UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

JOÃO MATEUS MENDES CERQUEIRA

TRANSFORMAÇÃO MALIGNA DA LEUCOPLASIA ORAL: UM ESTUDO MULTICÊNTRICO RETROSPECTIVO NA POPULAÇÃO BRASILEIRA

MALIGNANT TRANSFORMATION OF ORAL LEUKOPLAKIA: A MULTICENTRIC RETROSPECTIVE STUDY IN BRAZILIAN POPULATION

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Dissertação apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Mestre em Estomatopatologia, na Área de Estomatologia

Dissertation presented to the Piracicaba Dental School of the University of Campinas in partial fulfillment of the requirements for the degree of Master in Oral Medicine and Oral Patology, in Stomatology area

ORIENTADOR: PROF. DR. HELDER ANTONIO REBÊLO PONTES

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RESUMO

Antecedentes: Dentre os distúrbios orais potencialmente malignos, destaca-se a leucoplasia como o mais predominante. O objetivo deste estudo foi analisar as características clínico-patológicas de leucoplasia oral em grupos de pacientes oriundos de três grandes centros de patologia em duas diferentes regiões do Brasil, a fim de determinar quais fatores estariam associados ao risco clínico dos pacientes que tiveram transformação maligna. **Materiais e métodos:** Um total de 148 pacientes tiveram dados referente a sexo, idade, localização, classificação do subtipo clínico, hábitos deletérios como uso de tabaco e álcool e tempo de evolução e presença de displasia coletados e analisados. A associação entre os fatores de risco e a transformação maligna foi investigada utilizando o teste do qui-quadrado e o exato de Fischer para correlação de variáveis. Foi adotado nível de significância de 5% ($p \leq 0,05$). **Resultados:** A idade média dos pacientes era 60 anos, e 56% eram mulheres. Maior parte das lesões (34,5%) estava localizada nas regiões ventral e lateral da língua. Dos 148 pacientes, 90 tinham acompanhamento clínico. Transformação maligna ocorreu em 13 pacientes (8,8%), que tinham uma média de 44 meses de acompanhamento. **Conclusão**: Não fumantes, apresentação clínica não homogênea, localização na língua, e presença de alto grau de displasia foram fatores relevantes estatisticamente, associados com um alto risco de transformação.

Palavras-chave: Distúrbios pontecialmente malignos, leucoplasia, transformação maligna, carcinoma de células escamosas.

ABSTRACT

Background: Among the oral potentially malignant disorders, leukoplakia stands out as the most prevalent. The purpose of this study was to analyse the clinical-pathological features of oral leukoplakia in groups of patients from three major pathology centers in two different regions of Brazil, in order to determine which factors would be associated to the clinical risk of malignant transformation. **Methods**: A total of 148 patients was analyzed, and data regarding gender, age, site, classification of the clinical subtype, harmful habits such as use of tobacco and alcohol, time of evolution and presence of dysplasia were collected. The association between risk factors and malignant transformation was investigated using the chi-square test and Fischer's exact test for correlation of variables. A significance level of 5% ($p \leq 0.05$) was used. **Results**: The mean age of the patients was 60 years, and 56% were female. Most of the lesions (34,5%) were located in the lateral and ventral regions of the tongue. Of the 148 patients, ninety had clinical follow-up. Malignant transformation occurred in 13 patients (8.8%), with an average of 44 months of follow up. **Conclusion:** Non-smoker, nonhomogeneous clinical presentation, location at the tongue, and the presence of high degree of dysplasia were statistically relevant factors associated with a higher risk of transformation transformation.

Keywords: Potentially malignant disorders. Leukoplakia. Malignant transformation. Squamous cell carcinoma.

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1 INTRODUÇÃO

Considerando as desordens orais potencialmente malignas, a leucoplasia se posiciona como sendo a mais comum, possuindo uma prevalência mundial de 1% a 5%. Segundo a Organização Mundial da Saúde (OMS), ela se classifica como uma placa branca de risco discutível e cujo diagnóstico diferencial exclui outras doenças ou distúrbios já conhecidos que não apresentam risco aumentado para câncer (Wetzel et al, 2020). Estudos têm demonstrado taxas de transformação maligna das leucoplasias em torno de 9,3% (Iocca et al, 2020), outros se dedicam a estudar suas taxas de recorrência, que podem variar de 13,5% a 17%, além de discutir formas de tratamento (Holmstrup et al, 2006; Pandey et al, 2001).

Diante de um quadro em que se busca continuamente o diagnóstico precoce do carcinoma espinocelular oral, faz-se necessário o estudo das leucoplasias para que possam ser identificadas com maior eficácia e manejadas de forma a prevenir o surgimento dos distúrbios malignos de ruim prognóstico e que deixam comorbidades, dificultando a qualidade de vida dos pacientes. Este estudo visa identificar os diferentes fatores clínicos e microscópicos das leucoplasias orais que estejam associados a transformação maligna em uma amostra da população brasileira.

