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PRIKAZ SLUČAJA
CASE REPORT

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Važnost odabira pravog područja za biopsiju nodularne leukoplakije: prikaz slučaja

The Importance of a Proper Selection Area to be Biopsied in Nodular Leukoplakia: a Case Report

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Sažetak
Nodularna leukoplakija je nehomogeni oblik oralne leukoplakije obično s bijelom bradavičastom, nodularnom, ulceriranom ili eritematoznom (crvenkastom) površinom s velikim rizikom od pretvorbe u malignu tvorbu u usporedbi s homogenim oblikom. Najčešće zahvaća komisure usnica, obraznu sluznicu i meko nepce. Često je povezana s epitelnom displazijom ili karcinomom, pa je prijeko potrebna detaljna mikroskopska procjena, a poslije redovite kontrole. Temelj za postavljanje točne dijagnoze jest odabrati pravo mjesto za biopsiju, ali i bliska suradnja liječnika dentalne medicine i oralnog patologa.

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Uvod

Oralna leukoplakija klinički se klasificira kao homogena ili nehomogena (1) i jedan je od najčešćih potencijalno malignih poremećaja (2, 3). Nehomogeni oblik ima bijelu bradavičastu, čvorastu, ulceriranu ili eritematoznu površinu i češće se pretvara u zloćudni negoli homogeni (1).

Čvorasta leukoplakija, a najprije su je opisali Pindborg i suradnici (4), ima kliničke znakove poput bijelih čvorastih izraslina na eritematoznoj sluznici i zato se naziva eritroleukoplakijom (1). Najčešće zahvaća komisure usana (4), obraznu sluznicu (3) i meko nepce (5). Feller i njegovi kolege (6) istaknuli su da je ovaj oblik češći kod pacijenata pušača, premda nema statistički značajne razlike u usporedbi s idiopatskim lezijama. Suprotno tomu, Hosni i suradnici (5) uočili su u anamnezama pacijenata pušenje i konzumaciju alkohola kod njih 54 posto s čvorastom leukoplakijom.

Čvorasta leukoplakija, ili lezija s čvorićima, trebala bi se smatrati opasnom jer je često povezana s epitelnom displazijom ili rakom. Pritom karcinom može nastati čak tijekom

Introduction

Oral leukoplakia, clinically classified as homogeneous or non-homogeneous (1), is one of the most common potentially malignant disorders (2,3). The non-homogeneous type presents a white surface with verrucous, nodular, ulcerated or erythematous features, all including a greater risk of malignant transformation than homogeneous types (1).

Nodular leukoplakia, firstly described as speckled leukoplakia by Pindborg et al. (4), has a clinical feature of white nodular outgrowths on erythematous background mucosa, and for this reason the term erythroleukoplakia is also used (1). The most common sites of involvement include lip commissures (4), buccal mucosa (3) and the soft palate (5). As reported by Feller et al. (6), this form of leukoplakia has a tendency to be more common in patients with tobacco habits; however, there is no statistically significant difference when comparing to idiopathic lesions. On the other hand, Hosni et al. (5) observed history of smoking in all cases of nodular leukoplakia and consumption of alcohol in 54% of them.

pregleda, pa je zato potrebna detaljna mikroskopska procjena i poslije redovite kontrole (2, 4 – 6). Prema mišljenju Pindborga i suradnika (4), većina oralnih lezija s atipičnim epitelom klinički je čvorasta leukoplakija. Na temelju istraživanja obavljenih na 248 pacijenata, Pindborg i suradnici (3) ustanovili su da su se sve čvoraste leukoplakije razvile u rak za tri i pol godine, pa su kod ovog oblika leukoplakije istaknuli veliku opasnost od maligne transformacije te činjenicu da je ta promjena vrlo brza.

Pregledom literature na engleskom (PubMed, Scopus i Web of Knowledge) o čvorastoj ili šarenoj leukoplakiji povezanoj s pretvorbom u malignu, pronađeno je osam članaka (2– 9), uključujući i one o njezinoj češćoj pojavi na usnim komisurama i obraznoj sluznici (3,4,7,8) u usporedbi s drugim zahvaćenim područjima. Istaknuta je i visoka incidencija epitelne displazije i karcinoma.

U ovom tekstu opisan je slučaj oralnog skvamoznog staničnog karcinoma (OSCC-a) u leziji klinički dijagnosticiranoj kao čvorasta leukoplakija te je istaknuto koliko je važno odabrati pravo područje za biopsiju kako bi se postavila točna konačna dijagnoza.

