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Clinical and epidemiological profile of Oral Squamous Cell Carcinoma in young adults: a multicentric cross-sectional study in Argentina

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Corresponding Author:	Gerardo Gilligan, DDS, PhD Universidad Nacional de Cordoba Facultad de Odontologia Córdoba, ARGENTINA
First Author:	Gerardo Gilligan, DDS, PhD
Order of Authors:	Gerardo Gilligan, DDS, PhD
	Rosana Morelatto
	María Inés Criscuolo
	Marcelo Zapata
	Paola Belardinelli
	Nicolás Jorge Bolesina
	Romina Andrian
	Astrid Müller
	Ángeles Castrillo
	Verónica Flück
	Ignacio Molina Ávila
	Juan Martín Pimentel Solá
	María Fernanda Ponce
	María Eugenia Ingrassia-Tonelli
	Andrés Benetti
	Laura Werner
	Javier Gimenez
	Federico Garola
	Saman Warnakulasuriya
	Alan Roger Santos-Silva
	René Panico
	Eduardo Piemonte
Abstract:	Background: Oral squamous cell carcinoma (OSCC) is an increasingly prevalent disease, especially among young patients. Despite the importance of early detection, research on the factors influencing the progression of this disease is still limited in Latin America. Aim: The aim of this study is to analyze the sociodemographic, clinical and pathological characteristics as well as risk factors involved in young adults with OSCC. Methods: A multicentric cross-sectional study was performed across nine centres of Oral Medicine in Argentina. All data was extracted from databases and registries of each institution (from 2006 to 2024). Results: This study included 124 patients diagnosed with OSCC under 45 years of

	age. The mean age at diagnosis was 36.25 years (range 19-45, SD 6.65), with a higher prevalence in males (60%). The lateral tongue was the most affected site (68%). Ulcerative lesions were the most common clinical presentation (42%). Risk factors included tobacco consumption (31.5%), alcohol (26%), and cannabis use (14%). Chronic Mechanical Irritation was identified in 53.4%. OSCC de novo were prevalent compared to those arising from existing oral potentially malignant disorders (OPMD). Patients with OSCC-dn presented with ulcerative phenotypes (p=0.0163), were diagnosed at advanced stages (p=0.0001), and were strongly associated alcohol consumption (p=0.0359). Conclusion: this study highlights non-traditional risk factors and clinical features of OSCC in young adults associated with de novo-oral malignancies. The high frequency of young patients with less common risk factors suggests alternative carcinogenic pathways. Regional collaboration are essential to reduce OSCC incidence in young adults in Argentina.

April, 5 th

Dear Editor,

We are pleased to submit our manuscript, **"Clinical and epidemiological profile of Oral Squamous Cell Carcinoma in young adults: a multicentric cross-sectional study in Argentina",** for consideration for publication in *Oral Oncology*.

This multicenter, cross-sectional study investigated the sociodemographic, clinical, and pathological characteristics, along with risk factors, associated with oral squamous cell carcinoma (OSCC) in young adults (under 45 years) in Argentina. We analyzed data from nine Oral Medicine centers across the country, examining 124 patients diagnosed with OSCC between 2006 and 2024. This is the largest series of young adults-OSCC reported in our región.

Our findings highlight several key aspects: the frequent involvement of the lateral tongue, and the prominence of ulcerative lesions. Notably, we identified a strong association between *de novo* OSCC presentation and more advanced disease stages at diagnosis. Furthermore, our research suggests the involvement of non-traditional risk factors, such as chronic mechanical irritation, indicating potentially alternative carcinogenic pathways in this age group.

Given *Oral Oncology's* focus on cutting-edge research into the biology, prevention, and treatment of head and neck cancers, we believe our study is a strong fit for your readership. Our findings contribute valuable insights into the unique features of OSCC in young adults within a Latin American population, an area where research is currently limited. We believe this research will be of interest to researchers and clinicians focused on the diagnosis, prevention, and management of OSCC.

All authors have read and approved the manuscript, and we confirm that this work has not been published previously and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose.

Thank you for your time and consideration. We look forward to hearing from you soon.

Sincerely,

Gerardo Gilligan. DDS, PhD.

Assistant Professor Oral Medicine Department

Facultad de Odontologia UNC, Argentina

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Name and Title of Corresponding Author: GERARDO GILLIGAN DDS, PHD

Address: Haya de la Torre SN
Address: ……
Postcode and country: 5000
Tel No: +5493515118419
Fax No: ……
Email: ggilligan@unc.edu.ar

"I confirm that all the authors have made a significant contribution to this manuscript, have seen and approved the final manuscript, and have agreed to its submission to the *Oral Oncology*".

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HIGHLIGHTS

- **Argentina: multicenter study shows unique OSCC features.**
- **OSCC at early age warrants increased awareness in Argentina.**
- **Tongue cancer in youth: late diagnosis linked to *de novo* presentation.**
- **OSCC and non-common risk factors in young adults**

Clinical and Epidemiological Profile of Oral Squamous Cell Carcinoma in Young Adults: A Multicentric Study in Argentina

Authors: Gilligan, Gerardo[1*]; Morelatto, Rosana[1]; Criscuolo, María Inés[1]; Zapata, Marcelo[1]; Belardinelli, Paola[1]; Bolesina, Nicolás[1]; Andrian, Romina[2]; Müller, Astrid[2]; Castrillo, Ángeles[3], Flück, Verónica[3]; Molina Ávila, Ignacio[4]; Pimentel Sola, Juan Martín[5]; Ponce, María Fernanda[6]; Ingrassia, María Eugenia[7]; Benetti, Andrés[8]; Werner, Laura[9]; Gimenez, Javier[3]; Garola, Federico[1]; Warnakulasuriya, Saman[10], Santos-Silva, Alan Roger[11]; Panico, René[1] ; Piemonte, Eduardo[1].

***CORRESPONDING AUTHOR**

Gerardo Gilligan

Haya de la Torre SN

Ciudad Universitaria.

PC 5000.

Córdoba, Argentina

E-mail: ggilligan@unc.edu.ar

Affiliations

[1] Oral Medicine Department, Facultad de Odontología, Universidad Nacional de Córdoba, Argentina.

[2] Oral Medicine Service, Dr Victor Sanguinetti Regional Hospital. Comodoro Rivadavia. Chubut, Argentina.

[3] Oral Medicine and Oral Oncology Service, Marie Curie Oncological Hospital, Buenos Aires, Argentina.

[4] Dr Arturo Oñativia Hospital, Salta, Argentina.

[5] Oral Medicine Unit, Señor del Milagro Hospital, Salta, Argentina.

[6] Oral Medicine Service, Dr Guillermo Rawson Hospital, San Juan, Argentina.

[7] University Hospital, Universidad Nacional de Cuyo. Mendoza, Argentina

[8] Provincial Center of Oral Medicine and Oral Cancer Prevention Program, Health Ministery, Corrientes, Argentina.

[9] Alemán Hospital, Buenos Aires, Argentina.

[10] Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, WHO Collaborating Centre for Oral Cancer, UK.

[11] Oral Diagnosis Department, Piracicaba Dental School, State University of Campinas (UNICAMP), Brazil.

DISCLOSURES

The authors have no conflicts of interest regarding this work.

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The study was approved by the Ethics Committee of the Facultad de Odontología de la Universidad Nacional de Córdoba, based on the ethical principles of Helsinki and its respective modifications.