2 ARTIGO

MALIGNANT TRANSFORMATION OF ORAL LEUKOPLAKIA: A MULTICENTRIC RETROSPECTIVE STUDY IN BRAZILIAN POPULATION.

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ABSTRACT

Background: Among the oral potentially malignant disorders, leukoplakia stands out as the most prevalent. The purpose of this study was to analyse the clinical-pathological features of oral leukoplakia in groups of patients from three major pathology centers in two different regions of Brazil, in order to determine which factors would be associated to the clinical risk of malignant transformation.

Methods: A total of 148 patients was analyzed, and data regarding gender, age, site, classification of the clinical subtype, harmful habits such as use of tobacco and alcohol, time of evolution and presence of dysplasia were collected. The association between risk factors and malignant transformation was investigated using the chi-square test and Fischer's exact test for correlation of variables. A significance level of 5% ($p \leq 0.05$) was used.

Results: The mean age of the patients was 60 years, and 56% were female. Most of the lesions (34,5%) were located in the lateral and ventral regions of the tongue. Of the 148 patients, ninety had clinical follow-up. Malignant transformation occurred in 13 patients (8.8%), with an average of 44 months of follow up.

Conclusion: Non-smoker, nonhomogeneous clinical presentation, location at the tongue, and the presence of high degree of dysplasia were statistically relevant factors associated with a higher risk of transformation transformation.

Keywords: Potentially malignant disorders, leukoplakia, malignant transformation, squamous cell carcinoma.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity, representing 95% of all malignant neoplasms in this anatomical site[1]. In spite of the strides which have been made in multimodal therapy, the low survival rates have not significantly improved over the last decades[1,2]. Additionally, most patients with OSCC may be affected by several morbidities, including severe functional and cosmetic defects, mucositis, xerostomia and osteoradionecrosis, which impair the patients' quality of life[3].

Given this complex clinical scenario associated with oral cancer management, the search for effective screening methodologies that aim to identify oral potentially malignant desorders (OPMDs) with higher efficacy and therefore, improve the prognosis of these patients, remains desirable and must be performed. OPMDs represent a group of lesions which carry an increased risk of cancer progression, and most (if not all) OSCCs are preceded by these lesions, particularly oral leukoplakia (OL)[4]. OL has a worldwide prevalence of 1-5%, and it is defined by the World Health Organization (2017) as "a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer"[5].

A recent meta-analysis of 32 studies presented an estimated overall mean proportion rate of malignant transformation (MT) of 9,3% for OL[6]. Other studies have described an annual recurrence rate about 13,5%-17%, following surgical excision[7,8]. This is partly due to the study design, variation between ethnic groups, and geographical differences, as well as populations' local habits[9]. Therefore, this study aimed to evaluate the importance of different clinical and microscopic factors for malignant transformation of OL in a Brazilian sample.

MATERIAL AND METHODS

This study was conducted in accordance with the human ethics guidelines, and approved by the University Hospital João de Barros Barreto, Belém, Brazil (process no. 3.805.374).

Study population

All cases diagnosed as OL between January 2010 and November 2019 were retrospectively retrieved from the pathology files of three Brazilian institutions, as follows: Oral Pathology Service of the João de Barros Barreto University Hospital (Belém); Piracicaba Dental School of the University of Campinas (Piracicaba), and the School of Dentistry of the Universidade Federal de Minas Gerais (Belo Horizonte). All cases were confirmed by microscopic examination following incisional or excisional biopsies.

Inclusion criteria

The inclusion criteria comprised cases with clinical presentation of OL, which followed the current guidlines of the World Health Organization Classification of Head and Neck Tumours[10]. Only patients with OL diagnosis and no other concomitant lesions were included in this study.

Demographic and clinicopathological data retrieved included: gender, age, disease location, number ans size of lesions, smoking and/or drinking habit, clinical aspects of the lesion, histopathological diagnosis (including presence of epithelial dysplasia according to binary system), follow-up time (months), status at last follow-up (alive or dead), and time of malignant transformation (months). The patient's identity remained anonymous according to the Declaration of Helsinki.

According to the size, the lesions were classified as having less or more than 2cm, as suggested by Speight et al. (2018)[9]. The patients were divided according to their habits, into 4 groups: current smokers, non-smokers, drinkers, and non-drinkers.

