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Colegiado de Pós-Graduação em Odontologia

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AVALIAÇÃO DAS MANIFESTAÇÕES CLÍNICAS E MICROSCÓPICAS DOS LINFOMAS EM GLÂNDULAS SALIVARES MAIORES

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Tese apresentada ao Colegiado de Pós-Graduação em Odontologia da Faculdade de Odontologia da Universidade Federal de Minas Gerais, como requisito parcial à obtenção do grau de Doutor em Odontologia - área de concentração em Patologia Bucal.

Orientador: Prof. Felipe Paiva Fonseca

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GABRIELA RIBEIRO DE ARAÚJO

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“Ninguém caminha sem aprender a caminhar, sem aprender a fazer o caminho caminhando, refazendo e retocando o sonho pelo qual se pôs a caminhar.”

Paulo Freire

RESUMO

Os subtipos de linfomas não Hodgkin representam 2,8% de todos os novos casos de câncer no mundo, sendo o terceiro grupo mais comum de neoplasias malignas da região de cabeça e pescoço. As glândulas salivares maiores representam o terceiro sítio extranodal mais acometido pelo linfoma na região da cabeça e pescoço; entretanto, nas glândulas salivares maiores é muito raro, representando aproximadamente 1,7–3,1% de todas as neoplasias das glândulas salivares, acometendo a maioria dos casos as glândulas parótidas (79%), seguidas pelas glândulas submandibulares (18%) e sublinguais (1%). Os subtipos mais comuns são linfoma do tecido linfoide associado à mucosa (MALT), o linfoma folicular (FL) e o linfoma difuso de grandes células B (DLBCL), e a frequência destas neoplasias está associado com a ocorrência simultânea de condições sistêmicas que predispõem ao desenvolvimento de neoplasias linfoides como a Síndrome de Sjögren (SS). Entretanto, a literatura sobre linfomas em glândulas maiores permanece muito escassa e impede que conheçamos de forma apropriada as características destes pacientes. Assim, o objetivo deste estudo é avaliar as manifestações clínicas e microscópicas dos linfomas em glândulas salivares maiores. Para isto, foram recuperados de forma retrospectiva dos arquivos de patologia de algumas instituições todos os casos diagnosticados como linfomas acometendo estes sítios anatômicos. Foram coletados os dados clínicos referentes ao sexo, idade, localização, apresentação clínica, tempo de evolução, status, estadiamento e ocorrência da SS, e as informações histopalógicas foram coletadas de blocos de parafina e lâminas em hematoxilina e eosina e imuno-histoquímicas acessíveis. Os resultados obtidos foram avaliados de forma descritiva. As séries compreenderam de 7 casos de linfomas em glândula sublingual, 16 casos em glândula submandibular e 12 casos em glândula parótida. Clinicamente, os linfomas apresentam-se como aumento de volume assintomático, sendo os subtipos mais frequentes os de células B maduras de baixo grau (MALT, FL, MCL), mas subtipos de alto grau também foram observados (LDGCB, SOE). Dois pacientes, um de linfoma de células do manto (LCM) e outro de LDGCB,SOE em glândula sublingual apresentaram como doença disseminada, e apenas três casos de linfoma MALT em glândula parótida apresentam a SS. O tratamento dependeu do microscópico e estágio do tumor, variando de cirurgia, regimes quimioterápicos com R-CHOP e radioterapia. O prognóstico foi favorável principalmente para os casos de baixo grau (MALT,FL), e apenas dois pacientes de sublingual (LDGCB,SOE, MCL) e três de submandibular (LDGCB,SOE, linfoma plasmablastico e MALT) faleceram após o diagnóstico. Neste estudo concluímos que os linfomas em glândulas salivares maiores são afetados principalmente por neoplasias de células B maduras de baixo grau (MALT, FL, MCL) e esses pacientes devem passar por uma avaliação sistêmica criteriosa para determinar se a doença se trata de uma neoplasia primária ou disseminada.

Palavras-chaves: linfoma; glândulas salivares; glândula parótida; glândula submandibular; glândula sublingual.

ABSTRACT

Evaluation of clinical and microscopic manifestations of lymphomas in larger salivary glands

Non-Hodgkin's lymphomas account for 2.8% of all new cancer cases worldwide and are the third most common group of malignant neoplasms in the head and neck region. The major salivary glands represent the third most common extranodal site affected by lymphoma in the head and neck region; however, in the major salivary glands it is very rare, representing approximately 1.7-3.1% of all salivary gland neoplasms, affecting most cases in the parotid glands (79%), followed by the submandibular glands (18%) and sublingual glands (1%). The most common subtypes are mucosa-associated lymphoid tissue lymphoma (MALT), follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL), and the frequency of these neoplasms is associated with the simultaneous occurrence of systemic conditions that predispose to the development of lymphoid neoplasms such as Sjögren's Syndrome(SS). However, the literature on lymphomas in major glands remains very scarce and prevents us from properly understanding the characteristics of these patients. Therefore, the aim of this study was to evaluate the clinical and microscopic manifestations of lymphomas in the major salivary glands. To this end, all cases diagnosed as lymphomas affecting these anatomical sites were retrospectively retrieved from the pathology archives of a number of institutions. Clinical data was collected on gender, age, location, clinical presentation, time of evolution, status, staging and occurrence of SS, and histopathological information was collected from paraffin blocks and slides in hematoxylin and eosin and accessible immunohistochemistry. The results obtained were evaluated descriptively. The series comprised 7 cases of lymphomas in the sublingual gland, 16 cases in the submandibular gland and 12 cases in the parotid gland. Clinically, the lymphomas presented as asymptomatic enlargement, with the most frequent subtypes being low-grade mature B-cells (MALT, FL, MCL), but high-grade subtypes were also observed (LDGCB, SOE). Two patients, one with mantle cell lymphoma (MCL) and the other with LDGCB,SOE in the sublingual gland presented with disseminated disease, and only three cases of MALT lymphoma in the parotid gland presented with SS. Treatment depended on the microscopic subtype and stage of the tumor, ranging from surgery to chemotherapy regimens with R-CHOP and radiotherapy. Prognosis was mainly favorable for low-grade cases (MALT,FL), and only two sublingual patients (LDGCB,SOE, MCL) and three submandibular patients (LDGCB,SOE, plasmablastic lymphoma and MALT) died after diagnosis. In this study we conclude that lymphomas in the major salivary glands are mainly affected by low-grade mature B-cell neoplasms (MALT, FL, MCL) and these patients should undergo a careful systemic evaluation to determine whether the disease is a primary or disseminated neoplasm.

