UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

MARCUS VINÍCIUS RIBEIRO CARVALHO

LINFOMA DE CÉLULAS DO MANTO NA CAVIDADE ORAL E REGIÃO MAXILOFACIAL

MANTLE CELL LYMPHOMA IN THE ORAL AND MAXILLOFACIAL REGION

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Tese apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Doutor em Estomatopatologia, na Área de Patologia.

Thesis presented to the Piracicaba Dental School of the University of Campinas in partial fulfillment of the requirements for the degree of Doctor in Oral Medicine and Oral Pathology, in Pathology area.

Orientador: Prof. Dr. Felipe Paiva Fonseca

Este exemplar corresponde a versão final da tese defendida pelo aluno Marcus Vinícius Ribeiro Carvalho e orientada pelo Prof. Dr. Felipe Paiva Fonseca.

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RESUMO

O linfoma de células do manto (LCM) representa de 6 a 10% de todos os linfomas não-Hodgkin. Usualmente afeta nódulos linfáticos e está associado com um prognóstico pobre, embora algumas variantes possam demonstrar comportamentos mais indolentes e uma melhor taxa de sobrevida. Na região oral e maxilofacial o LCM é muito incomum, portanto, o objetivo deste estudo é investigar as características clinicopatológica e imunoistoquímicas de uma série de LCM que afetaram a boca e a região maxilofacial. Os arquivos de seis serviços de patologia foram avaliados, novos cortes histopatológicos corados em hematoxilina e eosina foram revisados por pelo menos dois patologistas e reações imunoistoquímicas foram realizadas para a confirmação diagnóstica. A detecção de EBV por hibridização in situ foi realizada como protocolo diagnóstico de nosso serviço em especial para linfomas de grandes células e os dados clínicos foram revisados por meio de análise dos prontuários clínicos dos pacientes. Vinte casos de LCM foram encontrados, afetando mais comumente a cavidade oral (palato) e depois a orofaríngea. Houve uma predominância de homens e a média de idade foi de 66 anos. Os tumores usualmente apresentaram-se clinicamente como um aumento de volume assintomático, mas dois casos revelaram-se como uma doença bilateral no palato. As variantes microscópicas clássica (12/20) e blastoide (5/20) predominaram, enquanto que 3/20 casos foram classificados como sendo do subtipo pleomórfico. Todos os casos expressaram CD20 e ciclina D1, enquanto que SOX11 foi observado em 9/13 casos. Seis casos expressaram CD5 e 16/19 casos expressaram Bcl2, ao passo que CD10 e Bcl6 foram encontrados em 2/20 e 4/16 casos, respectivamente. O índice de proliferação medido pela expressão de Ki67 variou significativamente, com um valor médio de 40% e o vírus EBV não esteve presente em nenhum dos casos investigados. Dados de acompanhamento clínico dos pacientes esteve disponível para seis pacientes, sendo que cinco pacientes permaneceram vivos e um paciente veio a óbito. Desta forma, concluímos que o LCM pode manifestar-se de forma incomum na cavidade oral e estruturas adjacentes, e a apresentação microscópica parece variar significativamente exigindo um alto grau de suspeição por parte de patologistas orais.

Palavras-chave: Linfoma de células do manto. Linfoma. Cavidade oral. Orofaringe, Tonsila.

ABSTRACT

Mantle cell lymphoma (MCL) represents 6 to 10% of all non-Hodgkin lymphomas. It usually affects the lymph nodes and is associated with a poor prognosis, although some variants may show more indolent behaviors and a better survival rate. In the oral and maxillofacial region MCL is very uncommon. Therefore, in this study we investigated the clinicopathological and immunohistochemical features of a series of MCL affecting this region. The files of six pathology services were searched, new histological sections stained in hematoxylin and eosin were revised by at least two pathologists and immunohistochemical reactions performed for diagnosis confirmation. In situ hybridization for EBV detection was done as a diagnostic protocol of our service in particular for big cell lymphomas and clinical data were retrieved from patients' pathology charts. Twenty cases were found, more commonly affecting the oral cavity (palate) and the oropharynx. Males predominated, and the mean age was 66 years-old. Tumors usually presented as an asymptomatic swelling, but two cases presented as a bilateral disease in the palate. The classic (12/20) and blastoid (5/20) microscopic variants predominated, while 3/20 cases were classified as small cell subtype and one as pleomorphic variant. All cases expressed CD20 and Cyclin D1, while SOX11 was seen in 9/13 cases. Six cases expressed CD5 and 16/19 cases expressed Bcl2, whereas CD10 and Bcl6 were found in 2/20 and 4/16 cases, respectively. The proliferation index measured by the Ki67 expression varied significantly, with a mean value of 40% and EBV was negative in all cases investigated. Follow-up data was available for six patients, five remained alive and one died. In conclusion, MCL may uncommonly manifest in the oral cavity and neighboring structures, and microscopic presentation varies significantly demanding high degree of suspicion by the oral pathologists.

Keywords: Mantle cell lymphoma. lymphoma. Oral cavity. Oropharynx. Tonsil

SUMÁRIO

1 INTRODUÇÃO

O Linfoma de Células do Manto (LCM) é um subtipo de linfoma derivado de células B localizadas na região do manto de folículos linfoides foi assim reconhecido por Banks et al. (1992) que na classificação Kiel era denominado de linfoma centrocítico. Ao longo dos anos, outros termos foram usados para este linfoma que nos ajudam a entender a origem de suas células. Durante o aprimoramento dos sistemas de classificação dos Linfomas Não-Hodgkin (LNH), outros termos foram usados como sinônimos: linfoma linfocítico de diferenciação intermediária, linfoma linfocítico intermediário e linfoma da zona do manto (Jaffe et al., 2016; WHO, 2017), linfoma maligno centrocítico, polipose linfomatosa maligna, linfoma de células do manto in situ (WHO, 2017).

O LCM foi primeiro descrito por Lennert em 1973 com o nome de Germinocitoma difuso. Na classificação de Kiel o termo foi alterado para Linfoma Centrocítico, publicado em 1974. Nesta época pensava-se que esta neoplasia se originava de centrócitos do centro germinativo (Gerard-Marchant et al., 1974). Nesta mesma época Berard e Dorfman descreveram o Linfoma Linfocítico grau intermediário baseando-se no conceito de que os núcleos das células tinham irregularidades intermediárias (Berard; Dorfman, 1974).

Na publicação da Working Formulation de 1982 não houve categoria específica para o LCM. A maioria se encaixava melhor na categoria de pequenas células difusas e clivadas. Os casos de LCM tipo clássico ficaram dentro de linfoma linfocítico pequeno e linfoma de células pequenas clivadas folicular. Casos de variantes blastoides provavelmente foram classificadas como linfoma difuso de grandes células ou linfomas linfoblásticos (Ioachim; Medeiros, 2009).

Quanto ao perfil epidemiológico do LCM, esta neoplasia representa de 6% a 10% de todos os LNH. Entre 1992 e 2001 este índice representava apenas 1,5% dos casos, provavelmente devido ao marcador ciclina D1 não estar disponível até então (Armitage; Weisenburger, 1998; Morton et al., 1992). Esta neoplasia afeta mais frequentemente homens na faixa etária da 6ª a 7ª década de vida com idade média de 63 anos, com uma maior incidência entre os indivíduos brancos (Armitage; Weisenburger, 1998; Samaha et al., 1998; Bosch et al., 1998; Barista et al., 2001).