All clinical images were evaluated to confirm the clinical diagnosis of OL and to determine the clinical subtype, as homogeneous or nonhomogeneous[10-12]. Homogeneous leukoplakia was characterized by a flat, thin or thick and uniform white plaque with well-defined margins, exhibitting shallow cracks within a smooth, wrinkled or corrugated surface of constant texture. Nonhomogeneous leukoplakia presents different areas of nodular, speckled, granular, and verrucous surface[12]. Proliferative verrucous leukoplakia (PVL) is a variant of nonhomogenous leukoplakia, with unknown etiology, which progressively becomes multifocal, and frequently involves the gingiva/alveolar mucosa, buccal mucosa and ventral surface of tongue, as defined by the World Health Organization Classification of Head and Neck Tumours[10]. It is an uncommum and ominous form of OL, with an elevated probability of recurrence after excision, and a high rate of MT. Thus, we separately assessed PVL from nonhomogenous leukoplakia.

Exclusion criteria

The cases were excluded from our sample according to the following criteria: 1) lack of access to the histological material to allow confirmation of clinical diagnosis; 2) follow-up time of less than 6 months, since a period which encompasses less than 6 months between initial diagnosis and malignancy diagnosis may suggest a simultaneous occurrence of OL and cancer, leading to an overestimated malignant transformation rate of OL[13].

Histological sample

Formalin-fixed, paraffin-embedded tissues were stained routinely with haematoxylin and eosin (H&E), and analysed by using conventional light microscope. Expert pathologists in the scope of this study without prior knowledge of the clinical data assessed the histological slides to establish histological grades for each case.

Oral epithelial dysplasia was classified following the binary grading system, proposed by Kujan et al.[14], which labelled the cases as having low risk and/or high risk of malignization.

Statistical analysis

All gathered data was organized into a database by using the GraphPad Prism (GraphPad Software, In., San Diego, CA), version 8.0. The clinicopathological variables were then submitted to the Chi-square test and Fisher exact test for association. A significance level of 5% ($p \leq 0.05$) was adopted.

RESULTS

Clinicopathological features

From january 2010 to november 2019, a total of 148 patients diagnosed with OL and that fulfilled the required criteria were included in this study. Most of the patients were females (56%), in which the male/female ratio was 1.3/1. The mean age of the patients was 60 years, and most were between 50 to 60 years old. The most involved sites were lateral/ventral surfaces of the tongue (51 cases; 34.5%), followed by multifocal areas (29 cases; 19.6%), palate (21 cases; 14.2%), buccal mucosa (21 cases; 14.2%), alveolar ridge (10 cases; 6.8%), gingiva (9 cases; 6%), and floor of mouth (7 cases; 4.7%). Homogeneous leukoplakia was found in 39.9% (59) of the cases, while nonhomogeneous lesions comprised 38.5% (57 cases). Thirty-two cases were diagnosed as PVL (21.6%). As demonstrated in **Table 1**, twenty-seven cases had a size of ≤ 2cm, and 121 cases were > 2cm. **Figure 1** illustrates the clinical presentation of different OLs, and **Figure 2** demonstrates 2 cases which progressed to OSCC. From the cases that showed dysplasia at the initial diagnosis, 39.2% (58 cases) were considered as having high risk of malignization. Most patients of the cohort

(79 cases; 53.4%) were non-smokers, and 30.4% reported regular alcohol consumption (**Table 1**).

Malignant transformation

Ninety patients had available clinical follow-up. A mean follow-up of 36 months was observed. A total of 13 OLs developed OSCC during the follow-up period, resulting in a MT rate of 8.8%, with a mean follow-up of 44 months (**Table 1**). We found that the progression from OL to malignacy mostly occured in women (8 cases; 61.5%). In addition, the cases who underwent MT comprised patients with an average age of 56 years, ranging from 31 to 76 years at the time of cancer diagnosis. The lateral and ventral surfaces of the tongue were the most common sites for OSCC development. Meanwhile, other tumour sites equally affected the buccal mucosa, gingiva, and alveolar ridge, comprising one case in each location. In relation the PVL, we found only 7.7% of MT rate.

Statistical analysis showed that the clinicopathological variables which were significantly associated with a higher risk of MT of OL were nonhomogenous lesions (p = 0,0231), lesions located on the tongue (p = 0,0313), OL with high-grade dysplasia (p = 0,0344), and non-smokers patients (p = 0,0047) (**Figure 3**).

DISCUSSION

Despite several proposals to characterize the clinical, molecular and microscopic risks of malignant transformation of OL[4,15-17], it is still difficult to predict which type OL will progress to a malignant neoplasm. The MT rate of OL seems to varies among different populations, showing the possible relevance of environmental and host factors[18,19]. Although Brazil is a country with the size of a continent, few studies have evaluated the malignant transformation rate of OPMDs, including OL[20].

We found a cumulative MT rate of 8.8% of OL, with an average period of follow-up of 44 months, similarly to the results found by Villa et al. (2018)[12] in northen Spain, and the records of a recent meta-analysis, which reported a MT rate of 9.7%[15]. In contrast, some studies have shown a MT rate about 12%[7], while other authors demonstrated a MT rate lower than 2%[16,21].