Keywords: lymphoma; salivary glands; parotid gland; submandibular gland; sublingual gland.

LISTA DE FIGURAS

LISTA DE TABELAS

LISTA DE ABREVIATURAS E SIGLAS

OMS Organização Mundial da Saúde

MALT Linfoma do Tecido Linfoide Associado a Mucosa

FL Linfoma Folicular

LDGCB SOE Linfoma Difuso de Grandes Células B Sem Outra Especificação

LCM Linfoma de Células do Manto

SS Síndrome de Sjögren

FISH Hibridização “In Situ” por Fluorescência

H&E Hematoxilina E Eosina

SUMÁRIO

1 INTRODUÇÃO

Os linfomas são um grupo altamente heterogêneo de lesões que surgem de linfócitos B, T e NK ao longo de diferentes momentos da maturação celular, representando o terceiro grupo de neoplasias malignas mais comuns na região de cabeça e pescoço após o carcinoma de células escamosas e as neoplasias malignas de glândulas salivares (COOPER *et al*., 2009). De acordo com a quarta classificação da Organização Mundial da Saúde (OMS) de tumores hematolinfoides, mais de 50 subtipos diferentes de linfomas podem ser reconhecidos com base nas características histológicas e eventos genéticos que exibem (SWERDLOW; CAMPO; HARRIS, 2017). Aproximadamente 75% dos linfomas acometem os linfonodos e 25% apresentam-se como uma doença extranodal (JEMAL *et al.,* 2010). O anel de Waldeyer é uma estrutura linfoide frequentemente acometida por linfomas na região de cabeça e pescoço (SWERDLOW; CAMPO; HARRIS, 2017). Já as glândulas salivares maiores são o terceiro local extranodal mais afetado pelos linfomas na região de cabeça e pescoço, seguido pelos anexos oculares e região naso-sinusal (WEBER; RAHEMTULLAH; FERRY, 2003). Entretanto, os linfomas primários das glândulas salivares são raros e as manifestações secundárias também representam eventos muito poucocomuns nestas estruturas anatômicas, correspondendo a aproximadamente 1,7–3,1% de todas as neoplasias das glândulas salivares, acometendo as glândulas parótidas em 79% dos pacientes, as glândulas submandibulares em cerca de 18% e as glândulas sublinguais em apenas 1% dos linfomas em glândulas salivares maiores (BARNES; MYERS; PROKOPAKIS, 1998).

Dentre os subtipos de linfomas, os que acometem com maior frequência a glândula parótida são o linfoma da zona marginal do tecido linfoide associado a mucosa (MALT), o linfoma folicular e o linfoma difuso de grandes células B sem outra especificação (LDGCB SOE), sendo o linfoma MALT especialmente predominante em pacientes com síndrome de Sjögren (SS) (FEINSTEIN *et al.,* 2013; RETAMOZO; BRITO-ZERÓN; RAMOS-CASALS, 2019). Já os linfomas mais comuns nas glândulas submandibulares e sublinguais são o linfoma MALT, o linfoma de células do manto e o linfoma folicular (ABUKRIAN *et al.,* 2020; HAYASHI *et al.,* 2015; HONDA *et al.,* 2004; IVERSEN *et al.* 2020; YOSHIBA *et al.,* 2011).

Clinicamente os linfomas podem apresentar diferentes manifestações, o que vai depender do subtipo microscópico e da localização, podendo muitas vezes

ser similares aos de outras lesões de glândulas salivares benignas, como o adenoma pleomórfico e sialodenites reativas, ou malignas, como os diferentes tipos de adenocarcinomas (IVERSEN *et al.,* 2020). Os linfomas de glândulas sublinguais apresentam-se como aumento de volume fibroso e endurecido, móvel e assintomático, sendo alguns casos sintomáticos relatados nos subtipos MALT e folicular (ABUKRIAN *et al.,* 2020; HAYASHI *et al.,* 2015; HONDA *et al.,* 2004; IVERSEN *et al.* 2020; YOSHIBA *et al.,* 2011). Já na glândula parótida, os linfomas exibem um aumento de volume endurecido à palpação, usualmente assintomático, podendo em alguns casos causar quadros de parestesia do nervo facial (BARNES; MYERS; PROKOPAKIS, 1998; GADODIA *et al.,* 2011; REVANAPPA *et al.* 2013).

Histologicamente os linfomas apresentam características morfológicas que permitem a caracterização de cada subtipo, mas é necessário para diferenciação e confirmação diagnóstica um painel imunoistoquímico específico (SWERDLOW; CAMPO; HARRIS, 2017). Portanto, para facilitar tal compreensão, sugerimos a tabela a seguir:

Tabela 1: Principais características morfológicas e painel imunoistoquímico dos subtipos de linfomas mais frequentes nas glândulas salivares maiores.

Tipo de linfoma	**Características Morfológicas**	**Painel imunoistoquímico**
MALT	Proliferação de células B neoplásicas de tamanho pequeno a médio, algumas células exibindo um citoplasma pálido relativamente abundante, consistente com células monocitoides	(+): CD20; CD79a (-): CD3, CD5, ciclina D1 Ki67 (baixo)
LF	Folículos neoplásicos compostos predominantemente por centrócitos organizados de forma compacta, apresentando focalmente um padrão de crescimento back-to-back e sem zonas do manto.	(+): CD20(difuso), CD10, Bcl-6, e Bcl-2 (dentro do centro germinativo neoplásico); CD3(interfolicular) (-): CD3 (folículos) Ki67 (variável)
LCM	Proliferação difusa de células de tamanho pequeno a médias com contornos nucleares ligeiramente irregulares, assemelhando-se a centrócitos.	(+): CD20; Ciclina D1(>95%); BCL-2, CD43; CD5 (-): CD3, CD10, BCL-6 Ki67(alto ou baixo)

LDGCB, SOE	Proliferação difusa de células de tamanho grande e médias com características centroblásticas e imunoblásticas.	(+): CD20, CD10 (variado), Bcl-2, Bcl-6 (variado), MUM1 (variado) (-): CD3, Cliclina D1 Ki67 (alto)

MALT: Tecido Linfoide Associado a Mucosa; LF: Linfoma Folicular; LCM: Linfoma de Células do Manto; LDGCB, SOE: Linfoma Difuso de Grandes Células B sem outras especificações.