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The authors dedicate this work to all the young Argentine patients included in this study who lost their battle against cancer. We hope this scientific contribution can provide useful evidence for state policies aimed at the early detection and prevention of oral cancer in our country.

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Author names:

Gilligan, Gerardo1*; Morelatto, Rosana1; Criscuolo, María Inés1; Zapata, Marcelo1; Belardinelli, Paola1; Bolesina, Nicolás1;

Andrian, Romina2; Müller, Astrid2; Castrillo, Ángeles3, Flück, Verónica3; Molina Ávila, Ignacio4;

Pimentel Sola, Juan Martín5; Ponce, María Fernanda6; Ingrassia, María Eugenia7; Benetti, Andrés8;

Werner, Laura9; Gimenez, Javier3; Garola, Federico1; Warnakulasuriya, Saman10, S

antos-Silva, Alan Roger11; Panico, René1 ; Piemonte, Eduardo1.

The authors whose names are listed immediately below report the following details of affiliation or involvement in an organization or entity with a financial or non-financial interest in the subject matter or materials discussed in this manuscript. Please specify the nature of the conflict on a separate sheet of paper if the space below is inadequate.

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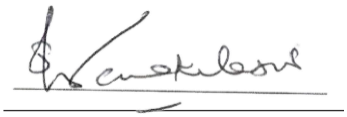
Saman Warnakulasuriya		April, 7th
Alan Roger Santos Silva		April, 7th
Eduardo Piemonte		April, 7 th
Ma Eugenia Ingrassia		April, th
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Paola Belardinelli		April, 8 th
Ines Criscuolo		April, 8th
Federico Garola		April, 7 th
Andrés Benetti		April, 7th
María Fernanda Ponce		April, 7 th
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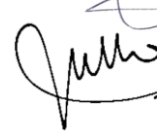
Verónica Fluck		April 8 th
Gerardo Gilligan		April, 7 th

Clinical and epidemiological profile of Oral Squamous Cell Carcinoma in young adults: a multicentric cross-sectional study in Argentina

ABSTRACT:

Background: Oral squamous cell carcinoma (OSCC) is an increasingly prevalent disease, especially among young patients. Despite the importance of early detection, research on the factors influencing the progression of this disease is still limited in Latin America.

Aim: The aim of this study is to analyze the sociodemographic, clinical and pathological characteristics as well as risk factors involved in young adults with OSCC.

Methods: A multicentric cross-sectional study was performed across nine centres of Oral Medicine in Argentina. All data was extracted from databases and registries of each institution (from 2006 to 2024).

Results: This study included 124 patients diagnosed with OSCC under 45 years of age. The mean age at diagnosis was 36.25 years (range 19-45, SD 6.65), with a higher prevalence in males (60%). The lateral tongue was the most affected site (68%). Ulcerative lesions were the most common clinical presentation (42%). Risk factors included tobacco consumption (31.5%), alcohol (26%), and cannabis use (14%). Chronic Mechanical Irritation was identified in 53.4%. OSCC de novo were prevalent compared to those arising from existing oral potentially malignant disorders (OPMD). Patients with OSCC-dn presented with ulcerative phenotypes (p=0.0163), were diagnosed at advanced stages (p=0.0001), and were strongly associated alcohol consumption (p=0.0359).

Conclusion: this study highlights non-traditional risk factors and clinical features of OSCC in young adults associated with de novo-oral malignancies. The high frequency of young patients with less common risk factors suggests alternative carcinogenic pathways. Regional collaboration is essential to reduce OSCC incidence in young adults in Argentina.

1- INTRODUCTION

Lip and oral cavity cancer are together the 16th most common cancer worldwide with approximately 389,846 new cases and the 15th in mortality, with 188,488 deaths annually[1]. Traditionally, OSCC has been considered a disease affecting older adults over the age of 60 years due to the time necessary for the accumulation of genetic mutations and exposure to risk factors[2]. However, some studies have demonstrated an increasing incidence of OSCC in young adults (YA)[2]. This rising trend is documented worldwide, with an estimated incidence ranging from 5% to 16.5%[3–6].

Although the criteria for defining YA in studies addressing OSCC are not clearly established, some authors suggest using 45 years as the cutoff age. The criteria for determining this cutoff vary among studies, with some considering patients younger than 40 years, while others use a threshold of 45 years[7,8]. In one of the largest series of young OSCC patients, the chosen cutoff was 45 years[8]. It appears that many in the 40–45 age group have traditional risk factor exposure and represent the tail end of the more typical patient group, whereas patients under 40 are more likely to be non-smokers[9].

Traditional risk factors for OSCC include tobacco and alcohol consumption, which act synergistically[10] to increase the likelihood of developing cancer[11]. However, there has been a decline in the number of tobacco and alcohol related head and neck carcinomas over the past 30 years, but an increasing incidence of HPV related cancers has been noted. Some studies showed that 70-90% of new oropharyngeal cancers have evidence of HPV infection. Moreover, these patients are more likely to be younger, never smokers and never drinkers[12]. Consequently, the role of HPV infection has been proposed as a risk factor for head and neck cancer, especially in younger populations[13–15]. Other factors, such as poor oral hygiene, chronic mechanical irritation (CMI), and dietary deficiencies, have also been suggested to contribute to the disease[4,16,17]. Genetic predisposition and familial syndromes may play a role in this specific subset of patients with OSCC[18,19]. Additionally, lifestyle changes, including the rise in recreational drug use, e-cigarettes, marijuana, and changing sexual practices leading to higher HPV transmission, have been hypothesized as contributing factors[4,15]. However, the evidence remains inconclusive, and further investigation is required to clarify these associations.

The prognosis of OSCC in younger patients has been debated extensively. Some studies suggest that YA may have better survival rates due to fewer comorbidities[20]. Other research indicates that OSCC in YA might present with more aggressive behavior and poorer outcomes. Such discrepancies highlight the need for a better understanding of this unique subset of patients[21].

In Latin America, regional risk factors, such as the consumption of traditional herbal infusions, and exposure to environmental carcinogens, may play a significant role in oral carcinogenesis. Moreover, in this region, OSCCs that are not preceded by oral potentially malignant disorders (OPMDs), referred to as *de novo* OSCCs, are more common than sequential OSCCs (seq-OSCC); those arising from OPMD [17]. This distinction underscores the need for studies addressing the landscape of OSCC in YA. Argentina, the southernmost country in America, presents single lifestyle factors, as well as distinct risk factors (such as mate consumption, coca chewing and extensive areas

polluted with arsenic), that may influence oral cancer[17,22]. Furthermore, disparities in healthcare access, particularly in remote areas, like Patagonia, large distances, extreme weather conditions, and a shortage of specialists contribute to delayed diagnosis and treatment, adversely affecting patient outcomes[22–25]. This multicenter study, involving Oral Medicine diagnostic centres across all geographical regions of Argentina, aimed to characterize and describe the clinicopathological features and risk factors of YA with OSCC.

2- MATERIALS AND METHODS

2.1 Study design

A multicenter cross-sectional study was conducted in 9 strategically selected hospitals and university-based Oral Medicine diagnostic centres in Argentina, including YA with OSCC (Figure 1). The STROBE guidelines for reporting cross-sectional studies were followed (checklist in Supplementary Materials Table-S1).