Prikaz slučaja

Bijelac u dobi od 66 godina s dijabetesom tipa 2, ne puši i ne pije, žalio se na leziju na obrazu i bockanje četiri godine nakon što je nastala. Tijekom prvog pregleda prije dvije godine u jednoj drugoj klinici koju je pacijent naveo, bila je obavljena biopsija bijele lezije na desnoj strani donje usnice, no sada se ponovno pojavila. Tada je postavljena mikroskopska dijagnoza – kronični stomatitis s lihenoidnim značajkama.

Nakon intraoralnog pregleda opazili smo samostalnu, mekanu, priraslu široku površinu s uglavnom bijelim čvorićima odvojenima malim crvenim područjima na donjoj usni, desnoj komisuri i obraznoj sluznici. Lezija je bila nepravilna s oštrim granicama, duga dva centimetra i široka jedan centimetar (slika. 1). Nije bilo limfadenopatije.

Obavljena je incizijska biopsija odabranog zahvaćenog područja koja je uključivala bijelo i crveno područje na obraznoj sluznici. Mikroskopskom analizom uočeno je da je oralna sluznica pokrivena hiperparakeratiniziranim i hiperplastičnim višeslojnim skvamoznim epitelom s papilarnom površinom i izduženim mrežastim grebenima. U donjoj trećini površinskog epitela nalazila su se displastična obilježja, pleomorfizam, uočljive jezgrice, diskeratoza, hiperplazija bazalnog sloja, epitelni grebeni u obliku kapljice i nešto atipičnih mitoza. Dodatno je u pojedinim područjima uočen gubitak epitelne arhitekture. Bilo je i Munrovih mikroapscesa, osobito u gornjim slojevima epitela, a nastao je i mikrobni biofilm na površini (slika 2. A). Kako bi se otkrile kolonije gljivica, obavljeno je bojenje periodično kiselim Schiffom (PAS) te su otkrivene hife *Candide*, uglavnom u površinskom slojevima epitela. U lamini propriji bilo je epitelnih otoka različitih veličina, što upućuje na mikroinvaziju okruženu in-

Nodular leukoplakia, or a lesion showing nodular features, should be regarded as a dangerous lesion since it is often associated with epithelial dysplasia or carcinoma; it may actually be a cancer during the examination, and it requires detailed microscopic assessment and regular follow-up (2,4-6). According to Pindborg et al. (4), most of oral lesions with epithelial atypia are clinically nodular leukoplakias. Based on a follow-up study of 248 patients, Pindborg et al. (3) also reported that all nodular leukoplakia developed into a cancer in up to 3.5 years, pointing to the high risk of malignant transformation of this leukoplakia, and to the fact that the transformation runs a rapid course.

A literature search in English (PubMed, Scopus and Web of Knowledge) regarding nodular or speckled leukoplakia associated to malignant transformation retrieved eight papers (2-9), including a large occurrence of nodular leukoplakia on lip commissures and buccal mucosa (3,4,7,8) when compared to other areas affected by this same condition and all revealed a high incidence of epithelial dysplasia and carcinoma.