O conhecimento da manifestação clínica do LCM revela que a maioria dos casos se apresenta com manifestações sistêmicas que configuram estágios avançados (III, IV) no momento do diagnóstico. Linfadenopatia é comum e generalizada, usualmente variando de 2 a 5 cm de tamanho e entre 30 e 60% dos pacientes afetados revelam quadros de hepatoesplenomegalia (Jares, Colome, Campo, 2007; Ioachim; Medeiro, 2009,

Wahed; Dasgupta, 2015; WHO, 2017; Naeim et al., 2018). Sintomas B (febre, sudorese noturna intensa e perda de mais de 10% do peso corporal em 6 meses) são relatados em aproximadamente 50% dos pacientes (Felle; Diebold, 2004; Ioachim; Medeiro, 2009; Swerdlow et al. 2017; WHO, 2017; Naeim et al., 2018). O sítio extranodal mais comumente envolvido pelo LCM é o trato gastrointestinal (Ferrer, et al., 2008) que se apresenta acometido em cerca de 75% (Ioachim; Medeiro, 2009). Outros locais também acometidos inclui o baço (Ioachim; Medeiro, 2009; Swerdlow et al. 2017; Naeim, et al., 2018) e o anel de Waldeyer (Swerdlow et al. 2017), enquanto a medula óssea está envolvida em cerca de 50 a 80% dos indivíduos (Felle; Diebold, 2004; Ioachim; Medeiro, 2009; Wahed; Dasgupta, 2015; Swerdlow et al. 2017). A cavidade oral é raramente acometida pelo LCM, geralmente apresentando-se como um crescimento assintomático e não-ulcerado em palato (Chang et al., 2003; Guggisberg et al., 2010; Wagner et al., 2021).

A maioria dos casos de LCM é muito agressiva; porém, alguns subtipos clínicos e microscópicos exibem um comportamento mais indolente (Naeim et al., 2018). A sobrevida média dos pacientes é bastante variável, mas diminui significativamente na presença de envolvimento leucêmico (Wahed; Dasgupta, 2015).

O estudo morfológico demonstra que o LCM se apresenta microscopicamente como uma proliferação monótona de células de tamanho pequeno a mediano com núcleos hipercorados e de formato irregular. O citoplasma é usualmente escasso e macrófagos podem ser identificados em alguns casos (Felle; Diebold, 2004). O padrão de crescimento do LCM geralmente resulta em apagamento da arquitetura do linfonodo podendo exibir três possíveis padrões: zona do manto, nodular e difuso. Incialmente há um infiltrado em forma de faixa no córtex do linfonodo denominado padrão de zona do manto com remanescentes circundantes do centro germinativo. Este padrão cresce em forma de banda em torno do centro germinativo reativo ou residual (Felle; Diebold, 2004). A zona do manto do folículo linfoide expande devido a proliferação de células neoplásicas formando um halo (Swerdlow et al. 2017). Posteriormente, o centro germinativo desaparece podendo resultar em um padrão de aspecto nodular. Isto ocorre através da infiltração do centro germinativo por células tumorais de forma maciça (Swerdlow et al. 2017). As células neoplásicas são arranjadas de forma imprecisa e devido ao crescimento centrípeto não há evidência do centro germinativo residual (Ioachim; Medeiro, 2009). Finalmente as células neoplásicas podem proliferar em um padrão difuso de crescimento. Nestes casos, os centros germinativos são observados apenas ocasionalmente de forma focal

(Swerdlow et al. 2017) e as células neoplásicas apagam a arquitetura do linfonodo (Swerdlow et al. 2017; Ioachim; Medeiro, 2009).

O LCM também apresenta variações morfológicas nas células neoplásicas. Sendo classificados como variantes: de células pequenas, clássica, blastoide ou pleomórfica. Na variante clássica ou típica as células neoplásicas de origem linfoide são monótonas, de tamanho pequeno a médio com citoplasma escasso. Os núcleos são irregulares com contornos levemente clivado e cromatina condensada, distribuída uniformemente; e nucléolo imperceptível (Naeim et al., 2018; Swerdlow et al. 2017). Em geral, o índice mitótico é baixo.

Na variante de células pequenas, o componente neoplásico assemelha-se fortemente ao encontrado na leucêmica linfocítica crônica, enquanto na variante blastoide as células neoplásicas estão entre o centrócito e o centroblasto, de tamanho médio semelhante aos linfoblastos. Com núcleo oval ou redondo, 2 a 5 nucléolos pequenos, basofílicos e ligeiramente aumentado. Seus nucléolos são mais proeminentes do que a variante clássica. Quase não há irregularidades nucleares. A cromatina é mais vesicular. Citoplasma escasso e ligeiramente basofílico com taxa mitótica muito maior do que a variante clássica. Geralmente apresenta padrão de crescimento mais agressivo (Ioachim; Medeiro, 2009; Naeim et al., 2018).

Na variante pleomórfica há predomínio de células grandes atípicas com características heterogêneas. Os núcleos são maiores e apresentam irregularidades. Com nucléolos mais proeminentes como na variante blastoide (Feller; Diebold, 2004). O índice mitótico é alto e comumente são observadas em pacientes que possuem históricos de recidivas (Norto, et al., 1995).

A variante clinicopatológica reconhecida pela OMS em 2017 como leucêmica não nodal denominada é também denominada de variante pró-linfoide devido a aparência das células ser semelhante aos pró-linfócitos (Swerdlow, et al., 2017) e estes casos são caracterizados pela presença de envolvimento do sangue periférico, da medula óssea e às vezes do baço, mas sem adenopatia significante (OMS, 2017).

Na variante denominada *like* zona marginal a zona do manto aparentemente é preservada, mas as células neoplásicas da zona marginal proliferam, expandindo-a. Estas células que se expandem para a zona marginal são semelhantes às chamadas células monocitoides que exibem um citoplasma amplo e claro, e um núcleo com morfologia semelhante à observada nas variantes clássicas e blastoides (Swerdlow, et al., 2017). Há predominância de células de tamanho médio com áreas que se assemelham aos centros

de proliferação observados no linfoma linfocítico de pequenas células (Naeim, et al., 2018; OMS, 2017).

Na neoplasia do manto in situ as células tumorais estão restritas a zona do manto que se apresenta hiperplásica e a arquitetura do linfonodo é preservada (OMS, 2017). A característica é de um linfonodo reativo sem evidência de expansão das células do manto (Swerdlow, et al., 2017). O diagnóstico se dá porque as células neoplásicas, principalmente da camada interna da zona do manto, exibem positividade nuclear para a proteína ciclina D1 (Naeim, et al., 2018; OMS, 2017; Swerdlow, et al., 2017).

A imunofenotipagem do LCM é característica de uma neoplasia de linhagem de células B madura e são positivas para IgM e especialmente para IgD. Preferencialmente, ao contrário de outros linfomas de células B, expressa a cadeia λ (cadeia leve lambda) em aproximadamente 50-60% dos casos. Além disto, expressa uma variedade de antígenos de células B incluindo CD19, CD20, CD22, CD75, CD79a, CD79b e FMC-7, sendo negativos para antígenos de célula T maduras como CD3 e CD45RO. Marcadores associados a células dendríticas foliculares (CDF) CD21, CD23 e CD35 também são negativos nos casos de LCM (Swerdlow et al. 2017; Ioachim; Medeiro, 2009).

O antígeno associado a células T CD5 é expresso de forma aberrante na maioria dos casos de LCM, porém há casos CD5-negativos (Navarro, et al., 2012). Marcadores de centro germinativo como CD10 e BLC-6 são geralmente negativos (Zanetto, et al., 2008). O LCM é quase sempre positivo para BCL-2 e de 90% a 95% dos casos são positivos para ciclina D1. A expressão nuclear de SOX11 também é uma característica desta neoplasia. O índice de proliferação celular mensurado por Ki67 é bastante variável e tem sido considerado um fator de determinação prognóstica em alguns estudos (Ioachim; Medeiro, 2009).

O evento genético característico do LCM é a translocação t(11;14)(q13;q32). Esta translocação cromossômica justapõe o gene da cadeia pesada da imunoglobulina (IgH) na região do cromossomo 14 a uma região em 11q13 que envolve o gene CCND1 responsável pela produção da proteína Ciclina D1 ou Bcl-1. Esta translocação ocorre em cerca de 95% dos casos no estágio pré-B de diferenciação na medula óssea (Royo, et al., 2011). Esta translocação resulta na sobre-expressão de ciclina D1 e consequentemente a desregulação do ciclo celular (Wahed; Dasgupta, 2015).