FONTE: Elaborado pela autora GABRIELA RIBEIRO DE ARAÚJO, 2024.

A detecção de alterações cromossômicas por meio de diferentes métodos laboratoriais como a hibridização “in situ” por fluorescência (FISH) tem sido cada vez mais utilizada para identificação de eventos que contribuem de forma determinante não apenas para a etiopatogênese de diferentes linfomas, mas também para seus diagnósticos. No linfoma MALT os rearranjos genéticos variam em frequência de acordo com o sítio anatômico primário da doença (PALS; DE GORTER; SPAARGAREN, 2007). E as alterações cromossômicas observadas mais comumente quando as glândulas salivares estão acometidas por este linfoma correspondem a t(14; 18) (q32; q21)–*IGH / MALT1* e t(11; 18) (q21; 21) -*API2 / MALT1*. No linfoma de células do manto a translocação t(11;14)(q13;q32) é observada em até 95% dos casos, ao passo que a translocação t(14;18)(q32;q21) é o evento genético típico do linfoma folicular e mutações nos genes MYC, BCL2 e BCL6 são frequentemente observados no LDGCB SOE (IVERSEN *et al.,* 2020; SWERDLOW; CAMPO; HARRIS, 2017). Desta forma, conhecer as alterações cromossômicas que sabidamente contribuem para a patogênese de vários tipos de linfomas e que podem ser uteis do ponto de vista diagnóstico é fundamental para compreendermos estas doenças e contribuirmos com a conduta de manejo clínico destes indivíduos, e a validação de cada uma destas mutações no contexto de glândulas salivares maiores se faz de grande importância a fim de demonstrar o grau de heterogeneidade cromossômico que estas neoplasias malignas podem exibir em função da distribuição anatômica.

O tratamento dos linfomas depende fundamentalmente do subtipo diagnosticado e diferentes esquemas quimioterápicos encontram-se atualmente disponíveis, podendo ser complementados por meio de abordagens terapêuticas adjuvantes (IVERSEN *et al.,* 2020). Além disto, o subtipo de linfoma também corresponde ao principal fator que definirá o prognóstico dos indivíduos afetados e dentre os linfomas que mais comumente acometem as glândulas maiores o LDGCB SOE corresponde à principal variante de alto grau e está associado com uma taxa de

sobrevivência ainda desfavorável, apesar de avanços nos esquemas terapêuticos mais recentes. O linfoma de células do manto também é considerado de alto grau, mas pode possuir manifestações clínicas indolentes e consequentemente o prognóstico destes pacientes varia de forma significativa. Por outro lado, o linfoma folicular e o linfoma MALT são neoplasias usualmente de baixo grau e costumam estar associados com prognósticos muitos mais favoráveis (FEINSTEIN *et al.,* 2013; GASCOYNE; CAMPO; JAFFE, 2018; IVERSEN *et al.* 2020; JACKSON *et al.,* 2015).

Tendo em vista as poucas informações na literatura que caracterizem adequadamente esses tumores em glândulas salivares maiores devido à sua raridade, esse estudo permitirá uma melhor compreensão quanto à distribuição dos tipos de linfomas nessas glândulas, otimizando o diagnóstico clínico e microscópio destes pacientes, permitindo, portanto, diagnóstico precoce, tratamentos mais rápidos e efetivos, e, consequentemente, melhores taxas de sobrevida.

2 OBJETIVOS

2.1 Objetivo geral

Caracterizar os aspectos clinicopatológicos dos linfomas que se manifestam nas glândulas salivares maiores.

2.2 Objetivos específicos

a) Determinar os subtipos mais comuns de linfomas em glândulas salivares maiores;
b) Investigar as características clínicas dos linfomas em glândulas salivares maiores;
c) Avaliar as características histopatológicas e imunoistoquímicas dos linfomas em glândulas salivares maiores.
d) Investigar de forma comparativa as características clínicas e microscópicas dos linfomas em função de cada tipo de glândula salivar maior.

3 METODOLOGIA EXPANDIDA

Esse estudo foi realizado após aprovação do Comitê de Ética da Universidade Federal de Minas Gerais, Brasil (CAAE: 58900722.1.0000.5149). Todos os procedimentos estavam de acordo com os padrões éticos do comitê responsável pela experimentação humana (institucional e nacional) e com a Declaração de Helsinque de 1975, revisada em 2008.

Inicialmente foram coletados os casos de linfoma que acometeram as glândulas sublinguais, obtidos nos arquivos anatomopatológicos do laboratório Getúlio Sales Diagnósticos (Natal/Brasil), da Universidade Federal do Pará (Belém/Brasil), da Universidade do País Basco (Bilbao/Espanha) e do Centro Clínico Cabeza y Cuello (Cidade da Guatemala/Guatemala). Os casos registrados como afetando o assoalho bucal também foram incluídos na estratégia de busca, pois as células neoplásicas poderiam envolver ambos os subsítios, via extensão para infiltrar a mucosa oral sobrejacente. Linfomas cervicais e nodais mais profundos que se estendiam em direção ao assoalho bucal foram excluídos do estudo. As lâminas H&E originais e imuno-histoquímicas e/ou os blocos de tecido fixados em formalina e embebidos em parafina de todos os casos foram recuperados para revisão histopatológica por pelo menos dois patologistas usando as diretrizes atuais da OMS para classificação de tumores de tecidos hematopoiéticos e linfóides (SWERDLOW; CAMPO; HARRIS, 2017).Os dados clinicopatológicos dos casos foram obtidos dos prontuários físicos e/ou eletrônicos dos pacientes, incluindo sexo, idade, localização da(s) lesão(ões), apresentação clínica, tempo de acompanhamento e estado dos pacientes na última consulta . Uma avaliação sistêmica dos pacientes, para determinar se os linfomas das glândulas sublinguais representavam uma manifestação primária da doença ou um processo disseminado, foi obtida, se disponível.

