CASE REPORT

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Early diagnosis of oral squamous cell carcinoma may ensure better prognosis: A case series

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Abstract
Oral squamous cell carcinoma is an extremely malignant tumour: in order to reduce mortality and morbidity, early diagnosis and treatment is the clinician's best weapon.

KEYWORDS
oral cancer, oral health, pre-malignancies, primary prevention, risk factors

1 | INTRODUCTION

Oral squamous cell carcinoma (OSCC) is a malignancy with high mortality and morbidity. Early diagnosis and treatment of OSCC and other potentially malignant lesions of the oral mucosa is the clinician's best weapon to improve prognosis, since it greatly worsens as the disease becomes more advanced. In Western countries, oral cancer represents a rather uncommon malignancy, with oral squamous cell carcinoma (OSCC) being most frequent.[1] OSCC has high mortality and morbidity,[2] which significantly increases with diagnostic delay.[3] As the most

common risk factors for OSCC are well known and are for the most part behaviors that can be eliminated, primary prevention consists in educating the population against these behaviors.[6] Once the cancer is present, early diagnosis is the single most important element in improving prognosis, since clinical and pathological staging is the most important factors that influence survival rates.[7] Furthermore, treatment for an early disease, which consists in surgical excision with tumor-free margins, prevents the morbidity that far more invasive surgery for a more advance disease would imply.[8] The prompt recognition of and correct treatment for conditions that present a

risk of transforming into cancer, such as leucoplakias[9] and erythroplakias, also play a very important role in improving the chances of survival.[10]

Oral squamous cell carcinoma mostly affects elderly men, although the latest literature seems to suggest a growing incidence in younger patients, especially in tongue cancer, and in particular when linked to chronic mucosal trauma caused, for instance, by sharp dental elements.[11] Furthermore, some authors suggest that younger patients bear a more aggressive disease, with higher locoregional recurrence rates and worse prognosis.[12]

The following case series reports four cases in which early diagnosis was essential in ensuring good prognosis to all individuals, as all are in good health and disease-free at the time of writing.

The present article was approved by the Ethics Committee of San Raffaele Hospital (20210422), in accordance with the Declaration of Helsinki. All patients gave their informed consent.

2 | CASE PRESENTATION

2.1 | Case 1

F.F. was a 32-year-old woman who was referred to our dental clinic for a burning sensation in correspondence of the left aspect of the tongue. Her past history included diagnosis of skin melanoma (Breslow stage I) about a year prior, for which she had undergone surgical excision.

Clinical examination revealed the presence of a solid, tender, ulcerated lesion of the left tongue border, with dyskeratotic areas (Figure 1). A biopsy of the lesion was carried out, with histologic examination showing the presence of a G2 (grade 2) squamous cell carcinoma, even though the patient apparently showed no risk factors, as she was neither a smoker nor a heavy drinker. Contrast-enhanced MRI (magnetic resonance imaging) confirmed

FIGURE 1 Case 1: Preoperative appearance of the lesion

FIGURE 2 Case 1: Squamous cell carcinoma associated with keratin pearl formation, infiltrating the intrinsic lingual muscle. (H&E)
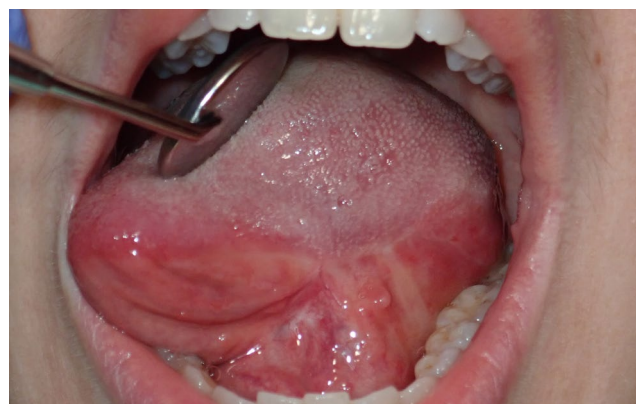

FIGURE 3 Case 1: Fully healed postoperative appearance of the tongue

the presence of a highly vascularized solid lesion, confined to the lingual body, without infiltration of the adjacent muscles and mandible.

The patient consequently underwent a partial marginal glossectomy with CO_2 (carbon dioxide) laser (type II glossectomy sec. Ansarin)[13] and sentinel lymph node biopsy. Histologic examination confirmed the presence of a G2 SCC (Figure 2), pT2 pN0 lesion, with a DOI (Depth of Invasion) of 4 mm.