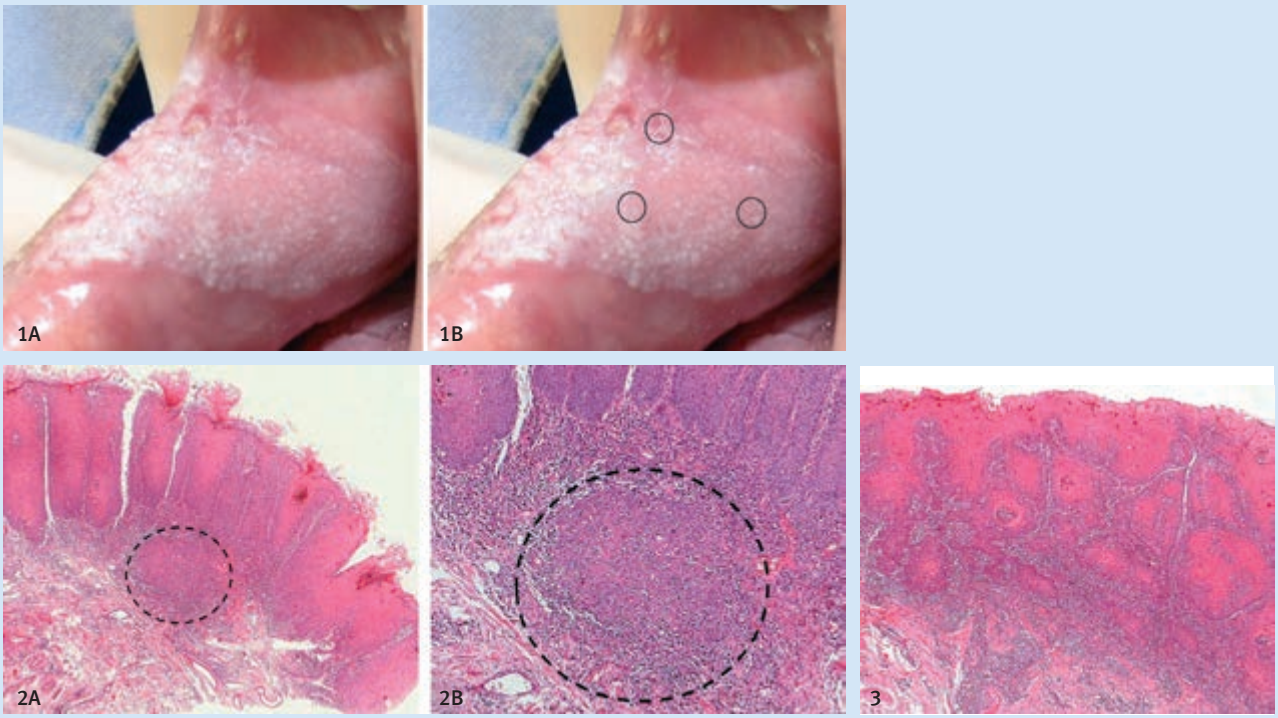
This case demonstrates an oral squamous cell carcinoma (OSCC) in a lesion diagnosed clinically as nodular leukoplakia, and highlights the importance of a proper selection of the area to be biopsied by a dentist, allowing an accurate final diagnosis.

Case report

A 66–year-old Caucasian man, with type 2 diabetes, non-smoker, non-drinker, complained about a cheek lesion with a pinch-like sensation presenting four years of development. During the first examination in another clinic, the patient reported that a white lesion on the right side of the inferior lip had been biopsied two years before, and it recurred. The microscopic diagnosis was chronic stomatitis with lichenoid pattern.

Upon an intra-oral examination, we observed a single, non-indurated, non-removable, extensive area of many white nodule separated by small red areas, located on the inferior lip, right oral commissure, and buccal mucosa. The lesion had irregular shape, with definite borders and clear limits measuring 2cm in length and 1cm in width (Figure 1A). No lymphadenopathy was observed.

An incisional biopsy was performed involving a selected area that had both white and red regions in the buccal mucosa. The microscopic analysis revealed oral mucosa lined by hyperparakeratinized and hyperplastic stratified squamous epithelium with papillary surface and elongated rete ridges. In the lower third of the epithelial lining, there were noticeable areas with dysplastic features, such as hyperchromatism, pleomorphism, evident nucleoli, dyskeratosis, basal layer hyperplasia, drop-shaped epithelial ridges and few atypical mitoses. In addition, loss of epithelial architecture in some regions of the lining was present. There were also Munro microabscesses, particularly in the upper layers of the epithelium, and microbial biofilm at the surface (Figure 2A). To better detect fungal colonization, the Periodic acid-Schiff (PAS) staining was performed and candidal hyphae were found,



Slika 1. (A) Oralna leukoplakija i njezin čvorasti izgled na desnoj oralnoj komisuri i obraznoj sluznici; (B) Različita odabrana područja tijekom druge biopsije
Figure 1 (A) Oral leukoplakia presenting nodular features on the right oral commissure and buccal mucosa. (B) Different areas selected during the second biopsy.
Slika 2. (A) Epitel s papilarnom površinom i izduženim mrežastim rubovima u lamini propriji i epitelnom otoku (krug) (hematoksilin-eozin 4 x). (B) Otok epitelnih stanica (krug) okružen intenzivnim mononuklearnim upalnim infiltratom (hematoksilin-eozin 10 x)
Figure 2 (A) Epithelium with papillary surface and elongated rete ridges and in the lamina propria an island of epithelial cells (circle). (haematoxylin-eosin 4x). (B) Island of epithelial cells (circle) surrounded by intense mononuclear inflammatory infiltrate. (haematoxylin-eosin 10x).
Slika 3. Invazivni oralni skvamozno stanični karcinom (OSCC) (hematoksilin-eozin 4 x)
Figure 3 Invasive oral squamous cell carcinoma. (haematoxylin-eosin 4x)

tenzivnim mononuklearnim upalnim infiltratom, što je otežavalo otkrivanje displazije (slika 2. B). Subepitelno područje također je sadržavalo mononuklearni upalni infiltrat poput vrpce, što je rezultiralo degeneracijom stanica bazalnog sloja i stvaranjem Civatte tjelešca.