2.2 **Participants and recruitment**

-Inclusion criteria: cases of patients under 45 years old with histopathological diagnosis of OSCC, including different OSCC histological subtypes, from anatomical sites: lip, mouth and tongue ICD 10 C00.0, C00 (excluding C00.0, C00.1 and C00.2), C02-C06. Patients diagnosed between 2006 and 2024 were included. Clinical data were obtained from the clinical records databases of all institutions, with each participating center contributing cases collected over a minimum period of one year. The sample was defined by the total number of eligible consecutive cases that met the inclusion criteria during the predefined study period across all centers.

-Exclusion criteria: cases with recurrent OSCC, lip skin cancer, patients without a confirmed histopathological OSCC diagnosis were excluded. Additionally, cases lacking sufficient data—such as low-quality photographic documentation of OSCC or OPMD areas, incomplete clinical or medical records, or follow-up information to allow proper classification—were also excluded.

2.3 Variables and measurement

The independent variables recorded were: age, gender, definitive clinical or histopathological diagnosis of OPMD, presence and subtype of OPMD, anatomical location, clinical phenotype, tobacco use, alcohol consumption, cannabis use, e-cigarette use, mate consumption, CMI, HPV infection, exposure to environmental or occupational carcinogens, and family history of cancer.

The dependent variables included: degree of cellular differentiation, tumor size at diagnosis, final cancer staging (TNM), treatment modality, follow-up duration from the time of diagnosis, and survival status.

OSCC was considered associated with previous OPMD (seq-OSCC) when the patient presented at the initial consultation with OSCC accompanied by OPMD; or when the patient under follow-up for OPMD developed cancer. OPMD could be located in the same area or distant from the OSCC. When OSCC was not associated with OPMD, the group was referenced as OSCC-dn[26,27]. Further details regarding the categorization of variables are provided in Supplementary Materials Table S2.

2.4 Data collection

Each participating center was responsible for collecting data from its databases and clinical records, based on standardized inclusion and exclusion criteria. Data extraction was conducted independently by each center's designated principal investigator, who supervised the accuracy of the recorded information. Once collected, the anonymized data were submitted to the coordinating center in Córdoba, where two independent researchers (GG-EP), both blinded to patient outcomes, reviewed and compiled the data into a single spreadsheet. In cases of unclear entries, a third investigator (RM) discussed the issue with the corresponding center to reach consensus.

2.5 Control of sources of bias

A virtual calibration meeting was conducted to standardize the recording of the retrieved variables among all the diagnostic centres. An explanatory video detailing the registration process for the variables was sent in advance to each centre. All investigators maintained constant communication throughout the data extraction process to address any issues or doubts.

2.6 Statistical analysis

A narrative descriptive synthesis was provided, using mean, standard deviation and range for quantitative variables, and absolute/relative frequencies for qualitative variables. The association of the variables sex, seq-OSCC vs OSCC-dn and CMI with the rest of the variables was statistically analyzed. Quantitative variables were analyzed using Student's t-test, and qualitative variables using chi-square and Fisher test. A *p*-value of ≤0.05 was considered statistically significant. YA with OSCC were categorized into two subgroups: younger than 40 years, and aged 40 to 45 years, to analyze differences between them. Statistical analysis was performed using the software Infostat 2020.

2.7 Missing data

The missing data were attributed to the absence of information in the original medical records. These were documented as “no data” (ND) during the descriptive analysis, and were excluded from the statistical analysis.

2.8 Ethical statement

This study adhered to the principles outlined in the Declaration of Helsinki and was coordinated by the Oral Medicine Department "A" at the Facultad de Odontología, Universidad Nacional de Córdoba. This study was approved by Comité Académico - Ético en Investigación de Ciencias de la Salud, Facultad de Odontología, Universidad Nacional de Córdoba, Argentina Protocol N°T08/2016, 31/2015 and updated to the Protocol 54/2024.

3-RESULTS

Clinical and demographical data

A total of 124 patients with a histopathological diagnosis of OSCC under 45 years of age were included. The mean age at diagnosis was 36.25 years (range: 19–45), with a higher prevalence of males (n=75, 60%) compared to females (n=49, 40%). The most frequently affected anatomical site was the lateral tongue (n=85, 68%), followed by the gingiva (n=13, 10%). Ulcerative lesions were the most common presentation (n=52, 42%), followed by ulcerated nodules (n=35, 28%), exophytic swellings (n=15, 12%), mixed patterns (n=10, 8%), white plaques (n=6, 5%), and red plaques (n=6, 5%).

Comorbidities were present in 28 patients (23%) (five cases of depression and psychiatric disorders, four cases of other malignancies -skin melanoma, leukemia, thyroid cancer, and skin cancer-, four patients with type 2 diabetes, two patients with AIDS, and one patient with selective IgA immunodeficiency syndrome).

OSCCs-dn were much more frequent than sequential ones (82% vs. 18%). Among OSCC-seq, leukoplakia was the most common OPMD (n=19; 15%), followed by oral lichen planus (n=11; 8.8%) (Table 1). Among 42 individuals with seq-OSCC, 16 (38%) had been diagnosed with an OPMD prior to their cancer diagnosis and 26 (62%) presented with a concurrent OPMD at the margin of the OSCC at the time of cancer diagnosis.

Histopathological and prognosis variables

Well-differentiated tumours accounted for 49 cases (39.5%), while moderately differentiated tumours represented 57 cases (45.9%), and poorly differentiated tumours accounted for 11 cases (8.8%). *In situ* carcinomas were diagnosed in 7 cases (5.8%).

At the time of diagnosis, Tis, T1 or T2 OSCC accounted for 70 cases (56%), whereas T3 or T4 OSCC were identified in 54 cases (44%). When categorized by tumour stage, cases were distributed as follows: Stage I (n=30, 24%), Stage II (n=32, 26%), Stage III (n=18, 14.5%), Stage IV (n=26, 21%). The most frequently applied treatment modality was surgery (n=56, 45.2%), followed by multimodal therapy combining surgery, radiotherapy, and chemotherapy (n=25, 20.2%).

Risk Factors

Tobacco consumption was reported by 39 patients (31.5%), with an average lifetime exposure of 15.9 pack-years. The remaining 85 (68.5%) were never smokers. Most patients were non-drinkers (n=88, 71%). Regular alcohol consumption was reported by only 4 (3%) patients. Cannabis use (marijuana) was reported by 17 (14%) cases. None reported e-cigarette use; data were missing in 59% of cases. Regular mate consumption was reported by 73 (59%) patients.

HPV infection status was available in 36% of cases. Among these, 14 (13%= patients tested positive, while 24 (19%) tested negative. The remaining 69% of cases lacked HPV data. PCR and immunohistochemistry with p16 were the most used tests to detect viral infection.

CMI was identified in 66 (53.4%) YA. The primary sources of CMI included dental trauma (23, 35%) and combined (dental and functional) trauma (41, 62%).