At 1 year postoperative, the patient is currently disease-free (Figure 3), as revealed by periodic clinical examination and contrast-enhanced MRI.

2.2 | Case 2

G.B. was a 61-year-old man with a history of active drinking (half a liter of wine per day). During a routine dental examination, an erythroleukoplakic lesion of the left

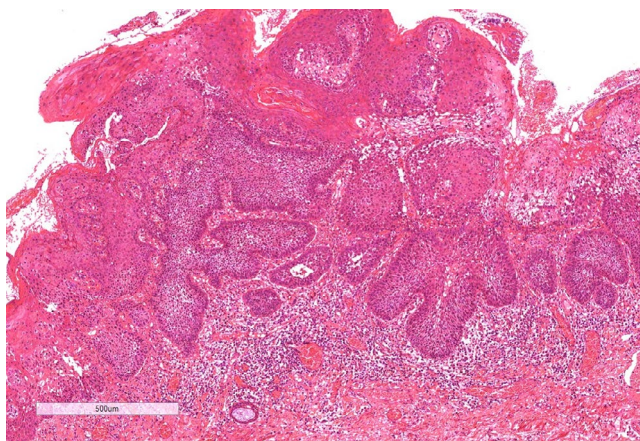**FIGURE 4** Case 2: Erythroleukoplakic lesion of the left retromolar area
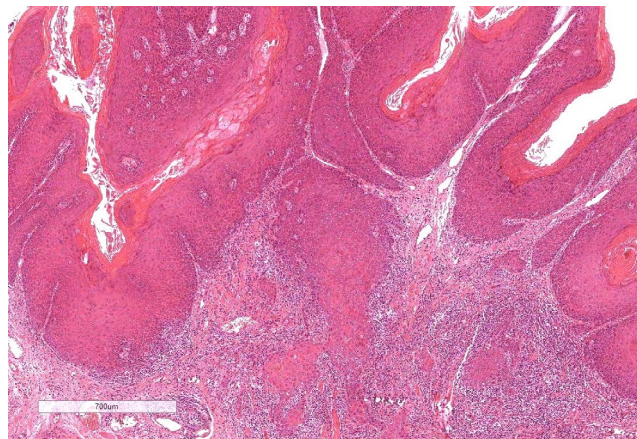

FIGURE 7 Case 3: Well-differentiated squamous cell carcinoma characterized by finger-like growth, infiltrating the superficial layers of the intrinsic lingual muscle. (H&E)

FIGURE 5 Case 2: Squamous cell carcinoma with basaloid features, demarcated by a mild layer of lymphocytes and plasma cells (H&E)

FIGURE 6 Case 3: A vast leukoplakic lesion of the right tongue border (2.5×2.5 cm) with a squamous cell carcinoma of 1 cm in greatest dimension in its context

retromolar area was identified (Figure 4). Given the risk factors presented by the patient and the appearance of the lesion, it was decided to perform an immediate biopsy. Histologic examination showed the presence of severe dysplasia.

Even though histologic examination did not show the presence of cancer, given the high risk that lesions such as erythroleukoplakia carry, it was nevertheless decided that the patient undergo surgery.

The lesion was excised by CO_2 laser. Histology showed the presence of a micro-focal T1 G2 squamous cell carcinoma in the context of a severely dysplastic mucosa (Figure 5).

Almost 2 years after surgery, the patient is undergoing regular follow-up and is disease-free.

2.3 | Case 3

T. D. was a 43-year-old man presented with a leukoplakic lesion of the right tongue border (Figure 6). A biopsy was carried out, showing a verrucous proliferation with atypia, which was dubious for neoplasia.

Contrast-enhanced MRI confirmed the presence of the lesion, which did not appear to infiltrate the intrinsic muscles of the tongue or neighboring structures.

It was thus decided to surgically excise the lesion by transoral mucosectomy with a CO_2 laser (type I glossectomy sec. Ansarin).[13] Histology showed the presence of a G1 squamous cell carcinoma (1 cm in greatest dimension, DOI 1 mm) in the context of a verrucous hyperplasia with lichenoid chronic inflammation (Figure 7).

Two years after surgery, the patient is disease-free, as shown by periodic clinical examinations and contrast-enhanced MRI.