Na temelju kliničke povijesti bolesti i mikroskopskih nalaza o svojstvima lezije postavljena je dijagnoza čvoraste leukoplakije s naglaskom na moguću pretvorbu u zloćudnu, ali to nije bilo konačno jer je bila moguća ne samo maligna transformacija nego i pseudoepiteliomatozna hiperplazija. Zato je učinjena i druga incizijska biopsija na obraznoj sluznici na trima različitim područjima otekline (označeno krugovima na slici 1. B), te su morfološka svojstva u skladu s OSCC-om bila pronađena u samo jednom od uzoraka (slika 3.).

Pacijent je upućen u Kliniku za tumore gdje je uklonjena cijela lezija. Mikroskopskom analizom postavljena je dijagnozu OSCC-a. Tijekom dvogodišnjih kontrola lezija se nije ponovno pojavila.

mainly in the superficial layers of the epithelium. In the lamina propria, there were a few islands of epithelial cells of various sizes, suggestive of microinvasion, surrounded by intense mononuclear inflammatory infiltrate, making the identification of dysplastic aspects difficult (Figure 2B). The subepithelial region also had intense band-like mononuclear inflammatory infiltrate, resulting in the degeneration of the basal cell layer with Civatte body formation.

Based on the clinical history and microscopic features of the lesion, the diagnosis of nodular leukoplakia with a focus of possible malignant transformation was suggested, but this was not conclusive since there was the possibility of a pseudoepitheliomatous hyperplasia rather than malignant transformation. Therefore, one month later, a second incisional biopsy was taken on the buccal mucosa at three different areas of the lesion (indicated by circles in Figure 1B) and the morphological features presented in only one of the sections were consistent with invasive OSCC (Figure 3).

The patient was referred to a Cancer Hospital and the lesion was totally excised. The microscopic diagnosis of this biopsy was OSCC. The patient is under a 2-year follow-up and no recurrence has been reported.

Rasprava

U ovom prikazu slučaja opisan je rani OSCC koji se pojavio s čvorastom leukoplakijom. Prema povijesti bolesti, vjerujemo da se je ovaj pacijent od početka imao čvorastu leukoplakiju koja je postala zloćudna jer je naveo da se sadašnja oteklina pojavila na istom području kao i ona već bioptirana. Smatramo da je to nedavna promjena jer smo pod mikroskopom uočili žarišna područja maligne transformacije, tj. od tri bioptirana područja samo je jedno pokazalo morfološke promjene nalik na OSCC. Ne možemo odrediti je li se OSCC *ab ovo* razvio sa svojstvima čvoraste leukoplakije ili iz već postojeće tvorbe.

Na temelju kliničkih pregleda dokazano je da je lezija bila zapravo čvorasta leukoplakija s potencijalno malignim svojstvima, ali ne obvezno. Pritom se mora istaknuti koliko je važno s kliničkog stajališta odabrati pravo područje za obavljanje biopsije u slučaju potencijalno zloćudne lezije. Problem u obradi pacijenata s potencijalno malignom oralnom lezijom jest razlučiti koja će se lezija na sluznici ili u zahvaćenom području pretvoriti u OSCC. Hosni i suradnici (5) pronašli su u svim eritroplastičnim područjima čvoraste leukoplakije – od displazije do invazivnog OSCC–a. Taj nalaz ističe potrebu biopsije u različitim područjima u slučaju čvoraste leukoplakije, uključujući uglavnom eritroplastičnu komponentu.