Tendo em vista que a manifestação oral e maxilofacial do LCM é incomum e pode representar um grande desafio diagnóstico para patologistas orais, o que pode comprometer o tratamento inicial dos pacientes afetados, o objetivo deste estudo é

caracterizar de forma detalhada as manifestações clínicas e microscópicas do LCM nestas regiões anatômicas.

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2 ARTIGO

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MANTLE CELL LYMPHOMA INVOLVING THE ORAL AND MAXILLOFACIAL REGION: A STUDY OF 20 CASES

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Abstract

Objective: To investigate the clinicopathological features of mantle cell lymphoma (MCL) involving the oral and maxillofacial region.

Methods: MCL cases were retrieved from the pathology database of six pathology laboratories. Original H&E slides and immunohistochemical reactions were reviewed for confirmation of the initial diagnosis. Clinical data of the cases were obtained from the patients' pathology and/or medical charts.

Results: Twenty cases were included in the study, showing a male predominance and a mean age of 66-years. The oral cavity (12 cases) and the oropharynx (5 cases) were the most commonly involved subsites. Most cases presented as asymptomatic swellings, with two cases showing bilateral involvement of the palate. The classic histological variant predominated (12/20 cases). All cases expressed CD20 with nuclear cyclin D1 positivity. SOX11 was seen in 9/13 cases, CD5 in 6/16 cases, Bcl2 in 16/19 cases, CD10 in 2/20 cases, and Bcl6 in 4/16 cases. Ki67 showed a mean proliferation index of 40.6%. EBV was negative in all cases investigated. Follow-up data was available for six patients, with five currently alive and one deceased.

Conclusion: MCL, albeit rare, may manifest in the oral and maxillofacial region. Its histological heterogeneity demands a high degree of diagnostic skill from pathologists.

Keywords: Lymphoma, Mantle cell lymphoma, Oral and maxillofacial region, Oropharynx, Tonsil.

Introduction

Mantle cell lymphoma (MCL) is a heterogeneous hematolymphoid neoplasm that represents 6 to 10% of all non-Hodgkin lymphomas (NHLs). It accounted for approximately 3,320 new cases diagnosed in Western countries in 2016, representing 4% of all lymphoid malignancies in the US and 7–9% in Europe.[1, 2] Elderly males are the most commonly affected patients, with lymph nodes being the most affected location. The neoplasm frequently manifests as a disseminated disease, usually associated with a poor prognosis, although rarer clinical variants may be associated with a better outcome.[1, 3]

MCL is histologically complex and may be composed of a monotonous proliferation of small-sized cells (classic and small cell/lymphocytic variants) or intermediate to large cells with abundant mitoses (blastoid variant), with the presence of significant pleomorphism and prominent nucleoli in some cases (pleomorphic variant).[4, 5] This heterogeneous morphology often complicates the diagnosis, demanding a high degree of diagnostic skill from pathologists. The molecular pathogenesis of MCL aids in its diagnosis, since this neoplasm is consistently associated with the t(11;14) (q13; q32) that leads to strong nuclear expression of cyclin D1 protein in neoplastic B cells, representing the hallmark oncogenic event of this neoplasm.[5] However, rare cases (< 5%) may not express cyclin D1, and in such cases, the expression of SOX11 significantly contributes to the final diagnosis.[2]

In the head and neck region its prevalence ranges from 1 to 10% of all NHLs. However, cases affecting the oropharynx, major salivary glands, and oral cavity are considered exceedingly rare.[6-10] Therefore, the aim of this study is to investigate the clinicopathological and immunohistochemical features of an original series of extranodal MCL affecting the head and neck, especially the oral and maxillofacial region.

Material and methods

Ethics statement

This study was conducted following approval by the Ethical Committee of the Piracicaba Dental School, University of Campinas, Piracicaba, Brazil (process no. 44647421.1.0000.5418). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Sample and data collection

All cases diagnosed as MCL affecting the oral and the maxillofacial region were retrieved from pathology database of the Universidade Federal de Minas Gerais (Belo Horizonte/Brazil), University of Campinas (Piracicaba/Brazil), Rio de Janeiro State University (Rio de Janeiro/Brazil), Private Pathology Service (Natal/Brazil), Pathology Institute of Araçatuba (Araçatuba/Brazil), University of Pretoria (Pretoria/South Africa) and Centro Clínico de Cabeza y Cuello (Guatemala City/Guatemala). The original H&E and immunohistochemistry slides, and/or the formalin-fixed paraffin-embedded tissues of all cases were obtained for histopathological revision by at least two pathologists using the current WHO guidelines for classification of Tumors of Hematopoietic and Lymphoid Tissues.[4] Clinicopathological data of the cases were obtained from the patients' pathology and/or medical charts, including sex, age, location of the lesion(s), clinical presentation, and status of the patient at their last follow-up appointment.

Immunohistochemistry (IHC)

Immunohistochemical reactions were performed on 3µm sections of the formalin-fixed paraffin-embedded tissues, which were dewaxed with xylene and rehydrated in an

ethanol series. The endogenous peroxidase activity was blocked using 10% hydrogen peroxide in a single bath for a duration of 15 minutes. Antigen retrieval was performed via pressure cooker heating with either Tris-HCl (pH 6.0) or EDTA (pH 9.0) solutions for 3 minutes. After washing with a PBS buffer (pH 7.4), the slides were incubated overnight with the following primary antibodies: CD20 (clone L26, dilution 1:300; Dako, Carpinteria, CA, USA), CD3 (polyclonal, dilution, 1:300; Dako, Carpinteria, CA, USA), CD5 (clone CD5/54/F6, dilution, 1:100; Dako, Carpinteria, CA, USA), Cyclin D1 (clone DCS-6, dilution 1:100; Dako, Carpinteria, CA, USA), SOX11 (clone CLO143, dilution 1:200; Sigma-Aldrich, St Louis, MO, USA), Bcl2 (clone 124, dilution 1:50; Dako, Carpinteria, CA, USA), Bcl6 (clone D-8, dilution 1:300; Santa Cruz, Santa Cruz, CA, USA), CD10 (clone 56C6, dilution 1:100; Dako, Carpinteria, CA, USA) and Ki67 (clone MIB-1, dilution 1:100; Dako, Carpinteria, CA, USA). The slides were subsequently exposed to highly sensitive horseradish peroxidase reagents (ADVANCE, Dako, Carpinteria, CA, USA) and diaminobenzidine tetrahydrochloride (DAB, Sigma-Aldrich, St Louis, MO, USA). Finally, the slides were counterstained with Carazzi hematoxylin for 3 minutes. Positive control sections were used for each antibody, while the negative control was obtained by omitting the specific primary antibody. Reactions were jointly evaluated by three Oral and Maxillofacial Pathologists and descriptively described for each marker, except for Ki67 whose positivity was obtained by counting the percentage of positive nuclei among 1000 cells in representative hotspot regions under higher magnification.

In situ Hybridization (ISH)

The presence of EBV was also investigated by ISH in several cases as part of the workflow protocol for lymphoma diagnosis, especially cases composed of intermediate

to large cells (aggressive microscopic variants). A fluorescein-labeled peptide nucleic acid probe (PNA) complementary to 2 nuclear-encoded RNAs (EBER) (Y5200, Dako, Glostrup, Denmark) was hybridized at 55°C for 90 minutes, following which labeling was performed using the PNA ISH detection kit (K5201, Dako). A single case of extranodal NK/T-cell lymphoma, nasal type, was used as a positive control. Carazzi hematoxylin was used for subsequent counterstaining. Cases were considered positive for EBV if dark blue staining was detected in the nuclei of the neoplastic cells.

Statistics

A descriptive analysis was performed, with categorical variables presented as absolute number and percentage, whereas continuous variables were presented as mean, standard deviation (SD), and range. SPSS software version 22.0 (IBM, Germany) was used for the statistical analyses.