Em seguida foram colhidos os dados de linfoma afetando as glândulas submandibulares, obtidos nos arquivos anatomopatológicos do Laboratório de Diagnóstico Getúlio Sales (Natal/Brasil) e do Laboratório de Imunohistoquímica da Faculdade de Odontologia de Piracicaba (Universidade de Campinas) em um período de janeiro de 2003 a dezembro de 2019. Casos de linfoma com origem conhecida no pescoço ou dos linfonodos circundantes que se estendiam e invadiam as glândulas

submandibulares não foram considerados neste estudo. Cortes histológicos originais corados com H&E e lâminas de imuno-histoquímica foram obtidos para confirmação do diagnóstico, que seguiu a 4ª edição revisada da classificação da Organização Mundial da Saúde para tumores de tecido hematopoiético e linfóides (SWERDLOW; CAMPO; HARRIS, 2017). Os dados demográficos e clínicos dos casos foram obtidos dos prontuários físicos e/ou eletrônicos dos pacientes e incluíram sexo, idade, apresentação clínica, tempo de acompanhamento, situação no último acompanhamento e possível manifestação da doença em outras partes do corpo.

Por fim, foram colhidos os dados dos linfomas acometendo as glândulas parótidas, obtidos dos arquivos anatomopatológicos do Laboratório de Imunohistoquímica da Faculdade de Odontologia de Piracicaba (Universidade de Campinas) no período de janeiro de 2008 a dezembro de 2018. Casos que se originam do pescoço ou de linfonodos cervicais com extensão para as glândulas parótidas e aqueles que não apresentavam blocos de tecido ou lâminas de vidro disponíveis para realizar reações coradas por H&E e imuno-histoquímica não foram incluídos. Por outro lado, foram incluídos casos que acometem linfonodos intraparotídeos e que surgiram em pacientes com diagnóstico de síndrome de Sjogren (SS). As seções histológicas originais coradas com H&E e as lâminas imuno-histoquímicas foram avaliadas para pelo menos dois patologistas e os casos classificados de acordo com a 4ª edição das diretrizes da Organização Mundial da Saúde para classificação de tumores de tecidos hematopoiéticos e linfóides (SWERDLOW; CAMPO; HARRIS, 2017). Os dados clinicopatológicos dos casos foram obtidos da patologia e/ou prontuário do paciente e incluíam sexo, idade, apresentação clínica, tempo de acompanhamento, situação no último acompanhamento e, quando possível, informações sobre o processo primário ou disseminado manifestação da doença em outras partes do corpo.

Em todos os três trabalhos foram realizadas análise descritiva, com variáveis categóricas apresentadas como números absolutos e porcentagens, enquanto as variáveis contínuas foram apresentadas como média, desvio padrão (DP) e amplitude. O software SPSS versão 22.0 (IBM, Alemanha) foi utilizado para as análises estatísticas.

4 ARTIGOS

4.1 Artigo publicado no periódico *Head Neck Pathology*

LYMPHOMAS AFFECTING THE SUBLINGUAL GLANDS: A CLINICOPATHOLOGICAL STUDY

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Abstract

Lymphomas affecting the sublingual glands are extremely rare and very few case reports are currently available, which avoid a better understanding of this clinical presentation. Therefore, the aim of the current study is to describe the clinicopathological and microscopic features of a series of lymphomas involving the sublingual glands. All cases diagnosed in four pathology services were assessed and the formalin-fixed paraffin-embedded tissue blocks were retrieved for diagnosis confirmation. Clinical data were obtained from patients' medical files. We obtained seven cases of lymphomas in the sublingual glands representing two follicular lymphomas, two diffuse large B cell lymphomas not otherwise specified (DLBCL NOS), two MALT lymphomas and one mantle cell lymphoma. In all cases the tumor cells infiltrated the glandular parenchymal, although in two of them the neoplastic cells were located more superficially and permeated the glandular acini and ducts. Clinically, the tumors presented as asymptomatic nodules and one patient (affected by DLBCL NOS) died, while the other cases remained alive at last follow-up. In conclusion, lymphomas affecting the sublingual glands are usually of the mature B cell lineage, usually representing low-grade subtypes and may clinically resemble other more common lesions in the floor of the mouth like salivary gland tumors.

Key-words: Lymphoma, MALT lymphoma, follicular lymphoma, sublingual salivary gland, oral cavity, floor of the mouth.

Introduction

Non-Hodgkin lymphomas are estimated to account for approximately 2.8% of all new cancer cases worldwide [1,2]. They are usually diagnosed in lymph nodes, however, extranodal tissues may also be involved [3]. In the head and neck region, the Waldeyer's ring accounts for 15 to 20% of the extranodal lymphomas [4], while in the oral cavity the disease usually affects the palate and the gingival [5,6]. Less common locations include the tongue, buccal mucosa, and the floor of the mouth (FOM) [7,8].

Lymphomas affecting major salivary glands, either primary cases or as an extension of disseminated disease, are very uncommon, representing approximately 1.7 to 3.1% of all salivary gland neoplasms. The sublingual glands are the rarest affected glands, accounting for only 1.5% of all cases affecting the major salivary glands [9,10]. If lymphomas affecting the FOM are included in this incidence, the number of cases still remains low, as this group of neoplasms represents only 0.14% of all FOM lesions [11,12].

Currently, only single case reports and small case series of lymphomas affecting the sublingual glands are available in the literature, precluding a thorough understanding of their clinical manifestations, most common histologic subtypes, and their prognostic significance [10,13,14]. Therefore, the aim of this study was to investigate the clinicopathological features of a series of lymphomas affecting the sublingual glands.

Material and methods

Ethics statement

This study was conducted following approval by the Ethical Committee of the the Universidade Federal de Minas Gerais, Brazil (CAAE: 58900722.1.0000.5149). All procedures 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

Lymphoma cases affecting the sublingual glands were obtained from the pathology files of the Getúlio Sales Diagnósticos laboratory (Natal/Brazil), the Federal University of Pará (Belém/Brazil),the University of the Basque Country (Bilbao/Spain), and the Centro Clínico Cabeza y Cuello (Guatemala City/Guatemala). The files of the oral pathology services of the Federal University of Minas Gerais (Belo

Horizonte/Brazil) and the University of Pretoria (Pretoria/South Africa) were also assessed, however, no cases were identified. Cases registered as affecting the FOM were also included in the search strategy, as the neoplastic cells could involve both subsites, via extension to infiltrate the overlying oral mucosa. Deeper cervical and nodal lymphomas that extended towards the FOM were excluded from the study. The original H&E and immunohistochemical slides, and/or the formalin-fixed paraffin-embedded tissue blocks of all cases were retrieved for histopathological revision by at least two pathologists using the current WHO guidelines for classification of Tumors of Hematopoietic and Lymphoid Tissues [8]. The 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, time of follow-up, and status of the patients at their last appointment. A systemic work-up of the patients, to determine if the sublingual gland lymphomas represented a primary manifestation of the disease or a disseminated process, was obtained if available.

