidence that in absence of other known risk factors, these Argentine and Bolivian patients could develop OSCC related to a strong coca-chewing habit. Clinicpathological profile of these malignancies was similar to the Indian cancer, usually described in Asia, associated with betel nut habit. Coca leaves and betel chewing habits may have similarities; however, the available studies addressing this matter are scarce and controversial. Further studies are needed to demonstrate that chronic coca leaves chewing could be considered as a risk factor for oral cancer development in a multifactorial context. Furthermore, more studies should be addressed focusing on the underlying mechanisms that link coca chewing and a possible role in oral carcinogenesis. These findings would be useful in developing preventive campaigns of OSCC in coca-chewer population as well as starting coca-chewing cessation interventions.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given

their consent for their images and other clinical information to be reported in the journal. The patients understand that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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