Results

A total of 20 cases of extranodal MCL affecting the oral and maxillofacial region were retrieved. The clinicopathological features of this sample are summarized in **Table 1.** There was a male predominance (15 males: 5 females) with a male-to-female ratio of 3:1, and a mean age of 66 years (range 38 to 95 years). Patients reported a disease duration ranging from two to six months before seeking medical consultation. The oral cavity was affected in 12 cases and the oropharynx in five cases. The parotid gland, rhinopharynx, and nasopharynx were each affected in one case. Bone destruction was observed in two cases, while a single case showed extension to involve the maxillary sinus. In four cases patients also demonstrated other clinical manifestations including lymphadenopathy (2 cases) and peripheral blood involvement (2 cases). An asymptomatic swelling was the

most common clinical presentation, occasionally manifesting as bilateral or multiple synchronous tumors. Six cases presented with ulceration, although non-ulcerated smooth-surfaced tumors were also noted.

Histologically, all cases presented with a diffuse growth pattern. Twelve cases were classified as the classic variant of MCL **(Figure 1 A, B)**, where the neoplastic cells were small with irregular or cleaved nuclei and inconspicuous nucleoli, diffusely infiltrating the affected tissues. Scattered eosinophilic macrophages were identified, but in the absence of a so-called "starry sky" pattern. Mitotic figures were uncommon and necrosis was absent. Five cases were classified as the blastoid variant of MCL **(Figure 1C, D)**, containing small to intermediate-sized neoplastic cells with dispersed or condensed chromatin and prominent nucleoli. Macrophages were also noted, again without the "starry sky" pattern. Necrosis was seen focally in one case, and mitotic figures were more easily identified in the blastoid variant. Three cases were defined as the pleomorphic variant of MCL **(Figure 1D, E)**, given the prominent nucleoli, the extent of cytological atypia, and the abundant atypical mitotic figures.

The results of immunohistochemical reactions are detailed in **Table 2**. All cases were strong and diffusely positive for CD20 **(Figure 2A)**, while CD3 was negative in the neoplastic cells in all cases. CD5 was only expressed in 6/16 cases **(Figure 2B)**. All cases showed strong nuclear positivity for cyclin D1 **(Figure 2C)**. Bcl2 expression was seen in 16/19 cases **(Figure 2D)**, and neoplastic cells were rarely positive for germinal center markers such as Bcl6 (4/16) and CD10 (2/20), with no cases showing positivity for both markers simultaneously. SOX11 was expressed in 9/13 cases (69.2%) **(Figure 2E)**. Ki67 expression showed a mean value of 40.6% (range from 15 to 90%) **(Figure 2F)**. All 11 cases investigated for the presence of EBV via ISH were negative.

Data on therapy was scarcely available; with two patients receiving the R-CHOP regimen and one patient receiving CHOP therapy alone. Follow-up data was available for six cases, ranging from one to 69 months, demonstrating that five patients were alive and one deceased due to unknown reason.

Discussion

Mantle cell lymphoma is a mature B-cell lymphoma with increasing trends in the USA and Europe.[3, 11-14] Lymph nodes are typically the most commonly affected sites for MCL. Extranodal involvement is rarer but may also be found, more usually in the gastrointestinal tract and the head and neck region, which account for 39.7% and 39.1% of all extranodal cases, respectively.[11] Recently, the oropharynx was demonstrated to be the most affected subsite (66%) in the head and neck, while the oral cavity was only involved in 8.4% of the cases.[12] The current original series further contributed to the understanding of oral and maxillofacial MCL by describing the clinicopathological features of primary lesions and manifestations of an already leukemic condition.

MCL patients usually present in their sixth to seventh decades of life, with a median age of 70 years.[3, 14] This is in accordance with the current series and has also been previously documented for head and neck cases. Males predominate in most of the reported series,[1, 15] a feature also documented in the current sample. Cases involving the oral cavity usually present as asymptomatic non-ulcerated swellings, with the palate being the most affected subsite.[10,16,17] Two of our cases presented as diffuse bilateral swellings, one of which also showed simultaneous involvement of the upper lip. Both of these cases represented a late manifestation of leukemic disease. Kamel et al. (2020)[18] described 71.9% of nodal MCLs affecting multiple sites. In addition, previous reports

have also described non-ulcerated oral lesions affecting multiple subsites, including the palate bilaterally.[6]

MCL is histologically diverse and the current WHO classification of lymphoid tumors recognizes several histological variants.[4] Although the majority of cases are classified as the classic variant, characterized by small monotonous neoplastic cells, cases composed of larger or pleomorphic cells (blastoid or pleomorphic variants) may also be found.[19] The histological heterogeneity of MCL results in a broad diagnostic category with a high degree of suspicion required from the pathologist in addition to ancillary tests to reach a final diagnosis. This is exemplified in the current series containing classic, blastoid, and pleomorphic variants, some of which were initially diagnosed as diffuse large B-cell lymphoma, not otherwise specified.[20]

In recent decades the molecular pathogenesis of MCL has been better elucidated, leading to important diagnostic improvements. This neoplasm derives from naïve B-cells located in the mantle zone and characteristically expresses mature B-cell markers including CD20 and CD79a, as well as IgD. Both CD5 and Bcl2 are also commonly expressed. CD5-negative cases, although rare, are well described in the literature. In the current series there was a higher number of CD5-negative cases than previously described.[4, 9, 21] CD23 is typically negative and helps to differentiate MCL from CLL/SLL. Germinal center markers such as CD10 and Bcl6 are also usually negative, however, they may be aberrantly expressed in approximately 15.8% of the cases, [22, 23] as seen in the current series.

The primary molecular event for MCL development is the t(11;14)(q13;q32) translocation that juxtaposes the *CCND1* gene at 11q13 to the immunoglobulin heavy chain complex (IGH) at chromosome 14q32. This results in cyclin D1 overexpression leading to cell cycle dysregulation and survival, representing an important diagnostic tool

present in over 95% of cases. In most cases the neoplastic cells are diffusely positive for cyclin D1, however, Fuseya et al. (2020)[24] recently described a dot-like staining pattern in a single rare case. Moreover, hairy cell leukemia should be excluded in cases if only scattered positive nuclei are seen.[25]

Cyclin D1 and translocation-negative cases of MCL are well described, albeit rare, with mutations in the *CCND2* oncogene identified, and subsequent expression of cyclin D2 and cyclin D3. These findings are not of diagnostic significance; rather, nuclear expression of SOX11 is a reliable marker for identifying both cyclin D1-positive and cyclin D1-negative cases.[2, 21] In the current series all cases showed nuclear expression of cyclin D1, while nine of 13 cases expressed SOX11. Although both markers were found in the majority of neoplastic cells, two pleomorphic variants showed nuclear expression of cyclin D1 in less than 70% of the neoplastic population. The prognostic significance of SOX11 is still debatable, usually being associated with a worse prognosis. Unfortunately, we were unable to investigate its significance in the current series, but it is noteworthy that the less-aggressive non-nodal leukemic variant of MCL, characterized by peripheral blood, bone marrow, and splenic involvement in the absence of lymphadenopathy, is usually negative or only weakly positive for SOX11.[26]

MCL is usually diagnosed in advanced stages. In contrast, head and neck extranodal MCLs are more commonly diagnosed in early-stage disease, often with a low-risk Mantle Cell Lymphoma International Prognostic Index (MIPI) score. Clinical symptoms in the head and neck region may prompt patients to seek medical consultation timeously, resulting in earlier detection.[1, 9, 12]

The clinical behavior of MCL is highly variable, with median survival ranging between three and five years. The survival rate ranges from 29.2% to 54.5%, with improvements following the introduction of rituximab and other novel biological agents.[3,

[15, 18, 26] Some authors have demonstrated important differences in prognosis and survival depending on the primary site of involvement. Nodal MCLs usually have a worse prognosis compared to extranodal cases, with head and neck MCLs having a better survival rate compared to gastrointestinal cases.[11, 18] In contrast, Breen et al. (2021)[12] failed to observe any significant differences among head and neck subsites. Moreover, the leukemic non-nodal MCL variant is associated with a better prognosis, [26] and the exceedingly rare *in situ* mantle cell neoplasia has an indolent course with excellent long-term survival.