FIGURE 8 Case 4: Preoperative appearance of the leukoplakic lesion

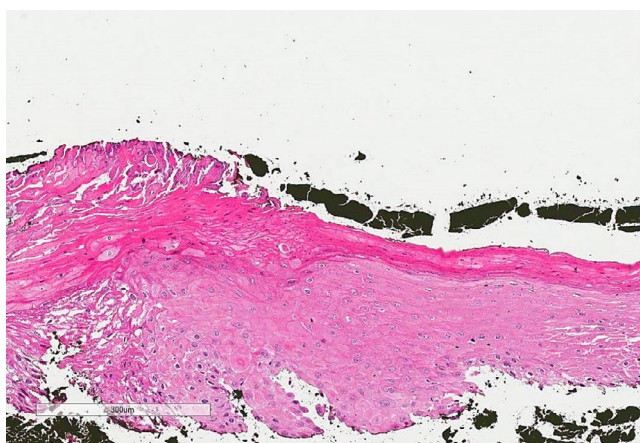**FIGURE 10** Case 4: Postoperative, fully healed, appearance of the tongue

FIGURE 9 Case 4: Superficial resection of squamous epithelia showing keratosis and dyskeratosis with mild nuclear irregularity of the squamous epithelia. (H&E)

2.4 | Case 4

L. D. was a 24-year-old woman presented with a leukoplakic lesion of the right border of the tongue (Figure 8), progressively growing in size. The lesion was biopsied on multiple occasions. The latest histological examination showed the presence of severe dysplasia, while the previous one showed only moderate dysplasia. Given that the lesion was constantly increasing in size (reaching an extension of 2 cm circa) and that the grade of dysplasia seemed to be progressively worsening, it was decided to surgically intervene.

The lesion was excised transorally by CO_2 laser. Histologic examination showed the presence of inflammation and keratosis (Figure 9). Two years after the excision, the lesion has not recurred (Figure 10).

3 | DISCUSSION

Oral cancer is an extremely malignant condition, with a very high risk of mortality and morbidity, albeit not common in Western countries. Diagnostic delay can contribute greatly to poor prognosis of the disease, since up to 50% of oral malignancies are diagnosed in a very advanced stage (III – IV), which translates into poor prognosis; this underlines the importance of early diagnosis and prevention of disease progression.[3] Overall, 5-year survival is estimated at around 50%,[1] while for advanced stage OSCC it decreases to 30%.[14] Clinical and pathological stage at presentation represents the single most important prognostic factor, with the presence of lymph node metastases being the most powerful predictor of outcome[15] since the presence of a single node metastasis confers up to a 50% decrease in overall survival.[16]

Up to 33% of patients present with occult cervical disease, undetectable by imaging techniques (mainly CT—computed tomography—and MRI)[17]; the use of sentinel node biopsy (SNB) represents an excellent solution in cases of T1-T2 tumors with a clinically N0 neck.[17,18] SNB is an extremely valuable method in detecting occult node metastases in head and neck cancer, with a negative predictive value of about 95%, and represents a solution for the management of a clinically N0 neck,[17] as it can better select patients for which nodal dissection is required and avoid unnecessary surgery.[18] SNB represents an alternative to management of the neck according to DOI, as lesions with DOI >4 mm can be either treated with an upfront neck dissection or kept under close follow-up for neck metastases[17]; a recent meta-analysis, however, demonstrated that upfront neck dissection is associated with a significantly better prognosis compared to close follow-up.[19]

Risk factors for oral cancer include heavy use of tobacco, alcohol drinking, and betel quid chewing.[4-6] Chronic mucosal trauma, originating from poor oral hygiene, poor dentition, missing teeth, or ill-fitting prosthetics,[20] has been postulated to be an etiological factor for oral cancer; this may be particularly true for younger patients presenting with no other risk factor for OSCC (mainly use of tobacco and alcohol),[14] as up to 30% of nonsmokers and nondrinkers presenting with OSCC present with some kind of dental abnormality in proximity to the tumor.[21] HPV (human papilloma virus) may have a role as a risk factor, although it cannot be considered an independent prognostic factor,[22] as for oropharyngeal cancer.[23] In the last decades, a global increase in incidence of OSCC in patients <45 years has been observed; in these patients, the role of alcohol and tobacco is still debated, as is the role of HPV.[24] Also, prognostic factors in younger patients are still unclear, perineural invasion and lymphovascular invasion being among the most probable.[24]