U našem prikazu slučaja, nakon neposredne i uspješne komunikacije između doktora dentalne medicine i oralnog patologa, odlučili smo obaviti drugu incizijsku biopsiju kako bi se dobila točna mikroskopska dijagnoza o invaziji tumora te odabrali najbolji postupci za pacijenta. Razlog za teškoće kod postavljanja mikroskopske dijagnoze tijekom prve biopsije bio u mogućoj pseudoepiteliomatoznoj hiperplaziji, a ne samo u tumorskoj invaziji. Osim displastičnog izgleda samo donje trećine obložnog epitela, bilo je nekoliko otočića epitelnih stanica u lamini propriji, ali bez vidljive displazije. Zbog posljedica preklapanja, smatramo da je dijagnoza malignosti bila preuranjena, a u dvogodišnjem kontrolnom razdoblju pacijent nije imao recidiva. Prisutnost gljivice *Candida* potvrđena je mikrobiološkim metodama i histološkom analizom u većini slučajeva čvoraste leukoplakije (3, 5, 10), što pokazuje i naš slučaj – pronađena je opsežna kolonija tih gljivica na površini obložnog epitela i Munovi mikroapscesi. Prisutnosti gljivice *Candida* i epitelne displazije češća je kod multiple oralne leukoplakije negoli u slučaju pojedinačne (11). Neka istraživanja pokazala su da invazija gljivicama *Candida* kod oralne sluznice može potaknuti hiperplastičnu reakciju kao zaštitni odgovor domaćina (12) i usko je povezana s umjerenom i teškom epitelnom displazijom (13). Prema mišljenju Chia i suradnika (11), nitrosamini koje stvara soj gljivica *Candida* mogu sami ili zajedno s drugim kemijskim kancerogenima aktivirati specifične protoonkogene i tako potaknuti razvoj maligne lezije. Razmišljajući na taj način, gljivična superinfekcija može se smatrati značajnim rizičnim čimbenikom za onkogenezu (14). No i dalje je nejasno je li *Candida* uključena u etiologiju ili progresiju leukoplakije (15), pa su potrebna daljnja istraživanja.

Discussion

This case demonstrates an early OSCC that occurred at a nodular leukoplakia. According to the reported history, we believe that this was a case of nodular leukoplakia from the beginning, which has undergone malignant transformation, since the patient reports that the current lesion occurred in the same location as the previously biopsied lesion; and according to the patient representing a recurrence. Also, we consider it to be a recent transformation, since we observed microscopically focal areas of malignant invasion; i.e. from three areas selected for incisional biopsy, only one of them showed morphological alterations compatible with OSCC. However, we cannot accurately determine whether the OSCC developed *de novo*, presenting features of nodular leukoplakia, or from preexisting leukoplakia.

Based on our clinical examination, the lesion was a nodular leukoplakia, with features of potentially malignant lesion but not necessarily malignant. Thus, one of the most important points that we want to emphasize here is the importance of choosing the critical area(s) to perform incisional biopsy, in the case of a potentially malignant lesion from a clinical standpoint. The difficulty in managing patients with potentially malignant oral lesions is deciding which mucosal lesions or areas will progress to OSCC. Hosni et al (5) found dysplasia to invasive OSCC in all the erythroplastic areas of nodular leukoplakias. This finding highlights the need for taking biopsies of various areas in cases of nodular leukoplakia, including mainly the erythroplastic component.

In our case report, after a direct and effective communication between the dentist and oral pathologist, we decided to perform a second incisional biopsy in order to achieve an accurate microscopic diagnosis regarding tumor invasion, and also to guide the best patient outcome. The reason for the difficulty in microscopic diagnosis based on first biopsy was the possibility of it being a pseudoepitheliomatous hyperplasia rather than a real tumor invasion. Besides, the dysplastic features were restricted to the lower third of the epithelial lining, and there were a few small islands of epithelial cells in the lamina propria but without an evident dysplasia. As a consequence of interdisciplinarity, we believe that the diagnosis of malignancy was early. Hence, the patient showed no recurrences in a follow-up of two years.

The presence of *Candida* has been observed in the majority of cases of nodular leukoplakia by means of microbiological and histological analysis (3,5,10), which corroborates our case, which presented extensive fungal colonization in the surface of epithelial lining as well as microabscesses of Munro. Besides, the presence of *Candida* and epithelial dysplasia is higher in multiple oral leukoplakia than in single oral leukoplakia (11). Some studies demonstrated that *Candida* invasion within the oral mucosa may induce an hyperplastic reaction that is a protective response of the host (12) and have an important association with moderate and severe epithelial dysplasia (13). According to Chiu et al. (11), nitrosamine compounds produced by *Candida* species may directly, or in concert with other chemical carcinogens, activate specific proto-oncogenes and thus initiate the development of malig-

Zaključno, u našem prikazu slučaja ostaje nerazjašnjeno je li se epitelna displazija razvila iz inficirane čvoraste leukoplakije zbog kancerogenog potencijala *Candida* ili je infekcija tom gljivicom nastala zbog nepravilne bradavičaste površine leukoplakije koja omogućuje kolonizaciju i nema ulogu u pojavi displazije.