Considering the clinical subtype of OL, our findings are in line with the literature, confirming the high potential of MT of nonhomogenous leukoplakia[12,21,22]. Although there is a consensus that PVL has a MT rate higher than 60%[9,12,23], we found a MT rate of only 8% among the cases described as PVL. It is likely that the short follow-up time (36-months) may in part justify our results, since a longer period can be necessary to the evolution of PVL to OSCC. This period may range from 7 to 15 years[23-25], with an average estimated time for MT of 5 to 6 years after diagnosis of PVL[9,26].

It has been stated that histopatholgy alone is not able to provide a MT risk assessment for OL. Besides, oral dysplasia is not considered an indispensable precursor of OSCC, and not all dysplasic OL will transform into cancer[9,16]. However, the role of microscopic evaluation cannot be neglected. In fact, our results indicated that the high grade of dysplasia had a significant association with greater risk of malignization, as reported in several studies[6,9,12,27,28]. We adopted the binary grading system because it has been considered to present more reproducibility, a best prognostic value, superior reliabiliry, and higher intra/interobserver agreement in comparison with the system proposed by the World Health Organization[9,14].

We also observed a significant higher risk of MT of OL involving the tongue as previously described[11,16,22,28,]. This is possibly because the cases of tongue OL mostly comprised nonhomogeneous subtypes and demonstrated a high degree of dysplasia.

Other possible explanation is related to the high frequency of aneuploidy and loss of heterozygosity of tongue OL, described by several reseachers[29].

Despite the literature has indicates that OL with a size > 200 mm^2 presented an increased risk for developing cancer[7,11,19], our results did not show any significant difference between the lesions with > 200 mm^2 and < 200 mm^2 sizes. This conflicting result may be explained by the fact that the approximately 25% of the lesions > 200 mm^2 was PVL, with a limited follow-up period.

Our study also found that smoking was not a significant risk factor for OL malignancy, which is in line with other studies[9,21]. Although there are similarities in the genetic alterations found in smokers and non-smokers whose cases suffered MT into oral squamous cell carcinoma[28], previous studies have described a significantly elevated risk for malignant progression in non-smokers[9,28-30], as we observed. Taken together, these data suggest that tobacco plays a crucial role in the formation of keratotic lesions. Subsequently, other factors, which remains unidentified, take the leading role in the progression to malignancy[9,29]. In fact, it is unclear why dysplasic OL in non-smokers presents higher risk for MT compared to those that affect smokers.

The major strength of our study was the paticipation of three oral pathology centers from two different regions of Brazil. In contrast, this study has some noteworthy limitations. First, as mentioned above, our sample presented a limited follow-up time for monitoring PVL cases. Second, the group of non-smokers included some ex-smokers with variable periods of habit cessasion, althoug most individuals had stopped smoking 10 years previously. Finally, 58 patients (39,2%) were lost to follow-up over the study period.

In conclusion, non-smokers, nonhomogeneous clinical presentation, location at the tongue, and the presence of high degree of dysplasia were associated with a higher risk of malignant transformation.

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Table 1. Distribution of risk factors of the 148 patients and malignant transformation rates.

Risk factors	Patients	
		Malignancy +
Sex		
Men	65 (44)	5 (38.5)
Woman	83 (56)	8 (61.5)
Age		
≤60	77 (52)	8 (61.5)
>60	71 (48)	5 (38.5)
Location		
Tongue	51 (34.5)	10 (76.9)
Floor of Mouth	7 (4.7)	-
Palate	21 (14.2)	-
Buccal Mucosa	21 (14.2)	1 (7.7)
Gingiva	9 (6)	1 (7.7)
Alveolar Ridge	10 (6.8)	1 (7.7)
Multifocal Areas	29 (19.6)	-
Clinical Subtype		
Homogeneous	59 (39.9)	2 (15.4)
Non-homogeneous	57 (38.5)	10 (76.9)
Non-homogeneous (LVP)	32 (21.5)	1 (7.7)
Size of lesion		
≤ 2 cm	27 (18.2)	-
> 2 cm	121 (81.8)	13 (100)
Numbers of lesions		
Simple	99 (67)	11 (84.6)
Multiple	49 (33)	2 (15.4)
Smoking habits		
Non-smoker	79 (53.4)	11 (84.6)
Smoker	49 (33.1)	2 (15.4)
Unknown	20 (13.5)	-
Alcohol consumption		
Non-drinker	78 (52.7)	8 (61.5)
Drinker	45 (30.4)	5 (38.5)
Unkown	25 (16.9)	-
Initial Histopathologic diagnosis		
Non-Dysplasia	36 (24.3)	1 (7.7)
Dysplasia	112 (75.7)	12 (92.3)
Grade of dysplasia (binary sistem)		
Low Risk	90 (61)	4 (30.8)
High Risk	58 (39)	9 (69.2)
Total	148	13 (8.8)