Since oral cancer can be considered a highly preventable disease, ideally screening campaigns should educate the population to eliminate risk factors for oral cancer, mainly tobacco smoking and alcohol consumption. This, however, has not proven to be effective. Additionally, even though cancer awareness has greatly increased in the last decades, the percentage of patients seeking medical attention with an advanced stage disease has not changed significantly in the last 40 years.[25] Once the carcinogenic process has been established, the best weapon a clinician has against the disease is early diagnosis. Unfortunately, unlike other more frequent cancers (ie, colorectal cancer), a population-based screening program for oral cancer does not exist and would not be feasible or cost-effective.[26] A group of oral conditions and diseases are known to be precursors to oral cancer; these include leucoplakias, erythroplakias, oral lichen planus, and chronic inflammatory lesions.[27] The prompt identification of these lesions and their treatment is of the utmost importance, as it represents a means of pre-venting cancerous transformation.[28] As not every premalignant lesion of the oral cavity transforms into cancer, the decision to excise the lesion or keep the patient under close follow-up must be made according to clinical and histopathological findings.[29,30]

As recommended by the American Dental Association, any lesion of the oral mucosa that does not regress within 3 weeks after elimination of the possible cause (ie, sharp teeth causing trauma) must be biopsied.[31] The identification of any suspect lesion of the oral mucosa starts with clinical examination, which consists in visual and tactile inspection of the oral cavity and can be carried out, for instance, in the context of a dental appointment.[7,32] Biopsy remains the gold standard in diagnosis, while a series of other tools are starting to be used as aids in diagnosis; these include toluidine blue staining, autofluorescence imaging, and salivary biomarkers for point-of-care testing.[6,33] Narrowband imaging, with or without magnifying endoscopy, can also be an important aid in early recognition of malignant lesions, as it allows better visualization of the mucosal surface texture and mucosal and submucosal vasculature.[34]

In all four cases presented herein, diagnosis was established starting from a simple clinical inspection carried out in the context of a dental appointment, which was nevertheless able to guarantee good prognosis. All lesions were thus diagnosed and excised in the early stages, making it possible to considerably reduce the morbidity associated with the disease and its treatment when in an advanced stage. In case 1, after the diagnosis of OSCC was made, it was also decided to carry out a sentinel lymph node biopsy. As histological examination showed the absence of any node metastases, it was possible to avoid further unnecessary surgery on the neck, while still obtaining oncological radicality. In case 3, however, the neck was managed according to DOI: Preoperative MRI showed the presence of a lesion with a maximum DOI of 3 mm, so that the surgical excision was carried out without performing a neck dissection. Oncological radicality was achieved nonetheless, as periodical clinical examinations and MRI imaging still demonstrate no recurrence and a N0 neck at 2 years postoperative.

In case 2, the decision to excise the erythroplakic lesion was taken before the diagnosis of OSCC was made, as the initial histology only showed the presence of high-grade dysplasia. As is well known, erythroplakia is the single most dangerous pre-cancerous lesion of the oral cavity, as up to 85% if erythroplakias show histological signs of carcinoma once biopsied or excised.[35,36] Indeed, in our case, histological examination of the entire lesion revealed the presence of a G2 squamous cell carcinoma, which was thus eradicated in its very early stages, avoiding the need for far more extensive surgery had the lesion been allowed to grow in size. Case 4 represents an example of a lesion (leucoplakia) that is not cancerous in itself, but which carries a risk of transforming into cancer,[37] even though not as high as that of erythroplakia.[35] Given that the lesion was rapidly increasing in size and its grade of dysplasia rapidly worsening, it was decided to completely excise the lesion surgically. Histological examination did not show the presence of cancerous foci; nevertheless, by excising the lesion in its entirety, the need for periodic biopsies was eliminated, while eradicating the risk of malignant transformation.

4 | CONCLUSIONS

Oral squamous cell carcinoma is an extremely malignant condition, with very poor prognosis when diagnosed at

an advanced stage. The best weapon to improve prognosis is to diagnose oral cancer as early as possible. Diagnosis starts with a simple visual and tactile examination of the oral cavity, which can be carried out in the context of a dental appointment. The cases presented herein show how early diagnosis, starting from a simple examination of the oral cavity, can ensure very good prognosis.

CONFLICT OF INTERESTS
The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
S.A., C.B., and M.T. involved in conceptualization. S.A., S.B., M.T., and A.L. involved in validation. S.A., F.F., and G.A. involved in data curation. C.B. involved in writing-original draft preparation. S.B., M.T., and A.L. involved in writing-review and editing. All authors have read and agreed to the published version of the manuscript.

ETHICAL APPROVAL
The present article has been approved by the Ethics Committee of San Raffaele Hospital (20210422), in accordance with the Declaration of Helsinki.