A family history of upper aerodigestive cancer was reported in 28 (22.5%) cases, whereas exposure to environmental carcinogens was documented in 21 (17%) patients, with arsenic pollution, pesticides, and agrochemicals being the most frequent sources. (Table 1)

Seq-OSCC vs OSCC-dn

When patients were categorized as seq-OSCC vs OSCC-dn, significant differences were observed. Patients with OSCC-dn presented with ulcerative clinical phenotypes compared to other clinical patterns($p=0.0163$), were diagnosed at more advanced stages ($p=0.0001$) and were more strongly associated with excessive alcohol consumption ($p=0.0359$). Figures 2 and 3 show a wide range of clinical phenotypes of OSCC-dn and seq-OSCC respectively. Seq-OSCC patients had a higher frequency of comorbidities ($p=0.0404$) and were more frequently treated with surgery alone without complementary treatments ($p=0.0017$). The other variables did not show statistically significant differences. (Table 2)

Other relevant findings showed that CMI was significantly associated with tongue location (61/85 vs 5/39, OR 17.2, CI 6.2-47.6; $p < 0.0001$), alcohol consumption (25/36

vs 41/88, OR 2.61, CI 1.16-5.86; p=0.0202), and early stages (42/67 vs 23/54, OR 2.26, CI 1.08-4.7; p=0.0274). Figure 4 shows cases of YA-OSCC associated with CMI.

Prognosis

A high percentage of missing data (51%) was evidenced for this variable. Among the cases where follow up was available, the mean follow-up duration was 34.9 months (1–289). Follow-up information at three years post-diagnosis was available for only 16 cases (12%). In these cases, all patients were alive with controlled oncologic disease, with 11 having early-stage tumours (TIS, T1, or T2) treated with surgery alone, and half of the cases corresponding to seq-OSCC.

When YA with OSCC were subcategorized into those younger than 40 years (74; 59%) and those aged 40 to 45 years (50; 41%), no statistically significant differences were observed in demographic variables or risk factors. However, patients under 40 years of age exhibited a higher frequency of tongue tumours compared to other anatomical locations (p=0.0158). Additionally, patients with OSCC in the 40–45-year age range presented with larger tumours and more advanced stages(p=0.0370; p=0.0249, respectively).

4- DISCUSSION

To establish a clearer picture of the burden of OSCC in YA in Argentina, this study aimed to provide a foundation for targeted public health interventions and policy-making to address this emerging challenge. The findings highlight clinical, epidemiological, and histopathological features that contribute to the understanding of this disease and represent the first multicentric collaboration addressing OSCC in Argentinians YAs.

The male predominance (60%) aligns with previous studies; however, it is noteworthy that this gender gap may be narrowing over time. A recent multicentric study on OSCC in Latin America reported an overall male-to-female ratio of nearly 1:1[17]. Other Latin American multicentric study on OSCC in YA, showed similar results to those obtained in the present study[28]. These findings regarding sex were similarly reflected in studies from other parts of the world, including regions with distinct OSCC profiles, such as India, where the disease is strongly associated with betel quid chewing [7,8,29,30]. In a recent study, Cheng et al demonstrated among 66 individuals with OSCC under 30 years old, females had no history of smoking or drinking or betel nut chewing, while all males were smokers[31]. In our study, women had lower tobacco and alcohol consumption, suggesting that male gender, was at a higher risk of OSCC.

Regarding anatomical location, and consistent with previous studies, the lateral tongue is the most frequent site of OSCC in YA, showing significant differences

compared to other locations. Moreover, the high prevalence of tongue SCC in this cohort has led to its consideration as a distinct OSCC subtype, potentially exhibiting unique characteristics[32,33]. This study describes the clinical presentation of OSCC in YA, identifying an ulcerative phenotype as the most frequent phenotype (Figure 2). Recognizing the clinical presentation of OSCC among YA could facilitate early detection and diagnosis, as oral cancer is often not initially suspected in YA leading to diagnostic delays. Besides, it aids in differentiating malignant ulcers from common benign lesions, such as traumatic or aphthous ulcers, thereby reducing the risk of misdiagnosis[34]. Understanding the predominant clinical pattern enables targeted awareness campaigns among healthcare professionals and the general population, emphasizing the importance of evaluating any non-healing ulcer persisting for more than two weeks. In addition, OSCC with a white-red plaque-phenotype (Figure 3) was observed in only 12% of cases. These findings allowed to categorize OSCC based on the presence or absence of OPMD, classifying them as either seq-OSCC or OSCC-dn[27].

In this regard, a high proportion of OSCC-dn cases (82%) was found compared to sequential cases (18%). This is consistent with the current literature on the frequency OSCC-dn vs seq-OSCC, based on recent studies indicating that OSCC-dn are more frequent than seq-OSCC (about 70% vs. 30%, respectively)[17,26]. The low frequency of seq-OSCC in YA could be associated with the low prevalence of OPMDs in this age group. In a recent systematic review, it was found that out of 1246 patients with leukoplakia, 115 (9.2%) were under 40 years of age[35]. A recent study from Brazil found that leukoplakia and erythroplakia are uncommon diseases in YA [36]. This phenomenon could be attributed to several factors. Among them, the underdiagnosis of OPMDs in YA might result from the perception that this age group is not considered at risk for such disorders. Furthermore, oral mucosa routine examination is not consistently carried out by most general dentists, which could also contribute to the low rate of OPMD detection in YA[37]. Therefore, it is logical to assume that the low frequency of OPMDs in YA aligns with the low frequency of seq-OSCC reported. Nevertheless, one of the proposed reasons for the low frequency of seq-OSCC and the high prevalence of OSCC-dn, is the late diagnosis of OSCC, where tumours have spread laterally, masking preexisting OPMDs [26].

In our study, we found that almost half of the included patients were diagnosed at early stages and with small tumour sizes, which contrasts with some studies that refer to the late diagnosis of OSCC in olders. De Morais and Farquhar et al found similar findings, with most studies showing a predominance of cases of OSCC in YA diagnosed in early stages[38,39]. However, Iype et al showed a high prevalence of late diagnoses in an Indian cohort of YA with buccal mucosa cancer[40]. We found heterogeneity of data

when analyzing by participating centres (Supplementary Materials Table S3). The prevalence of early-stage OSCC could be associated with inclusion bias. Cases from state capital cities (Córdoba and Buenos Aires), where rapid referral networks are available, showed more early stages than cases from areas with fewer Oral Medicine specialists (Figures 3D, 2D) (Salta and Chubut, which are located in the northern and Patagonian regions, respectively), where patients must travel long distances to reach specialized centres. Besides the geographical context, structural poverty and limited accessibility to the healthcare system are barriers that contribute to delays in OSCC diagnosis[24]. This should be considered when implementing cancer awareness and preventive measures, such as the development of Telemedicine referral networks and continuous training of primary healthcare professionals[23,25].

Our study demonstrated that seq-OSCC have a higher frequency of diagnoses at early stages, allowing for less aggressive treatments with surgical approaches alone and, consequently, better survival outcomes for patients. However, lack of clinical suspicion by non-specialized healthcare professionals could contribute to the late diagnosis of advanced OSCC in YA. This misdiagnosis of OSCC could be based on misconceptions such as OSCC usually occurring in older people. This scenario grows increasingly complex due to the lack of awareness in YA about the existence of head and neck cancer, its symptoms, and risk factors[41].

Surgical treatment alone was the most frequent, partly due to the high frequency of early-stage tumours, which are commonly managed with this approach, and this is consistent with the available literature. In a systematic review, the most common treatment was tumoral surgical resection alone or in combination with radio-chemotherapy[38]. However, an interesting finding is that seq-OSCC were more frequently treated with surgery alone without additional treatments, resulting in fewer adverse effects from oncological therapy beyond tumour resection. In these cases, the importance of monitoring OPMD in YA to intercept malignant transformation at an early stage is emphasized.