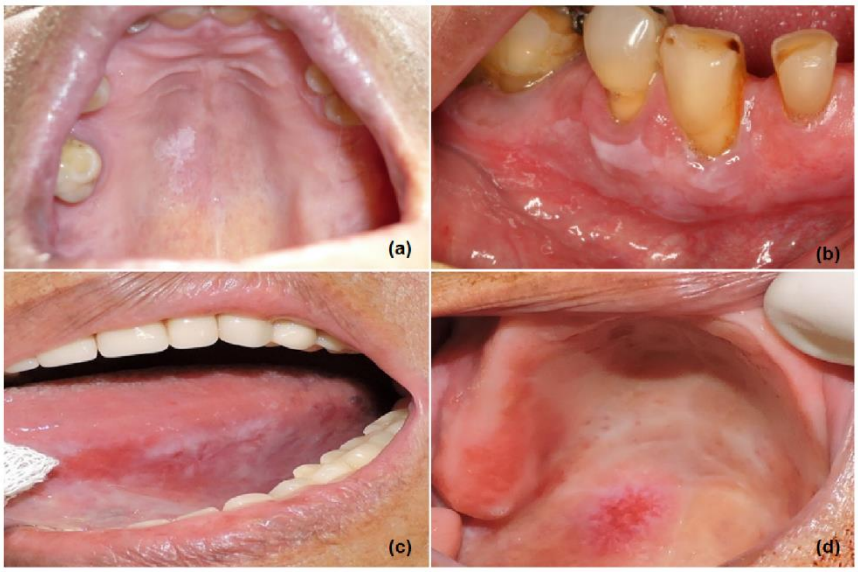
FIGURE LEGENDS

Figure 1. Different clinical presentations of oral leukoplakia.**1a:** A 63-year old male patient, non-smoker, presenting a single lesion on the hard palate, clinically diagnosed as homogeneous leukoplakia. Further microscopic analysis classified the specimen as being of low risk. **1b:** A flat, homogeneous leukoplakia involving the right inferior gingiva of a 78-year old , non smoker female, whose lesion was microscopically considered of low risk. **1c:** A 71 year-old female former smoker exhibiting an extensive lesion with variation of color, on the left border of the tongue, classified as nonhomogeneous leukoplakia. The case was classified as having high risk after microscopic assessment. **1d**: An 82year-old female and non smoker patient, presenting a reddish and white lesion on the palate, which did not show any dysplasia on the microscopic analysis, being classified as low risk.

Figure 2. Cases of proliferative verrucous leukoplakia. **2a**: White and reddish lesions of nodular and flat aspects involving the left and right sides of the palate, respectively. The patient is a 75-year old male smoker. The more dense lesion was microscopically classified as high risk. **2b:** A 74-year old male and tobacco user presenting a large lesion, which covered both sides of the hard palate. **2c:** A 31-year old non-smoker female patient, whose prior diagnosis was LVP, was diagnosed with squamous cell carcinoma in the left tongue border after a 71-month follow-up period. **2d:** Another case which progressed to OSCC. A 55-year old male, non-smoker, was initially diagnosed with nonhomogeneous leukoplakia. The malignant transformation occurred after 19 months of follow-up.

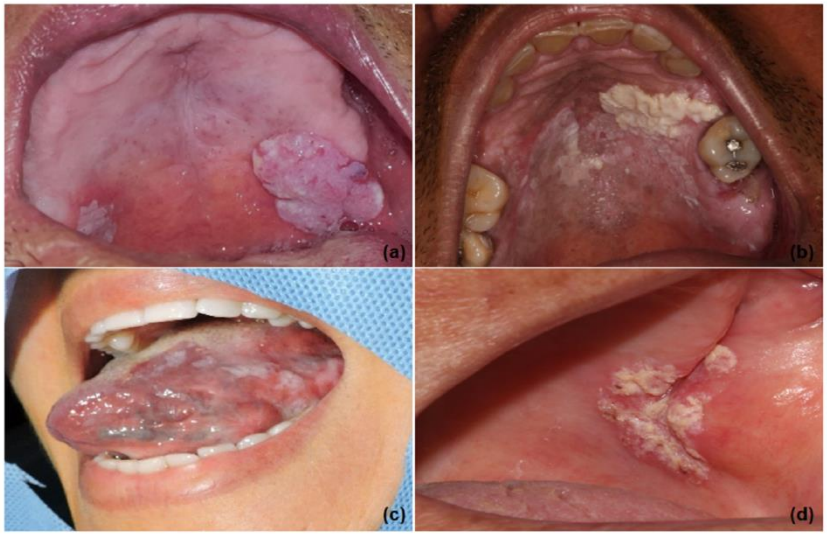
Figure 3. Comparison used the Fisher's test for the establishment of relations between the malignancy and lesions homogeneous x non homogeneous (**a**) high risk dysplasia x low risk (**b**) smokers x non-smokers (**c**) and location (**d**).