Data analysis

A descriptive analysis was performed, with categorical variables presented as absolute numbers and percentages, 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

Demographics and clinical features

A total of seven lymphomas affecting the sublingual glands were identified. The clinicopathological features of the included cases are detailed in **Table 1**. In summary, females were slightly more affected (4 females:3 males), with the patients' age ranging from 49 to 82 years, with a mean age of 64.3 years. Most of the lesions presented as asymptomatic swellings in the FOM **(Figure 1A-C)**, although associated pain was reported in one case. It was possible to confirm the involvement of the sublingual gland in all cases by either macroscopic evaluation **(Figure 1D)**, imaging studies, or histologic assessment. In two cases the neoplastic cells infiltrated the superior/superficial region of the sublingual gland, while in the other five cases the lymphoma totally infiltrated the glandular parenchyma.

Four patients were treated with surgery alone and one patient received chemotherapy and surgery. Another patient received a chemotherapy regimen

consisting of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), and one patient did not have this information available. Five patients remained alive at their last follow-up, which ranged from 2 to 152 months, with one patient succumbing to disease 27 months after initial diagnosis, whereas for one patient the follow-up data was not available.

Histopathological and immunohistochemical findings

According to the current WHO guidelines for the classification of hematolymphoid tumors [8], two cases were diagnosed as diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS), two cases as follicular lymphomas, two cases as MALT lymphomas, and one case as a mantle cell lymphoma.

Histologically, DLBCL, NOS cases presented a diffuse proliferation of large cells with either centroblastic or immunoblastic features. In one case, the neoplastic cells infiltrated and partially effaced the sublingual gland architecture, while the other case affecting the FOM showed superficial infiltration of sublingual ducts and acini. Immunohistochemically, the neoplastic cells were positive for CD20 and Bcl2, and negative for CD3 and Cyclin D1, showing a Ki67 proliferative marker achieving 90% and 95%, respectively **(Figure 2A and B)**.The single case of mantle cell lymphoma affected the FOM and infiltrated the sublingual gland. It was uncertain whether or not the hematolymphoid neoplasm originated in the glandular parenchyma or if the neoplastic cells infiltrated it. The neoplasm presented as a diffuse lymphoid proliferation, containing small-to-medium-sized neoplastic cells with slightly irregular nuclear contours, with a blastoid appearance. The neoplastic cells were diffusely positive for CD20 and Cyclin D1, and negative for CD3, Bcl2, CD10, and Bcl6, showing a moderate proliferation index (Ki67 ~ 30%) **(Figure 2C and D)**.

The two follicular lymphomas exhibited a follicular growth pattern with the follicles composed predominantly of centrocytes, with a variable number of centroblasts. One case was classified as low-grade follicular lymphoma with the other case being classified as follicular lymphoma grade 3A. The neoplastic cells were diffusely positive for CD20, and revealed positivity for CD10, and Bcl2 proteins in the neoplastic germinal centers**(Figure 3)**. Finally, the MALT lymphoma cases consisted of a diffuse proliferation of small-to-medium-sized neoplastic B cells with the presence of lymphoepithelial lesions. Some medium-sized cells exhibiting a relatively abundant pale cytoplasm consistent with monocytoid cells were noted. The neoplastic cells

diffusely expressed CD20, were negative for CD3, CD5 and Cyclin D1, and one case showed Kappa light chain monoclonality **(Figure 4)**. Patients affected by MALT lymphoma did not have signs and symptoms consistent with Sjögren syndrome.

Discussion

Lymphomas affecting major salivary glands are rare, with more published research required to understand their distribution, clinical manifestations, histologic subtypes, and ultimately their biological behavior and overall prognosis[9,10]. Lymphomas involving the sublingual glands specifically are even rarer, with only isolated case reports currently available in the literature **(Table 2)** [10,13-26]. In our series, despite the presence of two DLBCL NOS, we observed the presence of two follicular lymphomas, two MALT lymphomas, and a single mantle cell lymphoma, suggesting that this subsite is more frequently affected by low-grade variants of mature B cell lymphomas, especially MALT lymphomas.

The sublingual glands are exocrine glands mainly composed of mucinous acini, with the addition of a smaller serous component giving rise to the so-called demi-lune structures [27]. In contrast to the parotid salivary glands, no intra-glandular lymph nodes are found. Rather, a rich lymphatic network exists around these glands, which are located above the geniohyoid muscle, near the oral mucosa [28,29]. In the current series, it was possible to observe during the macroscopic analysis of two cases that the neoplastic infiltrate was strictly associated with the salivary glands. In all cases, the histologic findings demonstrated neoplastic cells infiltrating the glandular parenchyma, although hin two cases the neoplastic cells permeated the glandular ducts and the acini more superficially. It was therefore decided to also investigate lymphomas recorded as affecting the FOM, which represented a very rare manifestation. None of the seven cases included in this series represented tumors originating from cervical lymph nodes, nor extended from deeper soft tissues of the neck, as previously reported [30].

Follicular lymphoma of the sublingual glands is exceedingly rare, with only three cases previously reported in this subsite [10,31,32]. In accordance with our two cases, these patients seem to carry a favorable prognosis, even the single grade 3A follicular lymphoma in our series was alive at the last follow-up. In contrast, MALT lymphoma seems to be the most frequently described lymphoma subtype in the sublingual glands. The diagnosis of primary major salivary gland MALT lymphoma should prompt

clinicians to exclude the possibility of Sjögren syndrome [10,13,14,22]. In both of the current cases of MALT lymphoma, the patients did not have any evidence of the syndrome, with no signs of xerostomia or xerophthalmia observed during clinical examination. Mantle cell lymphoma is a heterogeneous neoplasm, both clinically and microscopically, that may also affect the oral and maxillofacial region [33.34]. Few cases of mantle cell lymphoma affecting the sublingual glands have been described in the literature, usually manifesting as submucosal swellings with other systemic involvement. Although mantle cell lymphoma cases are frequently aggressive, some indolent cases are found, usually associated with the classic histologic subtype rather than the more aggressive pleomorphic and blastoid variants, as observed in our case [20,24]. Moreover, the recently described leukemic non-nodal variant is also considered a less aggressive variant of mantle cell lymphoma. Unfortunately, we did not have complete systemic data to determine whether our mantle cell lymphoma case was consistent with this indolent subtype.