The mechanisms underlying oral carcinogenesis in YA may differ significantly through a differential pattern expression of some cell cycle control and local invasion-related proteins (e.g. C-ErbB2, EGFR, MMP-9, and SMA)[42]. In addition, some authors have even proposed that OSCC in YA constitutes a separate subtype of cancer with unique characteristics[43,44]. One interesting hypothesis to explain this phenomenon could be the immune system impairment[30]. Our study showed comorbidities associated with different congenital or acquired subtypes of immunosuppression (leukaemia, AIDS, selective IgA immunodeficiency syndrome), as well as chronic stress and depression, which could also alter the host's immune response due to disruption of

the hypothalamic-pituitary-adrenal axis through sustained cortisol release. Psycho-neuro-immunological factors influence cancer development and prognosis. Kumar et al. demonstrated a positive association between stress and salivary cortisol levels among OSCC patients[45]. This finding underscores the importance of a comprehensive and multidisciplinary approach in managing OSCC in YA, highlighting the need for personalized therapeutic strategies aimed at optimizing treatment effectiveness.

A noticeable aspect of this study is the high proportion of non-smokers (68.5%) and non-drinkers (71%). Cannabis and e-cigarettes use have been proposed as novel risk factors for oral cancer in YA[46,47]. However, in this group none reported using e-cigarettes and cannabis use was reported only by 14% of cases.

Interestingly, one of the first reported cases of OSCC in YA was published in 1984, showing a 25-year-old nonsmoking, nondrinking woman who developed a tongue malignant ulcer associated with a dental crown[48]. Our findings showed that CMI is frequent among YA with OSCC, with 53.4% of cases linked to traumatic stimuli. Moreover, anatomical factors, such as the lingual position of the mandibular second molar restricting the tongue space, have also been identified as potential risk factors in the development of tongue OSCC in YA[49]. Figure 4 depicts OSCC cases coexisting with orthodontic appliances. In these cases, parafunctional habits in the context of sharp and malpositioned teeth could have contributed to OSCC development.

The increase in the incidence of OSCC in YA has led to considering high-risk (HR) HPV infection as a contributing factor to oral carcinogenesis[12]. In our study, HPV frequency was identified in 36% of the cases; however, methodological limitations and heterogeneity in diagnostic techniques hinder a definitive interpretation. Despite incomplete and conflicting data, HPV frequency in these cases appears to be low. Miranda-Galvis et al showed a frequency of 29.4% of HR-HPV DNA in their cohort[50]. HPV could interact with other factors such as CMI, since prior trauma could provide access for the virus to reach the basal cells, which are the primary targets for initiating an infection [51]. Some studies have also demonstrated HPV association with marijuana use in YA, considering the immunosuppressive characteristics found in tetrahydrocannabinoids[52].

Mate consumption has been classified as carcinogenic by the IARC[53], and this is supported by local studies[54]. Our findings regarding hot mate consumption should be interpreted with caution, considering that nearly 60% of YA with OSCC reported consuming this hot infusion. However, mate consumption is very common among YA in Argentina. A study conducted among medical students in Argentina, who fall within the age range of the patients included, demonstrated mate consumption in 91% of the surveyed YA[55].

Other factors to consider are those associated with the genetic background. There is an increased risk of head and neck cancer in first-degree relatives of cancer patients, and while inherited syndromes associated with OSCC are rare, elucidating their genetic basis may help to uncover the underlying mechanisms in YA-OSCC[9]. However, in our study, 55% of the included cases did not present a family history of upper-aerodigestive tract cancer. Other factors such as occupational exposure to pesticides, agrochemicals or arsenic in rural areas emerge as potential contributing factors in Argentina, although further studies are needed to establish causality. Finally, coca chewing is an emerging risk factor for SCC of the buccal mucosa[22]. However, this practice is limited to northern regions, which explains its absence in reports from the other centers.

Limitations include the retrospective design and missing data. Additionally, certain variables, such as e-cigarettes among YA with OSCC, presented incomplete data since the earliest recorded patients were not chronologically exposed in an era when vaping was prevalent. HPV data varied due to differing center methodologies.

5- Conclusions

This study comprehensively evaluated OSCC in YA, revealing distinct characteristics. A significant proportion of cases occurred without common risk factors for OSCC, highlighting the potential role of alternative carcinogenic pathways, including CMI and environmental carcinogen exposure. Mate consumption should be further studied in OSCC patients in South America. Ulcerated dn-OSCC on the lateral tongue is a frequent presentation, emphasizing the importance of early identification of non-healing wounds at early age. These findings underscore the need for increased awareness of OSCC in youth.

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The authors dedicate this work to all the young Argentine patients included in this study who lost their battle against cancer. We hope this scientific contribution can provide useful evidence for state policies aimed at the early detection and prevention of oral cancer in our country.

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FIGURE LEGENDS

Figure 1. Map of the distribution of the different participating centers throughout the Argentine territory.

Figure 2. OSCC arising de novo (tumors developing in the absence of OPMD).

(A) A 34-year-old male patient, non-smoker, non-drinker, and without comorbidities. The patient presented bruxism and a habitual cheek-biting behavior. Clinically, the lesion appeared as an ulcer with raised and indurated borders. The diagnosis was moderately differentiated OSCC with lymphatic infiltration and involvement of the ipsilateral cervical chain.

(B) A 28-year-old female patient presented with a necrotic and indurated ulcer on the lateral border of the tongue with a two-month evolution. The patient had no known

risk factors but resided in an area with high exposure to agrochemicals and worked in agriculture. The diagnosis was moderately differentiated OSCC.

(C) A 31-year-old male patient presented with a mildly ulcerated and heterogeneous lesion on the lateral border of the tongue, with no history of chronic mechanical irritation or risk factors. A biopsy confirmed a moderately-differentiated OSCC.

(D) Ulcerated lesion with a necrotic base and granulomatous appearance on the free and attached gingiva of the upper premolar region in a male patient with no risk factors and good oral hygiene. The diagnosis was a moderately-differentiated OSCC.

(E) Extensive OSCC involving the lateral border of the tongue and floor of the mouth in a 28-year-old female patient with no risk factors, but presenting with root remnants and poor dental health. Treatment included tumor resection surgery, cervical lymph node dissection (superficial and deep chains), radiotherapy, and chemotherapy.

(F) A 40-year-old female patient presented with a tumoral lesion on the edentulous alveolar ridge, with an erythroplasic and granular surface. The patient had a history of coca leaf chewing on the same side. The diagnosis was a poorly-differentiated invasive OSCC.

Figure 3. Sequential OSCC (tumors developing in the context of OPMD).

(A) A 27-year-old female patient, non-smoker and non-drinker, presented with an erythroplasic lesion associated with chronic mechanical irritation caused by a lingually positioned molar. Peripheral whitish striated areas were observed. The patient had a history of mixed connective tissue disease, combining lupus and Sjögren's syndrome. The diagnosis was In Situ Carcinoma

(B) A 29-year-old female patient, non-smoker and non-drinker, presented with an ulcerated lesion with surrounding erythroleukoplastic areas, extending between the dorsum and the right lateral border of the tongue. Other areas of the oral cavity showed whitish lesions consistent with proliferative verrucous leukoplakia. The diagnosis was well-differentiated OSCC without lymph node involvement.