FIGURE 1



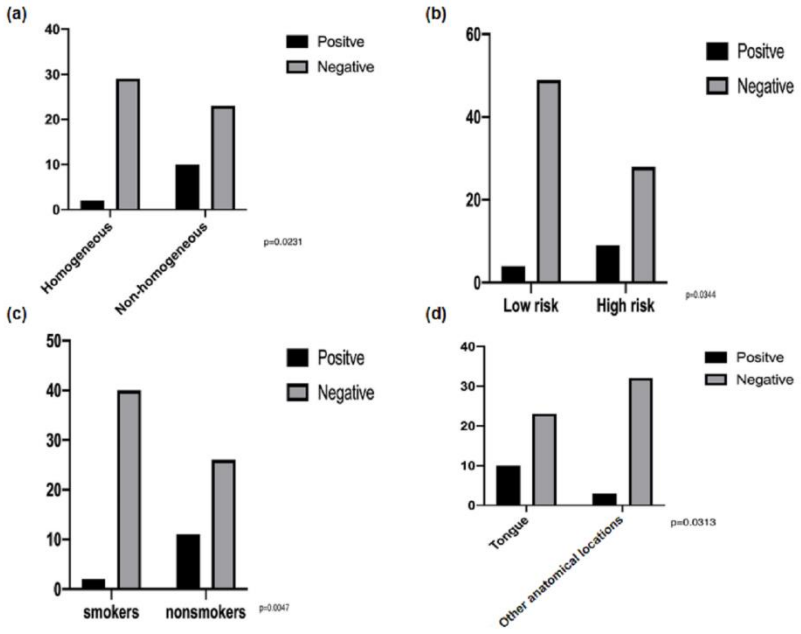
Different clinical presentations of oral leukoplakia.**1a:** A 63-year old male patient, non-smoker, presenting a single lesion on the hard palate, clinically diagnosed as homogeneous leukoplakia. Further microscopic analysis classified the specimen as being of low risk. **1b:** A flat, homogeneous leukoplakia involving the right inferior gingiva of a 78-year old , non smoker female, whose lesion was microscopically considered of low risk. **1c:** A 71 year-old female former smoker exhibiting an extensive lesion with variation of color, on the left border of the tongue, classified as nonhomogeneous leukoplakia. The case was classified as having high risk after microscopic assessment. **1d**: An 82year-old female and non smoker patient, presenting a reddish and white lesion on the palate, which did not show any dysplasia on the microscopic analysis, being classified as low risk.

FIGURE 2



Cases of proliferative verrucous leukoplakia. **2a**: White and reddish lesions of nodular and flat aspects involving the left and right sides of the palate, respectively. The patient is a 75-year old male smoker. The more dense lesion was microscopically classified as high risk. **2b:** A 74-year old male and tobacco user presenting a large lesion, which covered both sides of the hard palate. **2c:** A 31-year old non-smoker female patient, whose prior diagnosis was LVP, was diagnosed with squamous cell carcinoma in the left tongue border after a 71-month follow-up period. **2d:** Another case which progressed to OSCC. A 55-year old male, non-smoker, was initially diagnosed with nonhomogeneous leukoplakia. The malignant transformation occurred after 19 months of follow-up.

FIGURE 3



Comparison used the Fisher's test for the establishment of relations between the malignancy and lesions homogeneous x non homogeneous (**a**) high risk dysplasia x low risk (**b**) smokers x non-smokers (**c**) and location (**d**).

3 CONCLUSÃO

Nos grupos de pacientes estudados, oriundos de três grandes centros de patologia de duas diferentes regiões do Brasil, não fumantes, apresentação clínica não homogênea, localização na língua e presença de alto grau de displasia foram os fatores associados a um maior risco de transformação maligna.