Although rare, high-grade B cell lymphomas affecting the sublingual glands have also been described. DLBCL, NOS is the most common non-Hodgkin lymphoma in many parts of the body including in the oral cavity and oropharynx, where they are generally associated with a poor outcome [35]. This highly heterogeneous neoplasm has only been described once in the sublingual glands, but with incomplete clinical details and an inadequate diagnostic work-up for a definitive diagnosis [19]. Moreover, one case of plasmablastic lymphoma has also been described in the FOM, which despite its well-known aggressive behavior, presented as a rubbery submucosal swelling. Interestingly, there seems to be no report of any NK/T cell lymphoma affecting sublingual glands [25].

A diagnosis of lymphoma affecting the sublingual gland demands strict systemic evaluation of the patient to exclude the possibility of secondary dissemination of the hematolymphoid neoplasm [10]. In the current series, three patients were known to have tumors originating in the sublingual glands. For the other four cases in this series, it was not possible to assess the involvement of other organs or lymph nodes, therefore precluding the complete clinical staging of each patient.

The clinical presentation of lymphomas in the sublingual glands may cause diagnostic confusion, as they may resemble other more common neoplasms in this subsite [17]. Furthermore, although the diagnosis of salivary gland tumors, especially adenoid cystic carcinoma, and mesenchymal lesions in the sublingual glands and the

FOM is also uncommon, they are more frequent than lymphomas [12,36]. Therefore, because our lymphoma cases presented as nodular asymptomatic growths in the FOM, the main diagnostic hypotheses raised by the clinicians before the biopsy or the surgical removal of the lesions was of a salivary gland neoplasm; consequently, the use of fine needle aspiration cytology (FNAC) may be advocated in these cases, since the use of FNAC is a useful diagnostic tool for salivary gland tumors and has also been described in the context of lymphomas [37,38], although its diagnostic value was reported to be lower than for other major salivary glands [36]. Interestingly, when high-grade lymphomas like the DLBCL,NOS of our series, are diagnosed in the sublingual glands they usually present as less destructive neoplasms.

In conclusion, lymphomas involving the sublingual glands are very rare and more frequently represent low-grade mature B cell lymphoma subtypes including follicular lymphoma, MALT lymphoma and mantle cell lymphoma. Moreover, clinicians should be aware of hematolymphoid neoplasms arising in the major salivary glands and not misdiagnose these lesions as salivary gland tumors or other mesenchymal neoplasms. Finally, the diagnosis of lymphoma involving the sublingual gland should prompt further systemic evaluation of the patient to determine if it is a primary or a disseminated neoplasm.

Author Contributions FPF: Study concepts, FPF: Study design, GRdA, ALM-P, CVBLdC, MAL, JMA-U, RC, ER, WFPvH, LR, HARP, BABdA, CDS: Data acquisition, FPF, RSG, CDS: Quality control of data and algorithms, FPF, BABdA, RSG: Manuscript editing, All authors: Manuscript review.

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Data Availability The manuscript has no further associated data in a data repository.

Code Availability Not applicable.

Declarations

Conflict of interest We state that all authors confrm that they have no potential confict of interest that could bias the results obtained in the current study, that the material is original, has not been published nor previously submitted elsewhere.

Ethical Approval The questionnaire and methodology for this study was approved by the Human Research Ethics committee of the Universidade Federal de Minas Gerais (CAAE: 58900722.1.0000.5149).

Consent to Participate Informed consent was obtained from all individual participants included in the study.

Consent to Publish The participant has consented to the submission of the case report to the journal.

Research Involving Human and Animal Participants Not applicable.

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Table 1. Clinicopathological features of lymphomas affecting the sublingual glands.

Case	Subtype	Age/ Sex	Symptoms	Signs	IHC	Treatment	Follo w-up*	Status
1	Follicular lymphoma	63/F	Painless	Nodule	CD20+, CD3-, Bcl2+, CD10+f, CD21+, CD23+	Surgery	2	Alive
2	MALT lymphoma	72/F	Painless	Nodule	CD20+, CD3 +focal, Kappa+, Lambda-, Ki67 low	Surgery	6	Alive
3	MALT lymphoma	60/M	Painless	Nodule	CD20+, CD3+focal, CD23-, CD5-, cyclin D1-, CD10-, Bcl2+, Ki67 10%	Surgery	2	Alive
4	Follicular lymphoma	53/F	Painless	Nodule	CD20+, CD3-, CD10+, Bcl2+	Surgery	152	Alive
5	DLBCL	71/M	Painful	Tumor	CD20+, CD3-, CD5-, CD10+, Ciclin D1-, Bcl2+, Bcl6+, MUM1-, TdT-, c-Myc-, Ki67 ~95%	Chemot. + Surgery	27	Dead
6	DLBCL	82/M	NS	Tumor	CD20+, CD3-, Bcl2+, Ciclin D1-, Ki67 ~90%	CHOP	58	Alive
7	Mantle cell lymphoma	49/F	Painless	Nodule	CD20+, CD3-, Bcl2-, CD10-, Bcl6-, Ciclin D1+, Ki67 ~30%	NS	NS	NS

Table 2. Clinicopathoogical features of lymphomas affecting sublingual glands previously reported in the literature.