(C) A 38-year-old male patient from an agricultural region of Argentina, with high pesticide exposure, non-smoker, and non-drinker. The patient developed an extensive ulcerated lesion on the lateral border of the tongue, surrounded by leukoplastic areas and adjacent to poorly maintained teeth causing trauma. Induration was also evidenced on the contralateral side. The diagnosis was a poorly-differentiated OSCC with bilateral lymph node involvement. The patient underwent surgery, radiotherapy, and chemotherapy.

(D) A 37-year-old male patient, a former light smoker with a history of leukoplakia, presented with a whitish lesion containing red areas on the lateral border of the tongue,

with a firm induration at its base. Biopsy confirmed moderately differentiated OSCC in the context of OPMD. Treatment included surgery, neck dissection, radiotherapy, and chemotherapy.

(E-F) A 45-year-old male patient with graft-versus-host disease (GVHD) and a history of leukemia presented with multiple ulcerated and erythematous areas on the lower labial mucosa and gingiva (E), characteristic of GVHD. On the dorsal tongue, a slightly elevated white plaque with an ulcerated, erythematous area was observed. Biopsy confirmed moderately differentiated OSCC in the context of GVHD.

Figure 4. OSCC in young patients associated with chronic mechanical irritation and orthodontic appliances.

(A) A 28-year-old male patient, non-smoker and non-drinker, presented with an extensive lesion occupying the left lateral border of the tongue, showing erythroplasic and ulcerated areas. The lesion was in direct contact with sharp dental edges of lower teeth, which left indentations and marks on the mucosa. The patient had been undergoing orthodontic treatment for one year due to a narrow dental arch. The diagnosis was poorly differentiated OSCC. The patient died three years after diagnosis despite treatment, which included surgery, lymph node dissection, radiotherapy, and chemotherapy.

(B) A 22-year-old male patient, non-smoker and non-drinker, presented with a malignant ulcer on the lateral border of the tongue associated with dental trauma and orthodontic appliances.

(C-D-E) A 28-year-old patient with no risk factors presented with an indurated ulcer on the lateral border of the tongue, diagnosed as moderately differentiated OSCC. At rest, a unilateral crossbite was observed (C), along with lingual tilting of the lower left molars (teeth 34, 35, 36, and 37) (D), which were in close contact with the lesion. The patient also exhibited a cheek-biting habit.

Table 1 (Editable version)

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Table 1: demographic, clinical, histopatological and prognosis variables

		All OSCC		De Novo OSCC		Sequential OSCC	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**
n		124	100	82	100	42	100
Age	Average	36.25	---	35.87	---	37	---
	Range	19-45	---	21-45	---	19-45	---
Sex	Male	75	60	47	57	28	66
	Female	49	40	35	43	14	34
Location	Lateral Tongue	85	68	59	71	26	62
	Gingiva	13	10	9	10	4	10
	Buccal mucosa	10	9	6	7	3	5
	Labial mucosa/vermillion	4	3	2	3	2	4
	Palate	5	4.7	4	5	1	2
	Retromolar pad	2	1.6	0	0	2	5
	Tongue dorsum	2	1.6	0	0	2	5
	Multicentric	2	1.6	2	3	0	0
	Floor of the mouth	1	0.5	0	0	1	2
Clinical phenotype	Ulcer	52	42	36	44	16	40
	Ulcerated nodule	35	28	29	35	6	14
	White plaque	6	5	2	3	4	10
	Red plaque	6	5	3	4	3	5
	Exophytic/Swellings	15	12	9	10	6	14
	Mixed	10	8	3	4	7	16
Comorbidities	Yes	28	23	14	17	14	34
	No	96	77	68	83	28	66
Precursor OPMD	De Novo	---	---	---	---	82	67
	Leukoplakia	---	---	---	---	19	15
	Erythroplakia	---	---	---	---	3	2
	Oral lichen planus	---	---	---	---	11	8.8
	PVL	---	---	---	---	5	4.7
	AC/AK	---	---	---	---	3	2
	Graft vs Host Disease	---	---	---	---	1	0.5
Degree of differentiation	Well-differentiated	49	39.5	28	34	21	50
	Moderately-differentiated	57	45.9	44	54	13	30
	Poorly differentiated	11	8.8	8	9	3	9
	(In situ OSCC)	7	5.8	2	3	5	11
Tumor size	Early diagnosis (TIS, T1, T2)	70	56	45	54	25	60
	Late diagnosis (T3, T4)	54	44	37	46	17	40
Tumor stage	Stage I	30	24	15	18	15	35.7
	Stage II	32	26	17	21	15	35.7
	Stage III	18	14.5	16	19.5	2	4.7
	Stage IV	26	21	25	30.5	1	2.4
	No data	18	14.5	9	11	9	21.5
Treatment	Surgical (S)	56	45.2	27	33	29	69
	Radiotherapy (R)	1	0.8	1	1.2	0	0

	Chemotherapy (Ch)	2	1.6	2	2.4	0	0
	S+R	7	5.6	7	8.6	0	0
	S+Ch	2	1.6	1	1.2	1	2.5
	S+R+Ch	25	20.2	20	24.4	5	12
	R+Ch	5	4	4	4.8	1	2.5
	No data	26	21	20	24.4	6	14
Tobacco	Never Smoker	85	68.5	60	73	25	60
	Smoker	39	31.5	22	27	17	40
Tobacco lifetime exposure	Average (pack/year)	15.9	---	13	---	20.9	---
	Range (pack/year)	0.45-64	---	0.45-36.5	---	2.05-64	---
e-Cigarretes	Non user	50	41	34	41	16	16
	User	0	0	0	0	0	0
	No data	74	59	48	59	26	26
Alcohol	Non drinker	88	71	53	64	35	83
	Social Drinker	32	26	26	31	6	14
	Habitual Drinker	4	3	3	5	1	3
Cannabis users	Yes	17	14	9	10	8	20
	No	107	86	73	90	34	80
HPV infection	Yes	14	36	11	13	3	7
	No	24	19	19	23	5	12
	No data	86	69	52	64	34	81
CMI	Yes	66	53.4	41	50	25	60
	No	58	46.6	41	50	17	40
Subtype of CMI	Dental	23	35	11	27.5	12	46
	Prosthetic	2	3	2	5	0	0
	Dental + Functional	41	62	27	67.5	14	54
Mate consumption	Yes	73	59	48	60	25	60
	No	48	39	32	39	14	35
	No data	3	2	2	2	1	5
Oncological inheritance	Yes	28	22.5	20	24	8	20
	No	68	55	41	50	27	64
	No data	28	22.5	21	26	7	16
Environmental carcinogens	Yes	21	17	12	14	9	21
	No	67	54	42	52	25	60
	No data	36	29	28	34	34	9

OSCC: oral squamous cell carcinoma
CMI: chronic mechanical irritation
PVL: proliferative verrucous leukoplakia
AC/AK: actinic cheilitis/actinic keratosis