There is currently no gold standard therapeutic approach for MCL, with patients managed on different chemotherapeutic schemes, with or without radiation and bone marrow transplant.[2, 7, 27, 28] There are many different clinical and histological parameters that may influence prognosis, including cell proliferation and aggressive histological variants.[5] The MIPI score is used to stratify patients according to their prognostic risk and includes clinical parameters such as patient age, Eastern Cooperative Oncology Group (ECOG) performance score, lactate dehydrogenase level, and white blood cell count.[2, 28, 29] Hoster et al. (2016)[30] demonstrated that combining the MIPI score with the Ki67 proliferation index might lead to a more sensitive approach for risk stratification. Certain genetic mutations involving the *TP53* gene with subsequent p53 immunoexpression are also associated with a worse overall prognosis.[5]

In conclusion, because of its histological heterogeneity, MCL should always be considered in the diagnostic work-up of extranodal mature B-cell lymphomas in the oral and maxillofacial region. A broad immunohistochemical panel, including cyclin D1 and SOX11, must be evaluated in all suspected cases. Moreover, an extranodal MCL diagnosis should prompt clinicians to investigate the possibility of a leukemic manifestation of the disease.

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Figure legends

Figure 1. Microscopic presentation of MCL affecting the oral and the maxillofacial region. **A)** Classic variant characterized by a diffuse and monotonous proliferation of small-sized neoplastic cells (H&E; 100X). **B)** Neoplastic cells in the classic variant present as small centrocytes with irregular nuclear contours and inconspicuous nucleoli (H&E; 200X). **C)** Blastoid variant characterized by a proliferation of intermediate-sized neoplastic cells (H&E; 100X). **D)** Higher magnification reveals easily discernable nucleoli and scattered mitotic figures (H&E; 400X). **E)** Pleomorphic variant showing a diffuse and infiltrative growth pattern, with many large, atypical neoplastic cells and mitotic figures (H&E; 100X). **F)** Neoplastic cells with abundant pale to clear cytoplasm and prominent nucleoli with numerous mitotic figures (H&E; 200X).

Figure 2. Immunohistochemical findings of this MCL series. **A)** CD20 showed strong and diffuse positivity in all cases (DAB; 200X). **B)** CD5 positivity was observed in six cases, presenting as diffuse membranous staining of the neoplastic cells (DAB; 200X). **C)** Nuclear cyclin D1 positivity was present in all cases (DAB; 200X). **D)** Bcl2 showed cytoplasmic positivity in the majority of the cases (DAB; 200X). **E)** Nuclear SOX11 positivity was observed in nine out of 13 cases investigated (DAB; 200X). **F)** Ki67 showed a high proliferative index in a blastoid variant of MCL (DAB; 100X).

Table 1. Clinical features of the 20 cases of mantle cell lymphoma investigated in this study.

Case	Sex	Age	Site	Other sites	Pain	Ulcer	Swelling	Bleeding	Bone destruction	Duration	Treatment	Follow-up	Status
1	M	63	Hard palate	NS	NO	NO	YES	NO	NS	3	Radiotherapy	69	Alive
2	M	82	Hard palate	NS	NS	NO	YES	NS	NO	6	NS	NS	NS
3	M	86	Oropharynx	NS	NS	YES	YES	NS	NS	NS	NS	2	Alive
4	M	75	Upper lip and palate, bilateral	PB	NO	NO	YES	NO	NS	NS	NS	NS	NS
5	M	39	Upper lip	NS	NS	NO	YES	NS	NS	2	NS	NS	NS
6	F	49	Floor of the mouth	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
7	M	66	Retromolar trigone	NS	NS	YES	YES	NS	YES	NS	NS	41	Alive
8	M	76	Oral mucosa	NS	NS	NS	YES	NS	NS	NS	Chemo + Rad	6	Alive
9	M	38	Oropharynx	NS	NO	YES	YES	NS	NS	3	Chemotherapy	1	Deceased
10	M	69	Lower vestibular mucosa	NS	NO	NO	YES	NO	NO	NS	R-CHOP	NS	NS
11	F	74	Hard palate bilateral	LN and PB	NO	NO	YES	NO	NO	6	R-CHOP	NS	NS
12	M	44	Maxilla	Maxillary sinus	NO	NO	YES	NO	YES	2	NS	NS	NS
13	F	52	Nasopharynx	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
14	F	53	Cheek mucosa	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
15	M	68	Oropharynx	NS	YES	NO	YES	NO	NO	6	NS	NS	NS
16	M	78	Soft palate	NS	NO	YES	YES	NO	NO	6	NS	NS	NS
17	M	58	Oropharynx	NS	NS	YES	YES	NO	NO	NS	NS	NS	NS
18*	M	73	Palatine tonsil	NS	NO	YES	YES	NO	NO	2	CHOP	1	Alive
19	M	83	Rhinopharynx	Inguinal LN	NS	NS	NS	NS	NS	NS	NS	NS	NS
20	F	95	Parotid gland	NS	NS	NO	YES	NS	NS	NS	NS	NS	NS

M: male; F: Female; PB: Peripheral blood; LN: Lymph node; NS: Not specified; Chemo.: Chemotherapy; Rad.: Radiotherapy; Duration: in months; Follow-up: in months.
*Full description of this case can be found in Valente et al., 2021. doi: 10.1016/j.oraloncology.2021.105552.

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Table 2. Histological variants, immunohistochemical results and EBV-status of the 20 cases of mantle cell lymphoma investigated in this series.

Case	Variant	CD20	CD3	CD10	Bcl6	Bcl2	CD5	Cyclin D1	SOX11	Ki67	Proliferative index**	EBER
1	Classic	+	-	-	+	+	-	+	+	20	Low	-
2	Classic	+	-	-	+	+	-	+	+	30	Low	-
3	Pleomorphic	+	-	-	+	+	-	+	+	50	High	-
4	Classic	+	-	-	-	+	-	+	+	20	Low	-
5	Classic	+	-	-	-	+	-	+	+	20	Low	-
6	Blastoid	+	-	-	-	-	NS	+	NS	30	Low	-
7	Blastoid	+	-	+	-	+	NS	+	NS	35	High	-
8	Blastoid	+	-	-	-	+	-	+	+	20	Low	-
9	Classic	+	-	+	-	-	+	+	-	80	High	NS
10	Pleomorphic	+	-	-	+	-	+	+	-	60	High	-
11	Classic	+	-	-	-	+	-	+	+	NS	NS	NS
12	Blastoid	+	-	-	NS	+	NS	+	NS	NS	NS	NS
13	Classic	+	-	-	NS	+	NS	+	NS	NS	NS	-
14	Classic	+	-	-	-	+	-	+	-	15	Low	-
15	Pleomorphic	+	-	-	-	+	+	+	NS	40	High	NS
16	Classic	+	-	-	NS	+	+	+	NS	20	Low	NS
17	Classic	+	-	-	NS	NS	+	+	NS	NS	NS	NS
18*	Blastoid	+	-	-	-	+	+	+	-	90	High	NS
19	Classic	+	-	-	-	+	-	+	+	75	High	NS
20	Classic	+	-	-	-	+	-	+	+	45	High	NS

NS: Not specified. + positive; - negative.
*Full description of this case can be found in Valente et al., 2021. doi: 10.1016/j.oraloncology.2021.105552.
** Low proliferative index Ki67 ≤ 30%; High proliferative index Ki67 > 30%.

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Figure 1.