Study	Year	Sex	Age	Laterality	Diagnosis	Clinical presentation	Size (mm)	Enlarged lymphnodes	Symptoms	IHQ/FISH	Treatment	Outcome	Follow up (mo)
Leong	2001	ND	ND	3 lesions in FOM [1]	ND	ND	ND	ND	ND	ND	ND	ND	ND
Honda	2004	F	71	bilateral	MALT	swelling, hard, elastic, mobile, mass, shaped like a horseshoe	20x25	no	ND	ND	RT	alive	ND
Honda	2004	F	63	ND	MALT	hard, elastic, mobile tumor	40x14	ND	ND	ND	ND	ND	ND
Honda	2004	F	82	left	MALT	hard, elastic, mobile tumor	37x17	yes	pain	ND	ChT	dead	24
Rockacy	2007	F	72	right	MCL	submucosal swelling, nontender, smooth-surfaced	15	no	no	IHQ: (+) CD20, BCL2, CYCLIN D1	Surgery	alive	12
Kemp	2008	ND	ND	FOM [1]	NHL	ND	ND	ND	ND	ND	ND	ND	ND
Léon	2009	M	44	ND	DLBCL	ND	ND	ND	ND	IHQ: (+) CD45, CD20, EBER (-) CD3, CD15, CD30, EMA, kappa and lambda chains, EBV-LMP	ND	ND	ND
Guggisberg	2010	F	72	ND	MCL	ND	15	ND	ND	IHQ: (+) CD20, CD5,	ChT	alive	ND

										CD43, CCND1			
Yoshiba	2011	M	64	left	MALT	diffuse, firm swelling	24x22x11	no	no	IHQ: (+) CD20, CD79a, Ki67 (to scattered transformed large cells)	Surgery	alive	36
Hsu	2014	F	54	left	MALT	nonmovable mass	12x8	ND	dry eye and dry mouth	no	Surgery	alive	ND
Makihara	2014	M	81	right	MALT	fibrous enlargment	25x15x18	no	ND	ND	Surgery	ND	ND
Ananian	2015	ND	ND	FOM [1]	MALT[2]	ND	ND	ND	ND	ND	ND	ND	ND
Hayashi	2015	M	82	bilateral	MCL	submandibular, labial salivary and sublingual glands were elastic, hard and swollen	ND	yes	dry mouth	IHQ: (+)CD20, CD79a, CD5, BCL2, CYCLIN D1 (-) CD3, CD10	RT+ChT	dead	12
Samoon	2015	F	30	FOM [1]	PBL	small firm nodule	10	no	dysphagia	IHQ: (+) CD138, CD79a, CD56, MUM1/IFR4, Ki67 60% (-) CD20, CD3	ChT, then supportive care	alive	>2
Ainscough	2016	M	69	right	MCL	rubbery submucosal mass swelling	40x20	no[3]	no	ND	conservative	alive	ND
Abukhiran	2020	M	70	bilateral	MCL	enlargement of the sublingual glands	ND	ND	no	IHQ: (+) CD20, CD5, Cyclin D1, Ki67 20% (-) CD10,	ChT	alive	11

										CD3, BCL6, CD23			
Iversen	2020	M	61	left	EMZL[4]	mobile swelling	20	no	no	IHQ: (+) BCL2, CD20, Ki67 20% | FISH: IGH/MALT1 translocation (16%)	Surgery +ChT	alive	192
Iversen	2020	F	68	left	relapsing MCL	tender swelling	ND	yes	weight loss	IHQ: (+) PAX5, Cyclin D1, SOX11, CD5, Ki67 >80% | FISH: IGH/CCND1 translocation (65%) Flow Citometry: 70.1% clonal B-cells + for CD5, CD10, CD19, CD20, CD43, CD79 and with lambda light chain restriction	ChT	dead	18
Iversen	2020	F	75	left	FL	mobile process at the left caruncle covered by intact mucosa	15	no	ND	IHQ: (+) CD10, CD20, BCL2, BCL6, Ki67 20%	ChT+RT	alive	120

F=female; M=male; FOM=floor of the mouth; MALT=mucosa-associated lymphoid tissue; MCL=mantle cell lymphoma; PBL=plasmablastic lymphoma; EMZL=extranodal marginal zone lymphoma; FL=follicular lymphoma; ND=not described; IHQ=immunohistochemestry; FISH=fluorescence in situ hybridization; mo=months; RT=radiotherapy; ChT=chemotherapy

[1]Do not specify whether it was in the sublingual gland; [2]5 cases/21 cadavers; [3]Underwent staging investigations with positron emission tomography-computed tomography and found a 2cm lymph node in the neck; [4]Three years after the first presentation, the patient returned symptomatic, confirming relapsed EMZL and received again ChT. After 3 years it relapsed again, being treated with ChT and RT. After another 5