CONSENT
All patients gave their consent.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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REFERENCES
1. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol.* 2009;45(4–5):309-316. https://doi.org/10.1016/j.oraloncology.2008.06.002
2. Silverman S, Kerr AR, Epstein JB. Oral and pharyngeal cancer control and early detection. *J Cancer Educ.* 2010;25:279-281. https://doi.org/10.1007/s13187-010-0045-6
3. McCullough MJ, Prasad G, Farah CS. Oral mucosal malignancy and potentially malignant lesions: an update on the epi-demiology, risk factors, diagnosis and management. *Aust Dent J.* 2010;55(Suppl 1):61-65. https://doi.org/10.1111/j.1834-7819.2010.01200.x
4. Chow LQM. Head and neck cancer. *N Engl J Med.* 2020;382(1):60-72. https://doi.org/10.1056/NEJMra1715715
5. Della-Torre E, Campochiaro C, Cassione Bozzalla E, et al. Intrathecal rituximab for pachymeningitis. *J Neurol Neurosurg Psychiatry.* 2018;89(4):441-444. https://doi.org/10.1136/jnnp-2017-316519
6. Abati S, Bramati C, Bondi S, Lissoni A, Trimarchi M. Oral cancer and precancer: a narrative review on the relevance of early diagnosis. *Int J Environ Res Public Health.* 2020;17:9160. https://doi.org/10.3390/ijerph17249160
7. Ford PJ, Farah CS. Early detection and diagnosis of oral cancer: strategies for improvement. *J Cancer Policy.* 2013;1(1–2):e2-e7. https://doi.org/10.1016/j.jcpo.2013.04.002
8. Bacci C, Pollio A, Cerrato A, Lucchiari N, Valente M. The early diagnosis of small-sized oral squamous cell carcinoma: a challenge for the clinician. Report of two cases and literature review. *Ital J Dent Med.* 2017;2(1):18-23.
9. Bewley AF, Farwell DG. Oral leukoplakia and oral cavity squamous cell carcinoma. *Clin Dermatol.* 2017;35(5):461-467. https://doi.org/10.1016/j.clindermatol.2017.06.008
10. Villa A, Villa C, Abati S. Oral cancer and oral erythroplakia: an update and implication for clinicians. *Aust Dent J.* 2011;56(3):253-256. https://doi.org/10.1111/j.1834-7819.2011.01337.x
11. Randhawa T, Shameena PM, Sudha S, Nair RG. Squamous cell carcinoma of tongue in a 19-year-old female. *Indian J Cancer.* 2008;45(3):128-130. https://doi.org/10.4103/0019-509x.44071
12. Hirota SK, Migliari DA, Sugaya NN. Oral squamous cell carcinoma in a young patient - Case report and literature review. *An Bras Dermatol.* 2006;81(3):251-254.
13. Ansarin M, Bruschini R, Navach V, et al. Classification of glossectomies: proposal for tongue cancer resections. *Head Neck.* 2019;41(3):821-827. https://doi.org/10.1002/hed.25466
14. Singhvi HR, Malik A, Chaturvedi P. The role of chronic mucosal trauma in oral cancer: a review of literature. *Indian J Med Paediatr Oncol.* 2017;38(1):44-50. https://doi.org/10.4103/0971-5851.203510
15. Montero PH, Patel SG. Cancer of the oral cavity. *Surg Oncol Clin N Am.* 2015;24(3):491-508. https://doi.org/10.1016/j.soc.2015.03.006
16. Ho AS, Kim S, Tighiouart M, et al. Metastatic lymph node burden and survival in oral cavity cancer. *J Clin Oncol.* 2017;35(31):3601-3609. https://doi.org/10.1200/JCO.2016.71.1176
17. Schilling C, Stoeckli SJ, Haerle SK, et al. Sentinel European node trial (SENT): 3-year results of sentinel node biopsy in oral cancer. *Eur J Cancer.* 2015;51(18):2777-2784. https://doi.org/10.1016/j.ejca.2015.08.023
18. Wu JX, Hanson M, Shaha AR. Sentinel node biopsy for cancer of the oral cavity. *J Surg Oncol.* 2019;120(2):99-100. https://doi.org/10.1002/jso.25493
19. Oh LJ, Phan K, Kim SW, Low TH, Gupta R, Clark JR. Elective neck dissection versus observation for early-stage oral squamous cell carcinoma: systematic review and meta-analysis. *Oral Oncol.* 2020;105(March):104661. https://doi.org/10.1016/j.oraloncology.2020.104661
20. Gupta AA, Kheur S, Varadarajan S, et al. Chronic mechanical irritation and oral squamous cell carcinoma : a systematic review and meta-analysis. *Bosn J Basic Med Sci.* 2019;8601. https://doi.org/10.17305/bjbms.2021.5577. Epub ahead of print. PMID: 33823123.