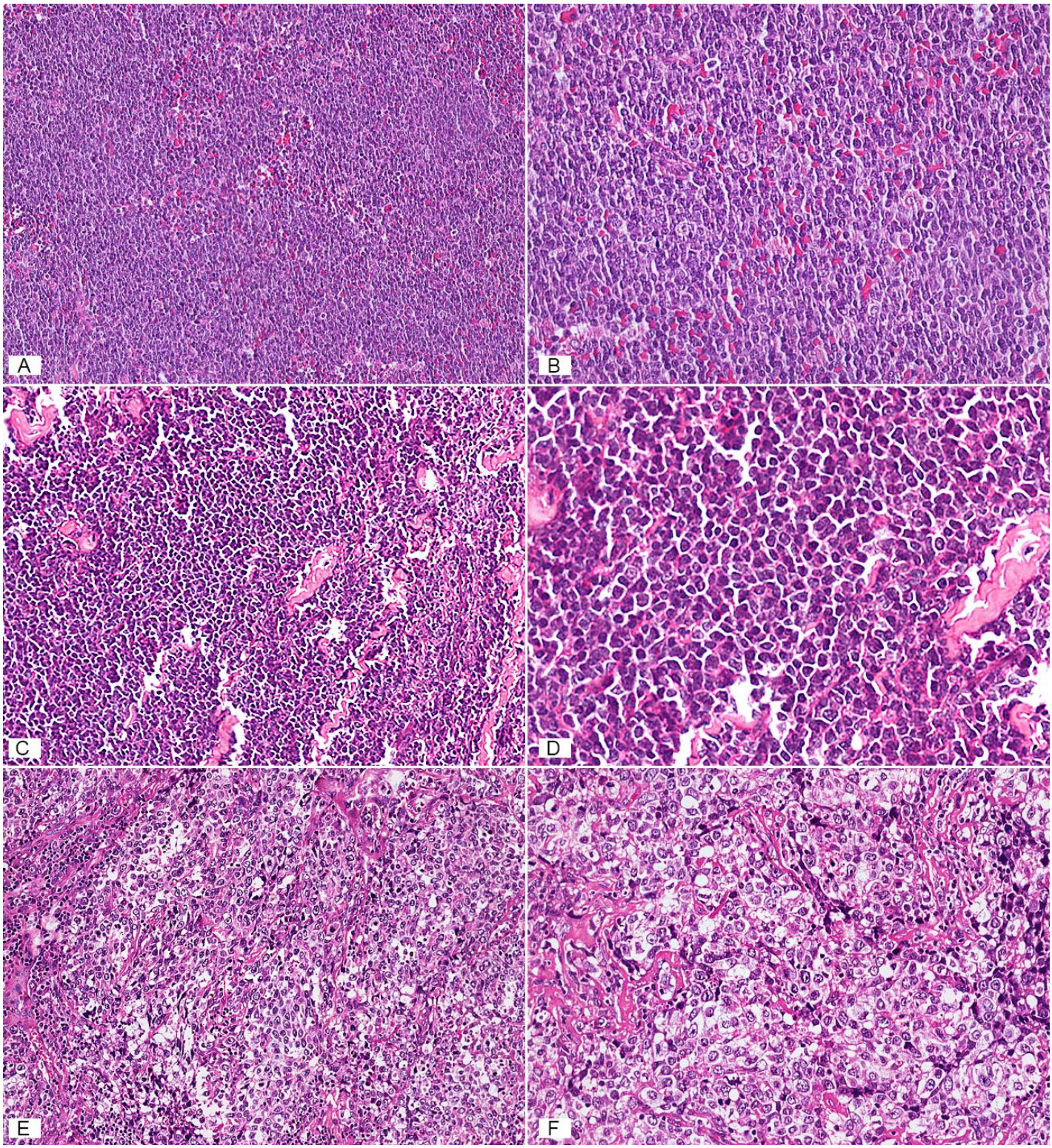

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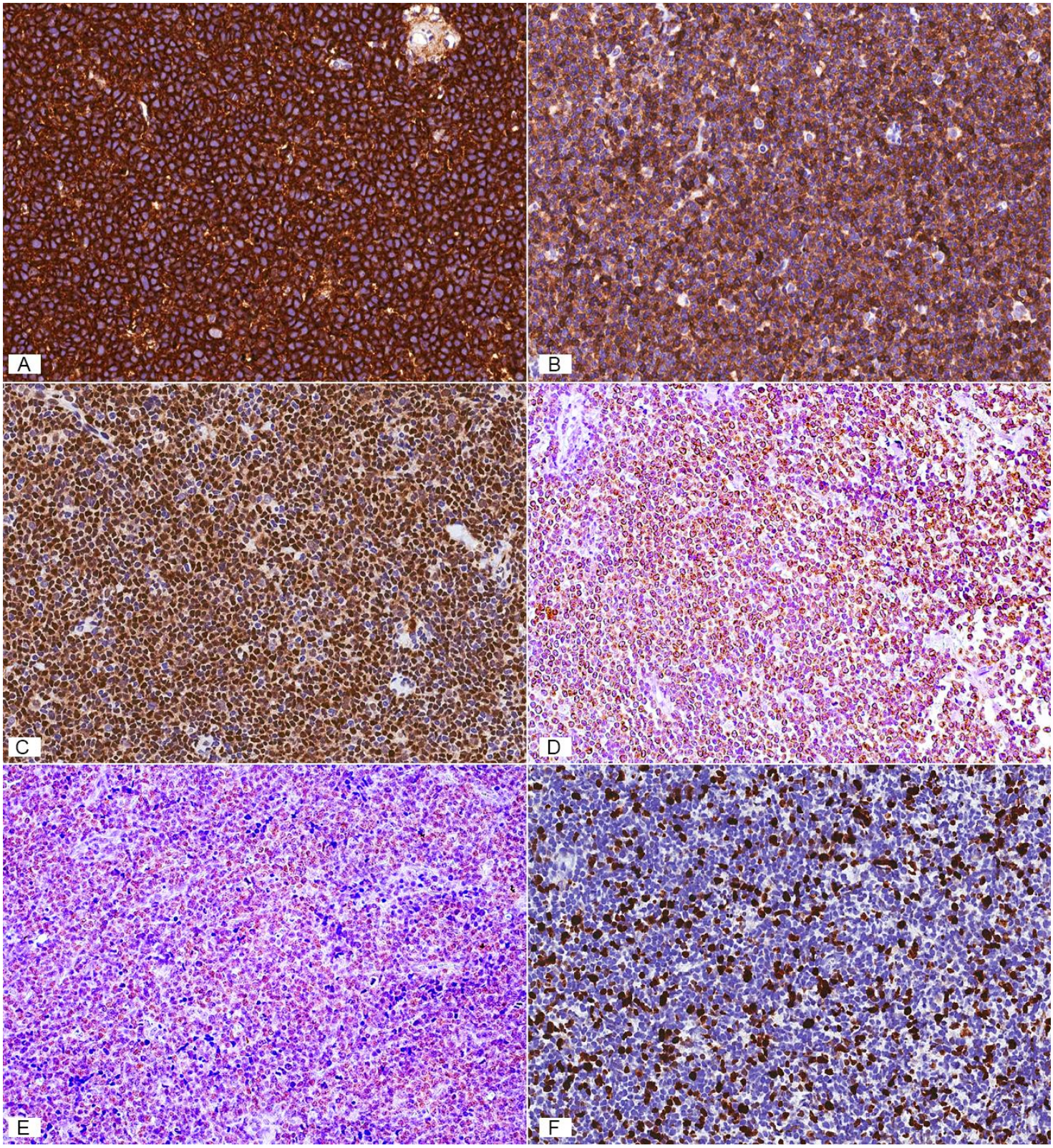
Figure 2.



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3 CONCLUSÃO

Apesar de incomum, o LCM também pode ser diagnosticado na região oral e maxilofacial, e a pesquisa de Ciclina D1 e SOX11 é aconselhável por causa da variabilidade microscópica que esta neoplasia pode demonstrar. Além disso, um diagnóstico de LCM na cavidade oral exige a investigação de uma possível manifestação leucêmica.

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ANEXOS

Anexo 1 - Certificado do Comitê De Ética em Pesquisa

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

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: ANÁLISE CLINICO-PATOLÓGICO E MOLECULAR DAS LESÕES LINFOIDES REATIVAS E DOS LINFOMAS DA REGIÃO MAXILOFACIAL

Pesquisador: Felipe Paiva Fonseca

Área Temática:

Versão: 4

CAAE: 44647421.1.0000.5418

Instituição Proponente: Faculdade de Odontologia de Piracicaba - Unicamp

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 5.217.186

Apresentação do Projeto:

O parecer inicial é elaborado com base na transcrição editada do conteúdo do registro do protocolo na Plataforma Brasil e dos arquivos anexados à Plataforma Brasil. Os pareceres de retorno, emendas e notificações são elaborados a partir dos dados e arquivos da última versão apresentada.