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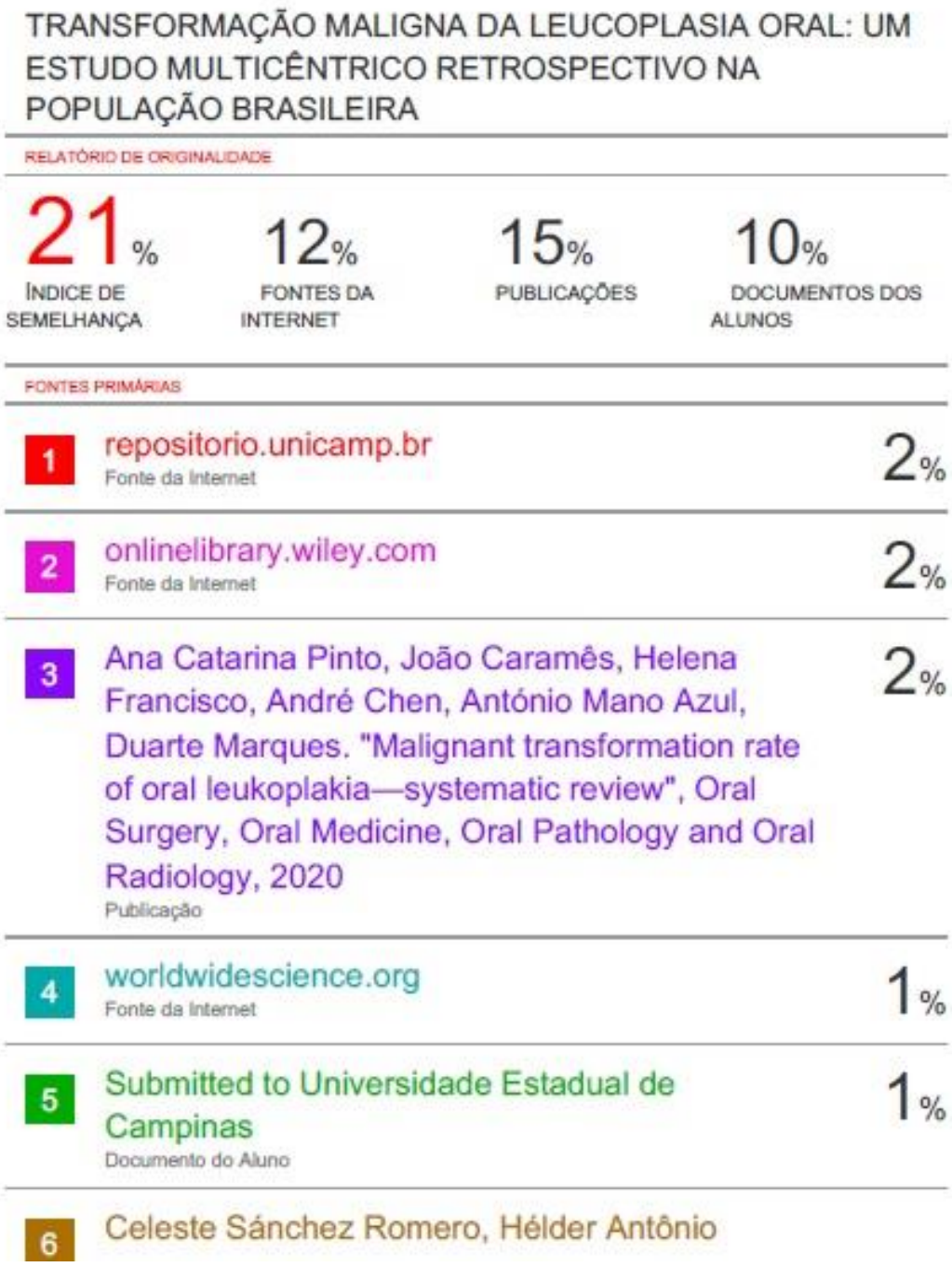
ANEXOS

Anexo 1 – Verificação de originalidade e prevenção de plágio



TRANSFORMAÇÃO MALIGNA DA LEUCOPLASIA ORAL: UM ESTUDO MULTICÊNTRICO RETROSPECTIVO NA POPULAÇÃO BRASILEIRA

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Anexo 2 - Certificado do Comitê de Ética em Pesquisa

UNICAMP - FACULDADE DE ODONTOLOGIA DE PIRACICABA DA UNIVERSIDADE DE CAMPINAS - FOP/UNICAMP

PARECER CONSUBSTANCIADO DO CEP

Elaborado pela Instituição Coparticipante

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: AVALIAÇÃO DE LESÕES LEUCOPLÁSICAS EM UM CENTRO DE REFERÊNCIA EM PATOLOGIA ORAL: ACHADOS EPIDEMIOLÓGICOS, CLÍNICOS E HISTOPATOLÓGICOS

Pesquisador: HÉLDER ANTÔNIO REBELO PONTES

Área Temática:

Versão: 2

CAAE: 18584719.1.3001.5418

Instituição Proponente: Faculdade de Odontologia de Piracicaba - Unicamp

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.818.000

Apresentação do Projeto:

Transcrição editada do conteúdo do registro do protocolo e dos arquivos anexados à Plataforma Brasil

A LISTA DE PESQUISADORES citada na capa do projeto de pesquisa inclui HÉLDER ANTÔNIO REBELO PONTES (Cirurgião Dentista, Docente da Faculdade de Odontologia/ Universidade Federal do Pará e Docente colaborador do Programa de Pós-Graduação em Estomatopatologia da FOP-UNICAMP, Pesquisador responsável, Orientador), FLAVIA SIROTHEAU CORREA PONTES (Cirurgiã Dentista, Docente da FO da UFPA, Pesquisadora participante) e LIGIA AKIKO NINOKATA MIYAHARA (Cirurgiã Dentista, Doutoranda no PPG em Estomatopatologia da FOP-UNIAMP, Pesquisadora participante, Orientanda), o que é confirmado na PB.