21. Perry BJ, Zammit AP, Lewandowski AW, et al. Sites of origin of oral cavity cancer in nonsmokers vs smokers possible evidence of dental trauma carcinogenesis and its importance compared with human papillomavirus. *JAMA Otolaryngol Head Neck Surg*. 2015;141(1):5-11. https://doi.org/10.1001/jamaoto.2014.2620

22. Hübbers CU, Akgül B. HPV and cancer of the oral cavity. *Virulence*. 2015;6(3):244-248. https://doi.org/10.1080/21505594.2014.999570

23. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of pa-tients with oropharyngeal cancer. *N Engl J Med*. 2010;363(1):24-35. https://doi.org/10.1056/NEJMoa0912217

24. Mascitti M, Tempesta A, Togni L, et al. Histological features and survival in young patients with HPV-negative oral squamous cell carcinoma. *Oral Dis*. 2020;26(8):1640-1648. https://doi.org/10.1111/odi.13479

25. McGurk M, Chan C, Jones J, O'Regan E, Sherriff M. Delay in diagnosis and its effect on outcome in head and neck cancer. *Br J Oral Maxillofac Surg*. 2005;43(4):281-284. https://doi.org/10.1016/j.bjoms.2004.01.016

26. Lingen MW, Kalmar JR, Karrison T, Speight PM. Critical evaluation of diagnostic aids for the detection of oral cancer. *Oral Oncol*. 2008;44(1):10-22. https://doi.org/10.1016/j.oraloncology.2007.06.011

27. Warnakulasuriya S, Johnson NW, Van Der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. *J Oral Pathol Med*. 2007;36(10):575-580. doi:10.1111/j.1600-0714.2007.00582.x

28. Walsh T, Liu JLY, Brocklehurst P, et al. Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults. *Cochrane Database Syst Rev*. 2013;2013(11):CD010173. https://doi.org/10.1002/14651858.CD010173.pub2

29. Neville BW, Day TA. Oral cancer and precancerous lesions. *CA Cancer J Clin*. 2002;52(4):195-215. https://doi.org/10.3322/canjclin.52.4.195

30. Trimarchi M, Bondi S, Della Torre E, Terreni MR, Bussi M. La perforazione del palato differenzia le lesioni destruenti della linea mediana indotte da cocaina dalla granulomatosi con poliangioite. *Acta Otorhinolaryngol Ital*. 2017;37(4):281-285. https://doi.org/10.14639/0392-100X-1586

31. Rethman MP, Carpenter W, Cohen EEW, et al. Evidence-based clinical recommendations regarding screening for oral squamous cell carcinomas. *J Am Dent Assoc*. 2010;141(5):509-520. https://doi.org/10.14219/jada.archive.2010.0223

32. Biafora M, Bertazzoni G, Trimarchi M. Maxillary sinusitis caused by dental implants extending into the maxillary sinus and the nasal cavities. *J Prosthodont*. 2014;23(3):227-231. https://doi.org/10.1111/jopr.12123

33. Alfano M, Grivel JC, Ghezzi S, et al. Pertussis toxin B-oligomer dissociates T cell activation and HIV replication in CD4 T cells released from infected lymphoid tissue. *Aids*. 2005;19(10):1007-1014. https://doi.org/10.1097/01.aids.0000174446.40379.3b

34. Vu A, Farah CS. Narrow band imaging: clinical applications in oral and oropharyngeal cancer. *Oral Dis*. 2016;22(5):383-390. https://doi.org/10.1111/odi.12430

35. Haim S. Oral leukoplakia. *Harefuah*. 1981;101(1–2):35-37.

36. Morassi ML, Trimarchi M, Nicolai P, et al. Cocaine, ANCA, and Wegener's granulomatosis. *Pathologica*. 2001;93(5):581-583.

37. Carrard VC, Van Der Waal I. A clinical diagnosis of oral leukoplakia; a guide for dentists. *Med Oral Patol Oral Y Cir Bucal*. 2018;23(1):e59-e64. https://doi.org/10.4317/medoral.22292