Trata-se de SOLICITAÇÃO DE EMENDA (E1) AO PROTOCOLO originalmente aprovado em 23/04/2021 para inclusão de novo pesquisador. O parecer foi atualizado de acordo com a documentação apresentada. A solicitação está detalhadamente descrita ao final do parecer.

A EQUIPE DE PESQUISA citada na capa do projeto de pesquisa inclui, em ordem alfabética, exceto pesquisador responsável, FELIPE PAIVA FONSECA (Cirurgião-Dentista, Docente no PPG em Estomatopatologia da FOP-UNICAMP, Pesquisador responsável), ANA LUÍSA MORAIS PERDIGÃO (Graduanda no curso de Odontologia da Faculdade de Odontologia da UFMG), CARLA ISABELLY RODRIGUES-FERNANDES (Cirurgiã-Dentista, Doutoranda no PPG em Estomatopatologia da FOP-UNICAMP), CINTHIA VERONICA BARDÁLEZ LÓPEZ DE CÁCERES (Cirurgiã-Dentista, Doutoranda no PPG em Estomatopatologia da FOP-UNICAMP), GLAUCE GUIMARÃES PEREIRA (Cirurgiã-Dentista, Doutoranda no PPG em Estomatopatologia da FOP-UNICAMP), HÉLDER ANTÔNIO REBELO PONTES (Cirurgião-Dentista, Docente na Universidade Federal do Pará, Docente no PPG em

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Estomatopatologia da FOP-UNICAMP), LUCAS LACERDA DE SOUZA (Cirurgião-Dentista, Mestrando no PPG em Estomatopatologia da FOP-UNICAMP, Incluído em E1), MARCUS VINÍCIUS RIBEIRO CARVALHO (Cirurgião-Dentista, Doutorando no PPG em Estomatopatologia da FOP-UNICAMP), OSLEI PAES DE ALMEIDA (Cirurgião-Dentista, Docente na Área de Patologia da FOP-UNICAMP), PABLO AGUSTIN VARGAS (Cirurgião-Dentista, Docente na Área de Patologia da FOP-UNICAMP), o que é confirmado na declaração dos pesquisadores e na PB.

Pendência 1 (atendida em 14/04/21): Foram ajustados os dados dos pesquisadores na capa do projeto.

DELINEAMENTO DA PESQUISA: Trata-se de estudo laboratorial, observacional, analítico, retrospectivo, com base em arquivo de três serviços de diagnóstico oral [Serviço de Patologia Oral do Hospital Universitário João de Barros Barreto da Universidade Federal do Pará (Belém/PA), Faculdade de Odontologia da Universidade Federal de Minas Gerais (Belo Horizonte/MG) e Faculdade de Odontologia de Piracicaba/Universidade Estadual de Campinas (Piracicaba/SP)], que envolverá cerca de 200 casos de lesões linfóide reativas e linfomas da região maxilofacial diagnosticados no período de 2000 a 2020 nos três serviços citados e obtidos de indivíduos/pacientes com idades entre 20 e 80 anos de idade, com prevalência presumida do sexo masculino. O objetivo deste estudo é determinar o perfil clinicopatológico, imunoistoquímico, molecular e prognóstico deste amplo e heterogêneo grupo de lesões de natureza linfoide que acometem a região maxilofacial. Para isto, serão recuperadas de forma retrospectiva dos arquivos de patologia oral de três instituições brasileiras os casos diagnosticados no período de 2000 a 2020 como hiperplasia linfoide folicular, úlceras mucocutâneas associadas ao vírus Epstein-Barr (EBV), ao uso de metotrexato e pós-transplantes, e a doença do IGG4, além de todos os subtipos de linfomas que acometeram a região maxilofacial. Os dados clinicopatológicos dos pacientes serão recuperados das fichas de requisição de exame anatomopatológico e/ou dos prontuários odontológicos. Os dados referentes ao sexo, idade, localização da lesão, sintomatologia, tratamento, presença de recidivas e evolução (paciente vivo ou morto), serão investigados quanto aos seus potenciais prognósticos e de determinação de sobrevida. Novos cortes histológicos serão realizados com o objetivo de confirmar os diagnósticos originais e guiar a subclassificação de cada caso de acordo com os critérios atuais da Organização Mundial da Saúde, utilizando-se colorações de hematoxilina e eosina, assim como reações imunoistoquímicas (quando as reações originais não estiverem disponíveis nos arquivos de patologia) e hibridização in situ para detecção do vírus

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Continuação do Parecer: 5.217.186

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Declaração de Instituição e Infraestrutura	DecInst.pdf	17/03/2021 15:46:28	Cinthia Veronica Bardalez Lopez de Cáceres	Aceito
Declaração de Pesquisadores	DecPesq.pdf	17/03/2021 15:46:09	Cinthia Veronica Bardalez Lopez de Cáceres	Aceito
Folha de Rosto	FolhaDeRosto.pdf	17/03/2021 15:45:26	Cinthia Veronica Bardalez Lopez de Cáceres	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

PIRACICABA, 30 de Janeiro de 2022

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

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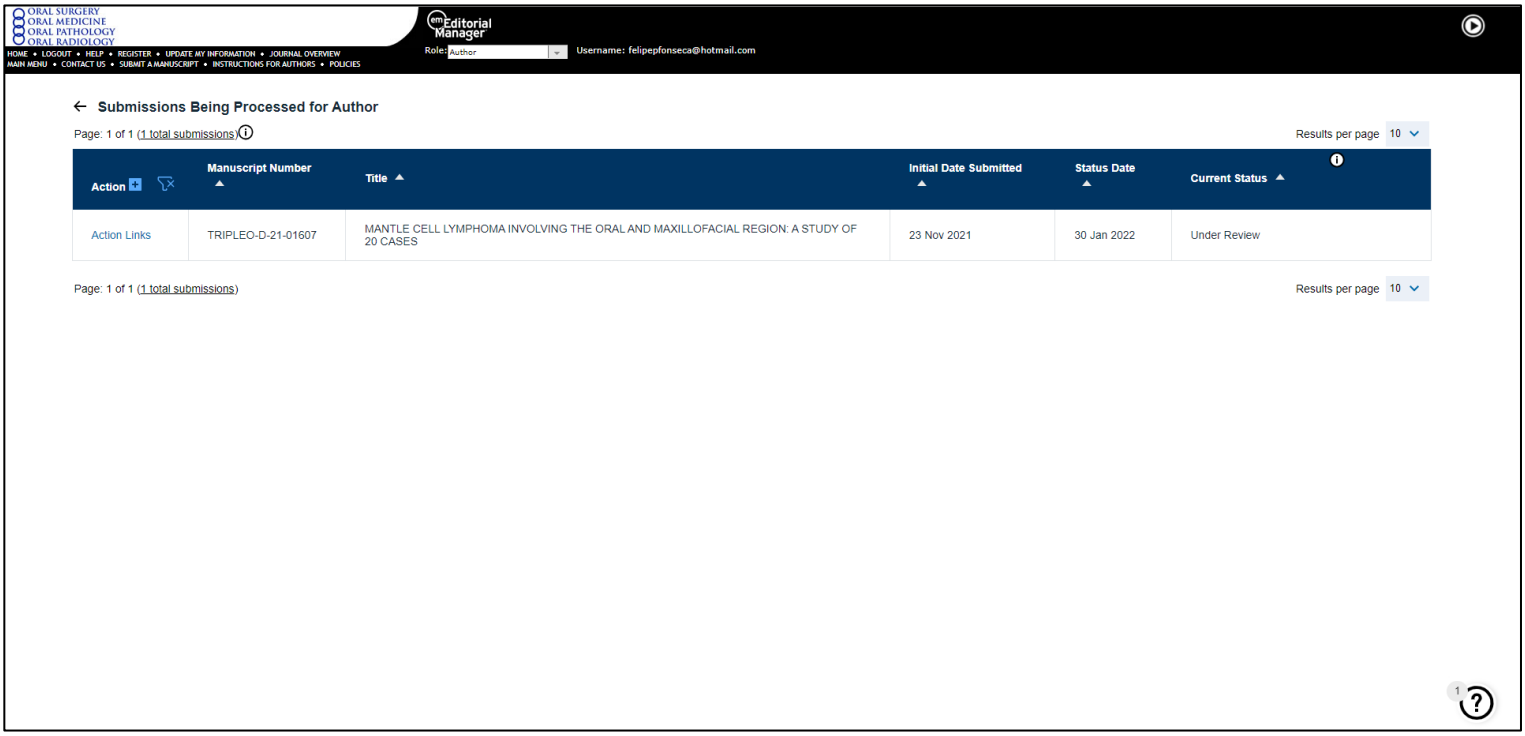
Anexo 2 – Comprovante de submissão do artigo