Bez obzira na sve što je navedeno, klinički homogena leukoplakija povezana s infekcijom *Candida albicans* može se promijeniti i postati ulcerirana ili po izgledu eritematoznija. Na kraju se takve lezije mogu razviti u čvorastu leukoplakiju (1). Za nju je indicirano korištenje antimikotika, premda lezija ne nestaje nakon što se uklone površinske mikoze. Uklanjanje gljivica može promijeniti klinički izgled nehomogene leukoplakije poput čvoraste, u homogeni oblik (1, 3, 10, 15).

Premda u našem prikazu slučaja nije bilo dokaza o kilocitima, ne možemo isključiti povezanost humanog papiloma virusa (HPV) s lezijom zbog hiperplastičnog epitela i nepušenja navedenog u anamnezi. HPV, posebice tip 16, pronađen je kod više od 80 posto oralnih leukoplakija, bez obzira na stupanj epitelne displazije (16) te u 50 posto orofaringealnih karcinoma skvamoznih stanica (17). Ipak je, suprotno navedenome, HPV pronađen u 12,5 posto čvorastih leukoplakija, što je niža prevalencija nego u drugim oblicima leukoplakija (18).

I na kraju, prikazani slučaj pokazuje koliko je za postavljanje točne dijagnoze važno odabrati pravo područje za biopsiju kod klinički nehomogenih leukoplakija, ali se ističe i nužnost uske suradnje između liječnika dentalne medicine i oralnog patologa.

Sukob interesa

Autori potvrđuju da zbog ovoga prikaza nisu u sukobu interesa.

nant lesions. Thus, following this line of reasoning, the fungal superinfection could be considered a significant risk factor for oncogenesis (14). However, it is still very controversial whether the *Candida* species are involved in the etiology or progression of leukoplakia (15) requiring additional studies for a better understanding. In conclusion, in our case report, there remains an unresolved question whether epithelial dysplasia developed from an infected nodular leukoplakia due to the carcinogenic potential of the fungus or if the *Candida* infection was due to irregular verrucous surface of leukoplakia that provides niches for colonization, having no participation in the occurrence of dysplasia.

Regardless, the clinically homogeneous leukoplakia associated with a *Candida albicans* infection may change and become ulcerated or have a more erythematous appearance. Such a lesion may eventually develop into a nodular leukoplakia (1). The use of antifungals has been indicated for nodular leukoplakia; although the lesion does not disappear on eradication of this surface mycosis, eliminating the fungus may change the clinical aspect of non-homogeneous such as nodular to the homogeneous type of leukoplakia (1,3,10,15).

Although our case report showed no evidence of koilocytes, we cannot rule out the possibility of an association of human papillomavirus (HPV) with the lesion due to hyperplastic epithelium and absence of tobacco history. The HPV, especially the type 16, has been found in more than 80% of oral leukoplakias, irrespective of the degree of epithelial dysplasia (16), and in 50% of oropharyngeal squamous cell carcinoma (17). On the other hand, the HPV infection has been encountered in 12.5% of the nodular leukoplakias, demonstrating lower HPV prevalence than in other types of leukoplakia (18).

Finally, the present case reinforces the importance of a proper selection of the area to be biopsied in clinically non-homogeneous leukoplakias, and a close collaboration between a dentist and oral pathologist to establish an accurate diagnosis.

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Abstract

Nodular leukoplakia is a non-homogeneous type of oral leukoplakia presenting a white surface with verrucous, nodular, ulcerated or erythematous features with a greater risk of malignant transformation when compared to the homogeneous type. Common sites of involvement include lip commissures, buccal mucosa and soft palate. It is often associated with epithelial dysplasia or carcinoma and requires detailed microscopic assessment and regular follow-up. The importance of a proper selection of the area to be biopsied and the close teamwork between a dentist and oral pathologist is the basis of providing an accurate final diagnosis.

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Key words
Oral Leukoplakia; Squamous Cell Carcinoma; Precancerous Conditions; Biopsy; Mouth Mucosa

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