Table 2: differences between OSCC de novo and sequential OSCC in young patients

Variable	Category	De Novo OSCC	Sequential OSCC	OR	CI 95%	p-value
n		82	42			
Age	Average (SD)	35.8 (6.5)	37 (6.9)	---	---	0.3759[a]
Sex	Male	47	28	1.49	0.68-3.23	0.3125[b]
	Female	35	14			
Location	Lateral Tongue	59	26	0.63	0.29-1.38	0.2542[b]
	Other sites	23	16			
Clinical phenotype	Ulcer	36	16	---	---	**0.0163**[b]
	Ulcerated nodule	29	6			
	White plaque	2	4			
	Red plaque	3	3			
	Exophytic/Swellings	9	6			
	Mixed	3	7			
Comorbidities	Yes	14	14	2.43	1.04-5.68	**0.0404**[b]
	No	68	28			
Degree of differentiation	Well-differentiated	28	21	---	---	0.0819[b]
	Moderately-differentiated	44	13			
	Poorly differentiated	8	3			
Tumor size	Early diagnosis (TIS-T1-T2)	45	25	1.2	0.56-2.57	0.6242[b]
	Late diagnosis (T3-T4)	37	17			
Stage	Early (Stages 1-2)	32	30	12.8	3.58-45.8	**<0.0001**[b]
	Advanced (Stages 3-4)	41	3			
Treatment	Surgical (S)	27	29	---	---	**0.0017**[b]
	Surgical+other	28	6			
	Non surgical	7	1			
Tobacco	Never Smoker	60	25	0.54	0.24-1.18	0.1213[b]
	Smoker	22	17			
Tobacco LE	Average (pack/year)	13 (13.2)	20.9 (19.7)	---	---	0.1644[a]
Alcohol	Non/social drinker	56	36	2.78	1.04-7.43	**0.0359**[b]
	Habitual Drinker	26	6			
Cannabis users	Yes	9	8	1.9	0.67-5.37	0.2161[b]
	No	73	34			
HPV infection	Yes	11	3	1.03	0.2-5.19	0.6354[c]
	No	19	5			
CMI	Yes	41	25	1.47	0.69-3.12	0.3149[b]
	No	41	17			
Mate consumption	Yes	48	25	1.14	0.51-2.54	0.7401[b]
	No	32	14			
Oncological inheritance	Yes	20	8	0.6	0.23-1.57	0.3032[b]
	No	41	27			
Environmental carcinogens	Yes	12	9	1.26	0.46-3.41	0.6467[b]
	No	42	25			

OSCC: oral squamous cell carcinoma
SD: standard deviation
LE: lifetime exposure
CMI: chronic mechanical irritation
[a] test T
[b] chi-square
[c] test de Fisher

Figure 1

Total OSCC under 45 years old
n=124 (100%)

Northern Region
Señor del Milagro Hospital (Salta)
n=16 (12%)

Eastern Region (Mesopotamia)
Provincial Center of Oral Medicine and Oral Cancer Prevention Program (Corrientes)
n=14 (9%)

Center Region
Oral Medicine Department A and B, Universidad Nacional de Córdoba
(Córdoba)
n=40 (33%)

Buenos Aires Region
Oncological Hospital Marie Curie
n=39 (31%)
Alemán Hospital
n=4 (3%)
(Buenos Aires)

Western Region (Cuyo)
Guillermo Rawson Hospital (San Juan)
n=7 (6%)
University Hospital Universidad Nacional de Cuyo
(Mendoza)
n=4 (3%)

Southern Region (Patagonia)
Hospital Regional Comodoro Rivadavia
(Chubut)
n=4 (3%)