Trata-se de protocolo em que a FOP-UNICAMP foi classificada como centro coparticipante da pesquisa originalmente aprovada pelo CEP da UFPA - HOSPITAL UNIVERSITÁRIO JOÃO DE BARROS BARRETO DA UNIVERSIDADE FEDERAL DO PARÁ em data não informada (o parecer de aprovação inicial não foi disponibilizado). A inclusão da FOP-UNICAMP como centro coparticipante foi solicitada em emenda em 09/10/2019 e aprovada em 21/01/2020.

Pendência 1 (atendida em 01/02/20)– Foi apresentado o parecer de aprovação original do

UNICAMP - FACULDADE DE ODONTOLOGIA DE PIRACICABA DA UNIVERSIDADE DE CAMPINAS - FOP/UNICAMP

Continuação do Parecer: 3.818.000

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

PIRACICABA, 01 de Fevereiro de 2020

Assinado por:
jacks jorge junior
(Coordenador(a))

Anexo 3 – Documento de submissão do artigo

Journal of Oral Pathology and Medicine - Proof for Peer Review

MALIGNANT TRANSFORMATION OF ORAL LEUKOPLAKIA: A MULTICENTRIC RETROSPECTIVE STUDY IN BRAZILIAN POPULATION

Journal:	*Journal of Oral Pathology and Medicine*
Manuscript ID	JOPM-06-20-OA-6193
Manuscript Type:	Original Article
Date Submitted by the Author:	12-Jun-2020
Complete List of Authors:	Cerqueira, João Mateus; Department of Surgery and Oral Pathology - João de Barros Barreto University Hospital; Dental School, UNICAMP, Oral Diagnosos Pontes, Flávia Sirotheau; João de Barros Barreto University Hospital, Federal University of Pará, Service of Buccal Pathology Santos-Silva, Alan Roger; Dental School, UNICAMP, Oral Diagnosis Vargas, Pablo Agustin; School of Dentistry-UNICAMP, Oral Diagnosis - Oral Pathology Almeida, Oslei; Oral Pathology Costa, Rafael; Federal University of Minas Gerais, Department of Oral Surgery and Pathology Fonseca, Felipe; Universidade Federal de Minas Gerais, School of Dentistry - Department of Oral Surgery and Pathology Gomez, Ricardo; Universidade Federal de Minas Gerais, Departament of Oral Surgery and Pathology, School of Dentistry Conte Neto, Nicolau; João de Barros Barreto University Hospital, Federal University of Para, Service of Buccal Pathology Miyahara, Ligia ; João de Barros Barreto University Hospital, Oral Pathology; Dental School, UNICAMP, Oral diagnosis Rodrigues-Fernandes, Carla; Universidade Estadual de Campinas, Oral Diagnosis Galvão Neto, Elieser; João de Barros Barreto University Hospital, Federal University of Pará, Belém/Brazil, Service of Oral Pathology Araújo, Anna Luiza; Oral Diagnosis Department Lopes, Marcio; Dental School, UNICAMP, Oral Diagnosis; Pontes, Hélder; João de Barros Barreto University Hospital, Service of Oral Pathology; Dental School, UNICAMP, Oral diagnosis
Methods:	Epidemiology
Keywords:	Potentially malignant disorders, Leukoplakia, malignant transformation, squamous cell carcinoma
Abstract:	Background: Among the oral potentially malignant disorders, leukoplakia stands out as the most prevalent. The purpose of this study was to analyse the clinical-pathological features of oral leukoplakia in groups of patients from three major pathology centers in two different regions of Brazil, in order to determine which factors would be associated to the

	clinical risk of malignant transformation. Methods: A total of 148 patients was analyzed,and data regarding gender, age, site, classification of the clinical subtype, harmful habits such as use of tobacco and alcohol, time of evolution and presence of dysplasiawere collected. The association between risk factors and malignant transformation was investigatedusing the chi-square test and Fischer's exact test for correlation of variables. A significance level of 5% ($p \leq 0.05$) was used. Results:The mean age of the patients was 60 years, and 56% were female. Most of the lesions (34,5%) were located in the lateral and ventral regions of the tongue. Of the 148 patients, ninety had clinical follow-up. Malignant transformation occurred in 13 patients (8.8%), with an average of 44 months of follow up. Conclusion: Non-smoker, nonhomogeneous clinical presentation, location at the tongue, and the presence of high degree of dysplasia were statistically relevant factors associated with a higher risk of transformation.