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Anexo 3 – Comprovante de avaliação anti-plágio

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MANTLE CELL LYMPHOMA INVOLVING THE ORAL AND MAXILLOFACIAL REGION: A STUDY OF 20 CASES

Abstract

Objective: To investigate the clinicopathological features of mantle cell lymphoma (MCL) involving the oral and maxillofacial region.

Methods: MCL cases were retrieved from the pathology database of six pathology laboratories. Original H&E slides and immunohistochemical reactions were reviewed for confirmation of the initial diagnosis. Clinical data of the cases were obtained from the patients' pathology and/or medical charts.

Results: Twenty cases were included in the study, showing a male predominance and a mean age of 66-years. The oral cavity (12 cases) and the oropharynx (5 cases) were the most commonly involved subsites. Most cases presented as asymptomatic swellings, with two cases showing bilateral involvement of the palate. The classic histological variant predominated (12/20 cases). All cases expressed CD20 with nuclear cyclin D1 positivity. SOX11 was seen in 9/15 cases, CD5 in 8/16 cases, Bcl2 in 18/19 cases, CD43 in 2/20 cases, and Bcl6 in 4/16 cases. Ki67 showed a mean proliferation index of 40.6%. EBV was negative in all cases investigated. Follow-up data was available for six patients, with five currently alive and one deceased.

Conclusion: MCL, albeit rare, may manifest in the oral and maxillofacial region. Its histological heterogeneity demands a high degree of diagnostic skill from pathologists.

Keywords: Lymphoma, Mantle cell lymphoma, Oral and maxillofacial region, Oropharynx, Tonsil.

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de Marcus Vinicius

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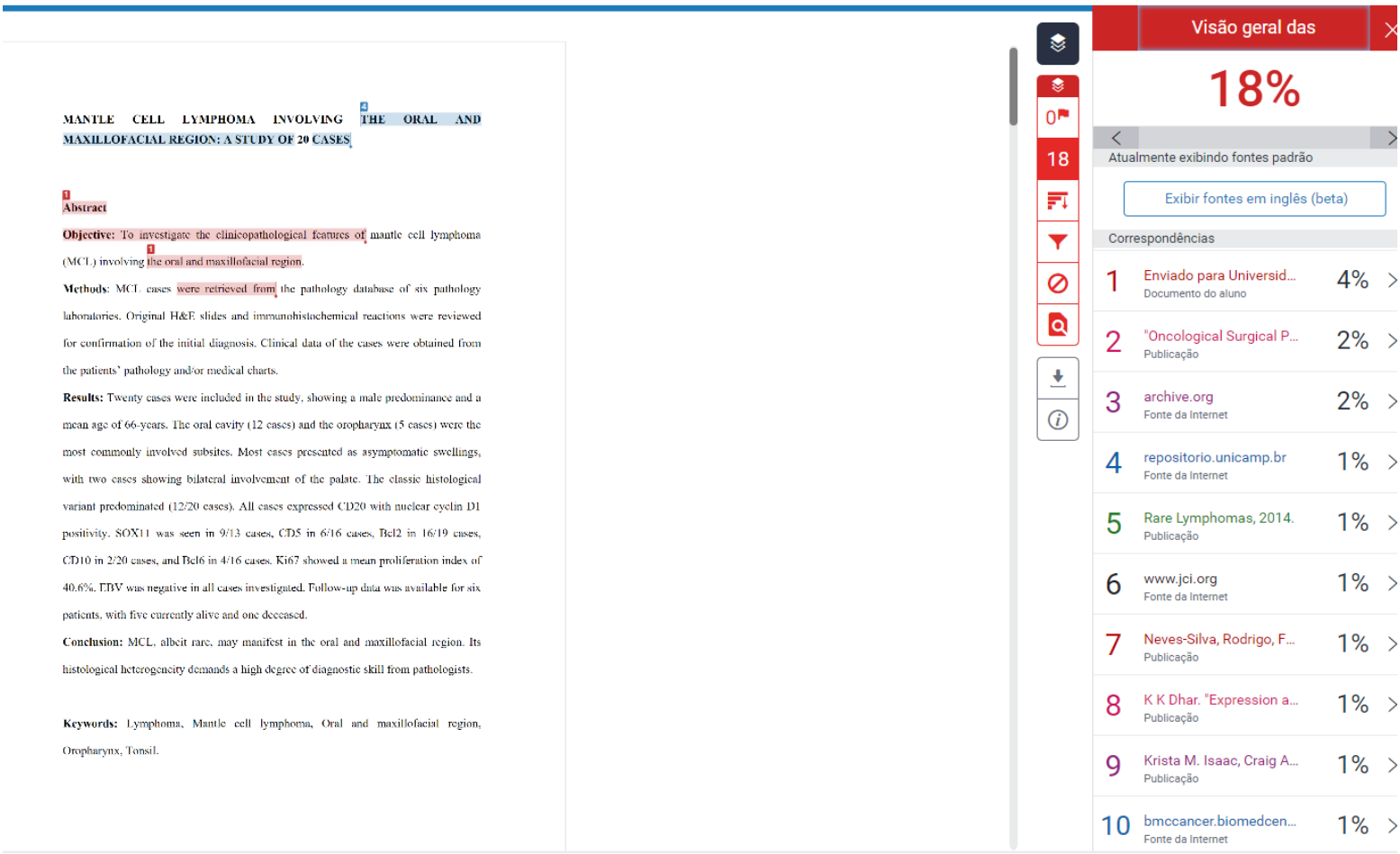

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Abstract

Objective: To investigate the clinicopathological features of mantle cell lymphoma (MCL) involving the oral and maxillofacial region.

Methods: MCL cases were retrieved from the pathology database of six pathology laboratories. Original H&E slides and immunohistochemical reactions were reviewed for confirmation of the initial diagnosis. Clinical data of the cases were obtained from the patients' pathology and/or medical charts.

Results: Twenty cases were included in the study, showing a male predominance and a mean age of 66-years. The oral cavity (12 cases) and the oropharynx (5 cases) were the most commonly involved subsites. Most cases presented as asymptomatic swellings, with two cases showing bilateral involvement of the palate. The classic histological variant predominated (12/20 cases). All cases expressed CD20 with nuclear cyclin D1 positivity. SOX11 was seen in 9/13 cases, CD5 in 6/16 cases, Bcl2 in 16/19 cases, CD10 in 2/20 cases, and Bcl6 in 4/16 cases. Ki67 showed a mean proliferation index of 40.6%. EBV was negative in all cases investigated. Follow-up data was available for six patients, with five currently alive and one deceased.

Conclusion: MCL, albeit rare, may manifest in the oral and maxillofacial region. Its histological heterogeneity demands a high degree of diagnostic skill from pathologists.

Keywords: Lymphoma, Mantle cell lymphoma, Oral and maxillofacial region, Oropharynx, Tonsil.

* De acordo com as normas da UNICAMP/FOP, baseadas na padronização do International Committee of Medical Journal Editors - Vancouver Group. Abreviatura dos periódicos em conformidade com o PubMed.