Figure 2

Click here to access/download;Figure;Collage 1.jpg

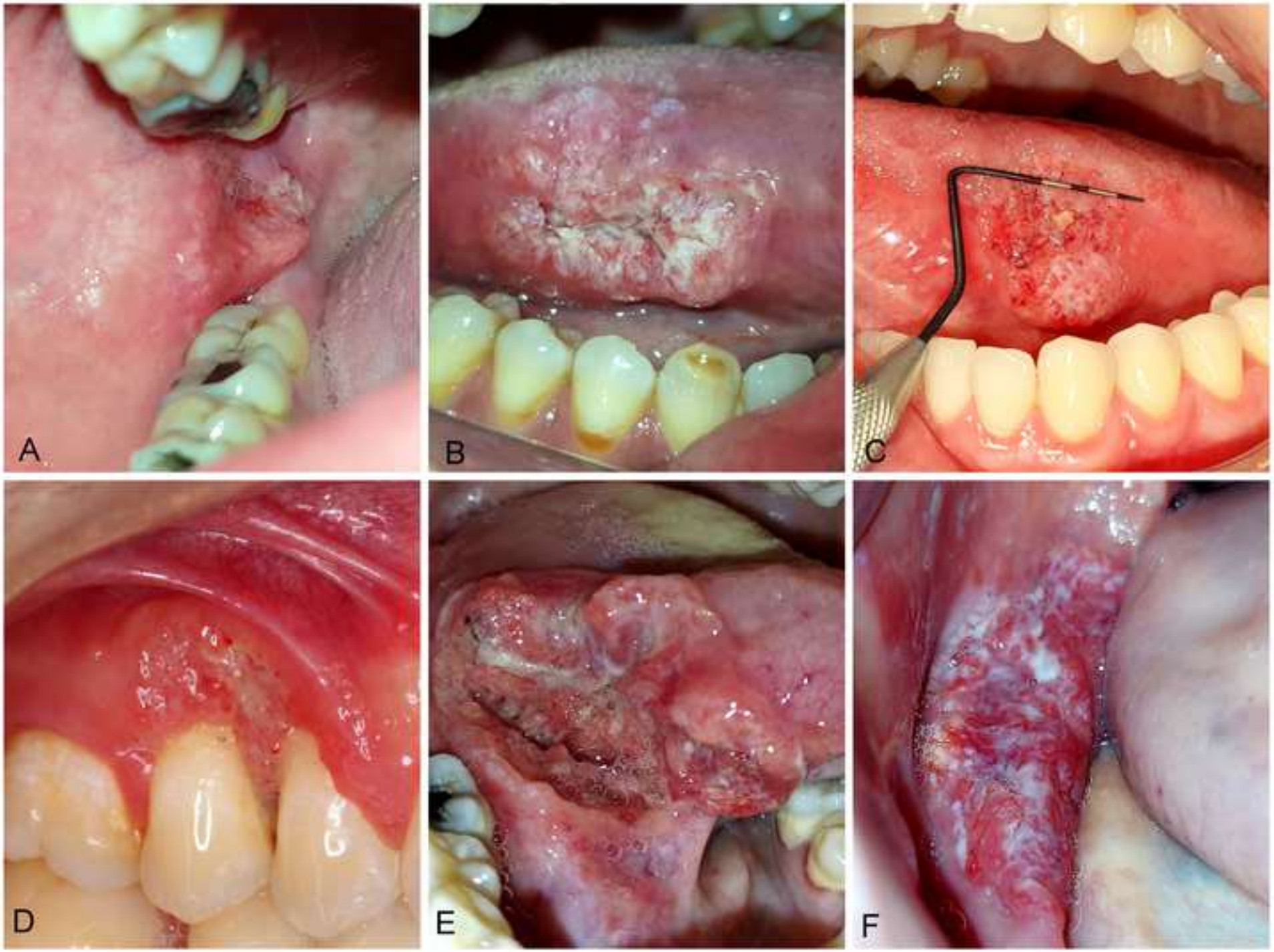

Figure 3

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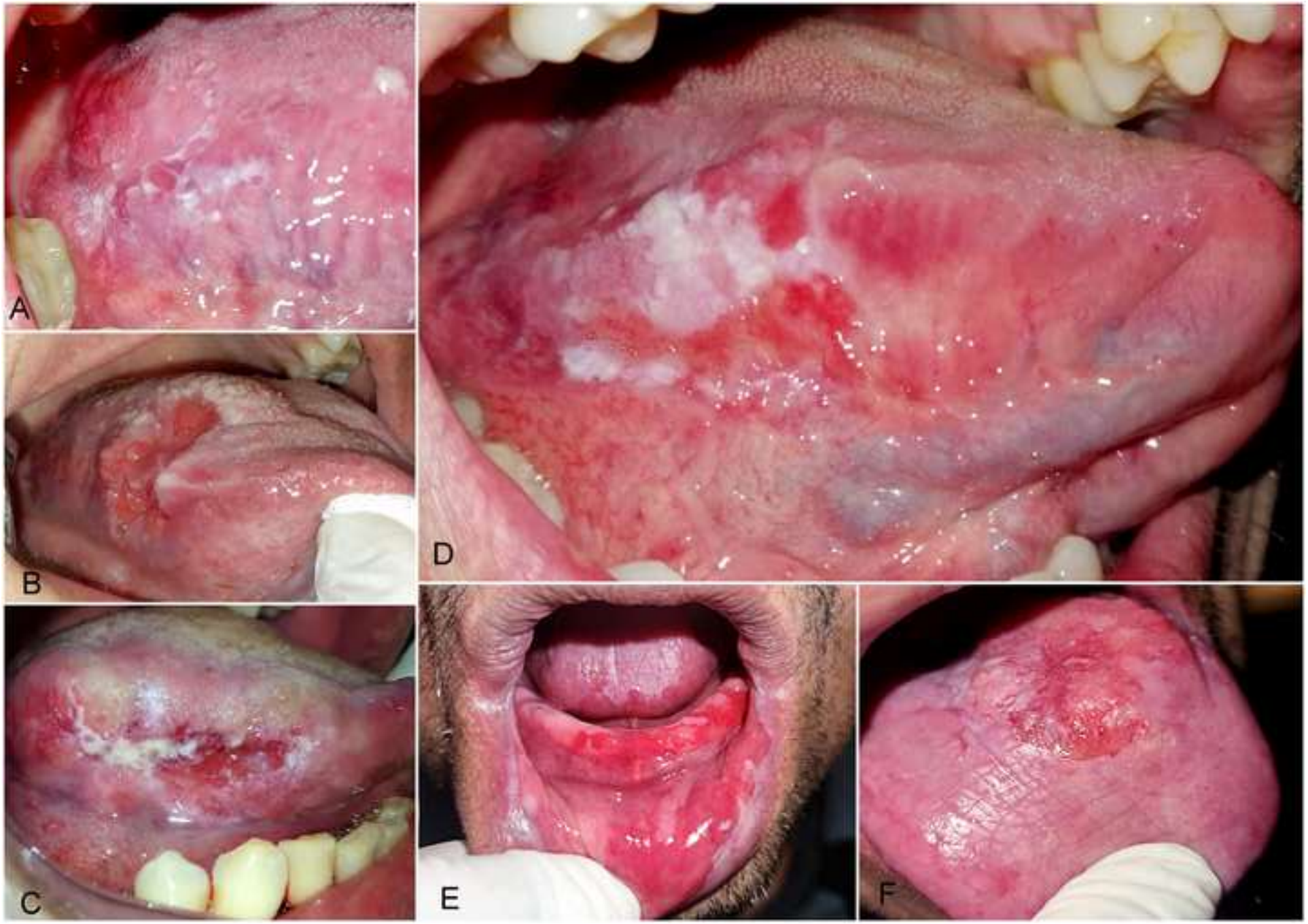

Figure 4

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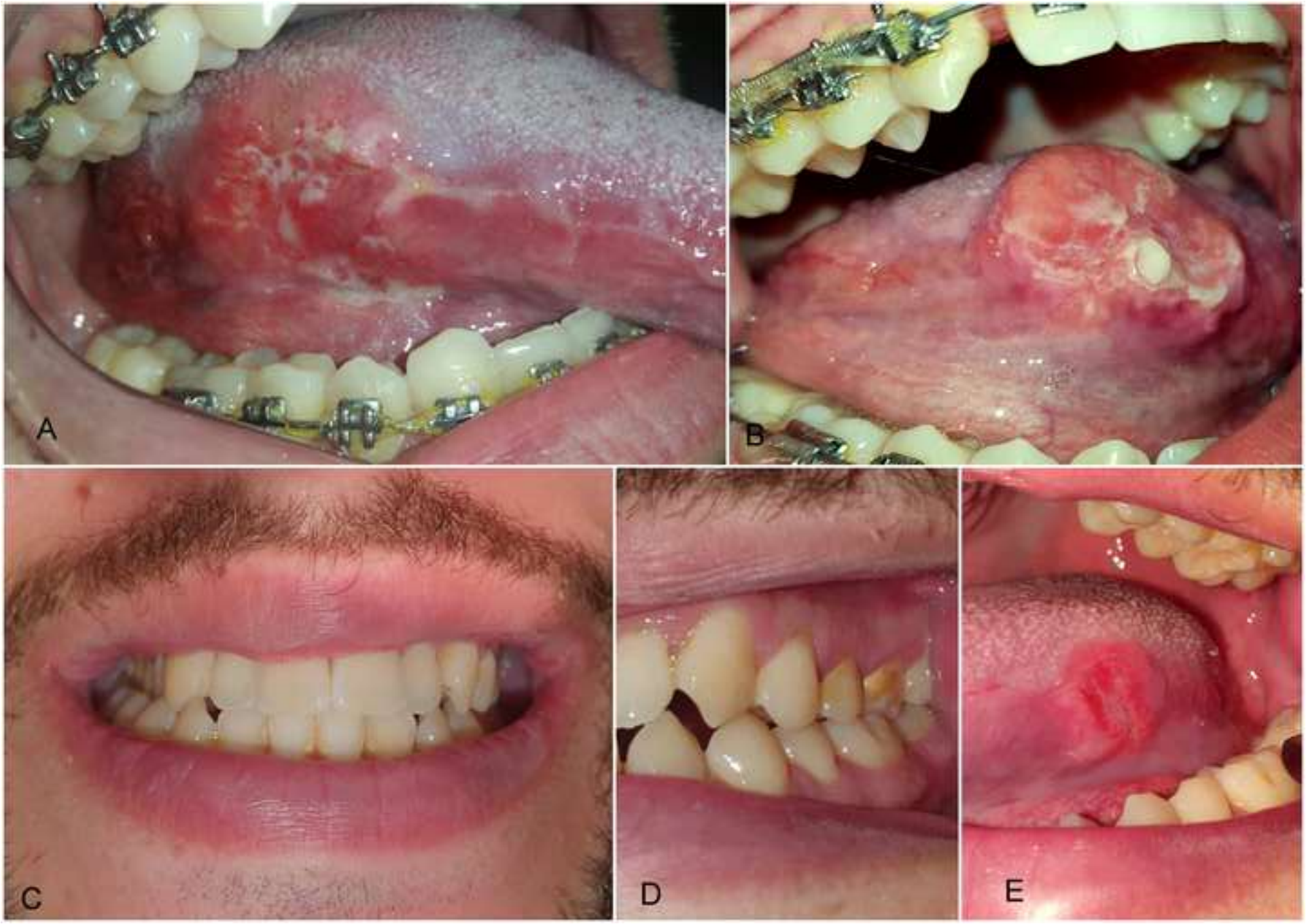

Suppl Table 1

Supp Table 2

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Supplementary Data (online only)

Supplementary_Table_S3_early vs late.docx