Figures

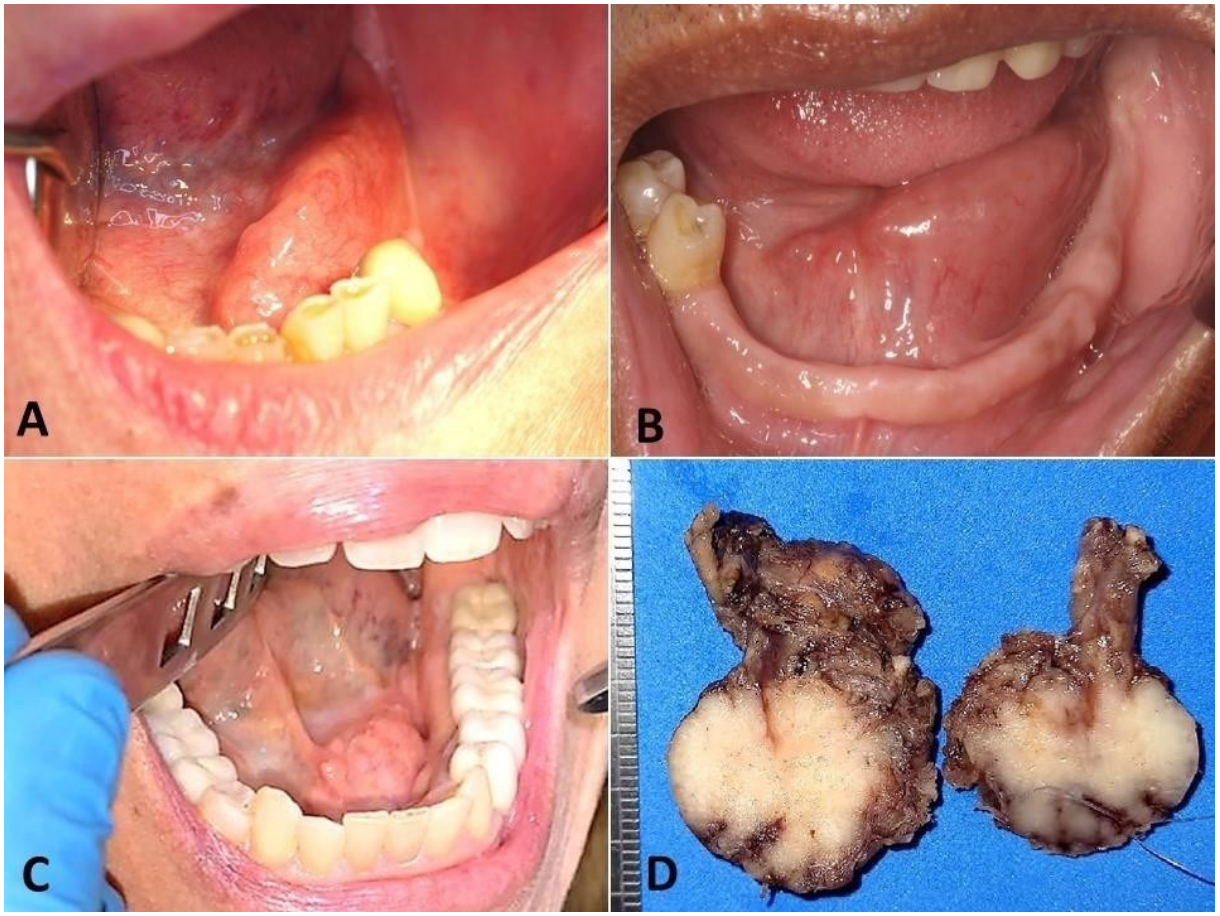

Figure 1. Clinical presentation of lymphomas affecting the sublingual glands. A) MALT lymphoma in a 72-year-old female patient presenting with a painless swelling in the floor of the mouth (Case #2). B) MALT lymphoma in a 60-year-old female patient presenting as a painless fibrotic swelling (Case #3). C)Follicular lymphoma in a 63-year-old female presenting as an asymptomatic swelling in the floor of the mouth (Case #1).D)Surgical specimen of a follicular lymphoma affecting the sublingual gland (Case #1). The tumor presented with an irregular shape and smooth surface, with a whitish-to-brown coloron cut-section.

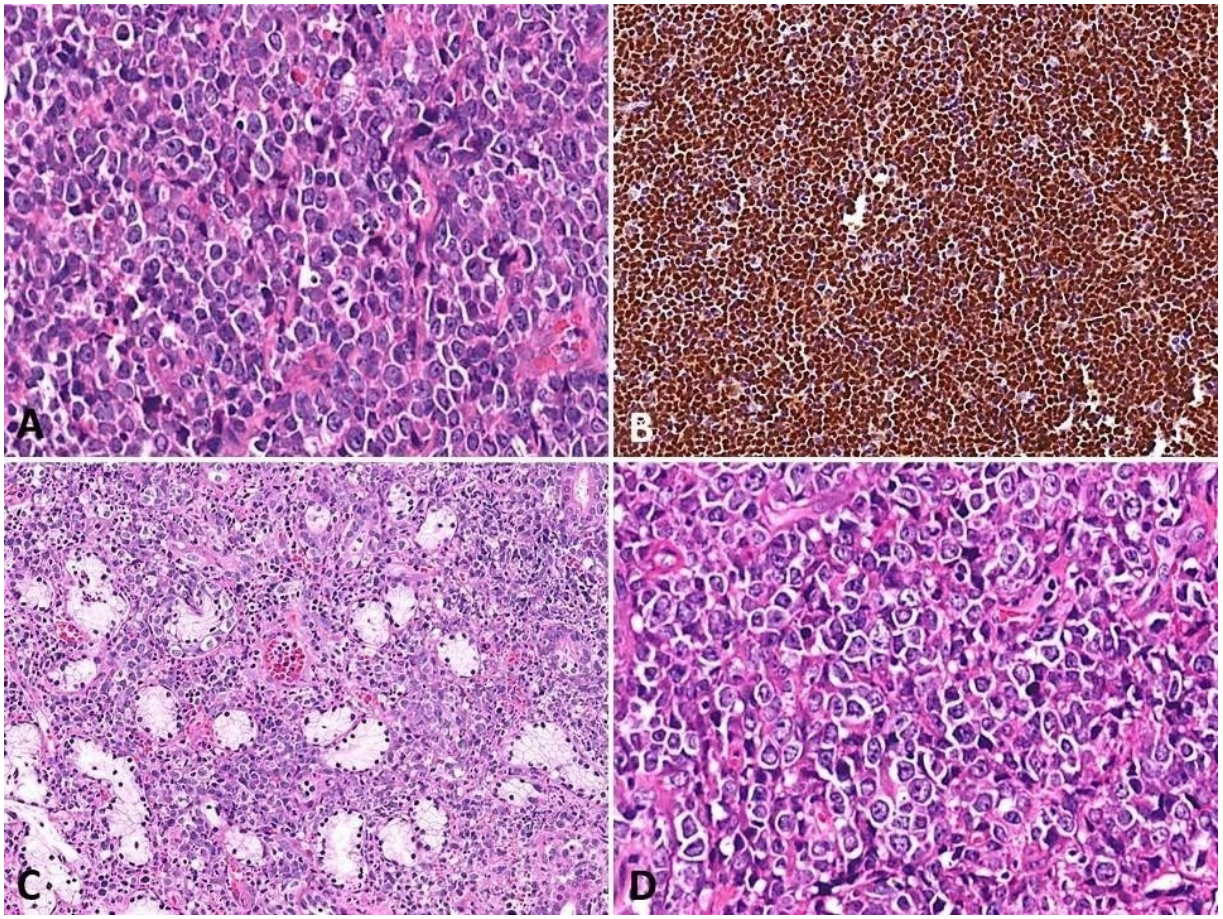

Figure 2. Microscopic features of mantle cell lymphoma and DLBCL, NOS affecting the sublingual gland. A) The mantle cell lymphoma case exhibited small to moderate-sized cells with a blastoid aspect. Mitotic figures were seen(H&E; 200x). B) Cyclin D1 was strongly and diffusely expressed in the nuclei of tumor cells (DAB; 100x). C) DLBCL, NOS exhibited a diffuse proliferation of tumor cells that infiltrated the glandular ducts and acini (H&E; 400x). D) Neoplastic cells were predominantly composed by large immunoblasts and centroblasts with prominent nucleoli (H&E; 50x).

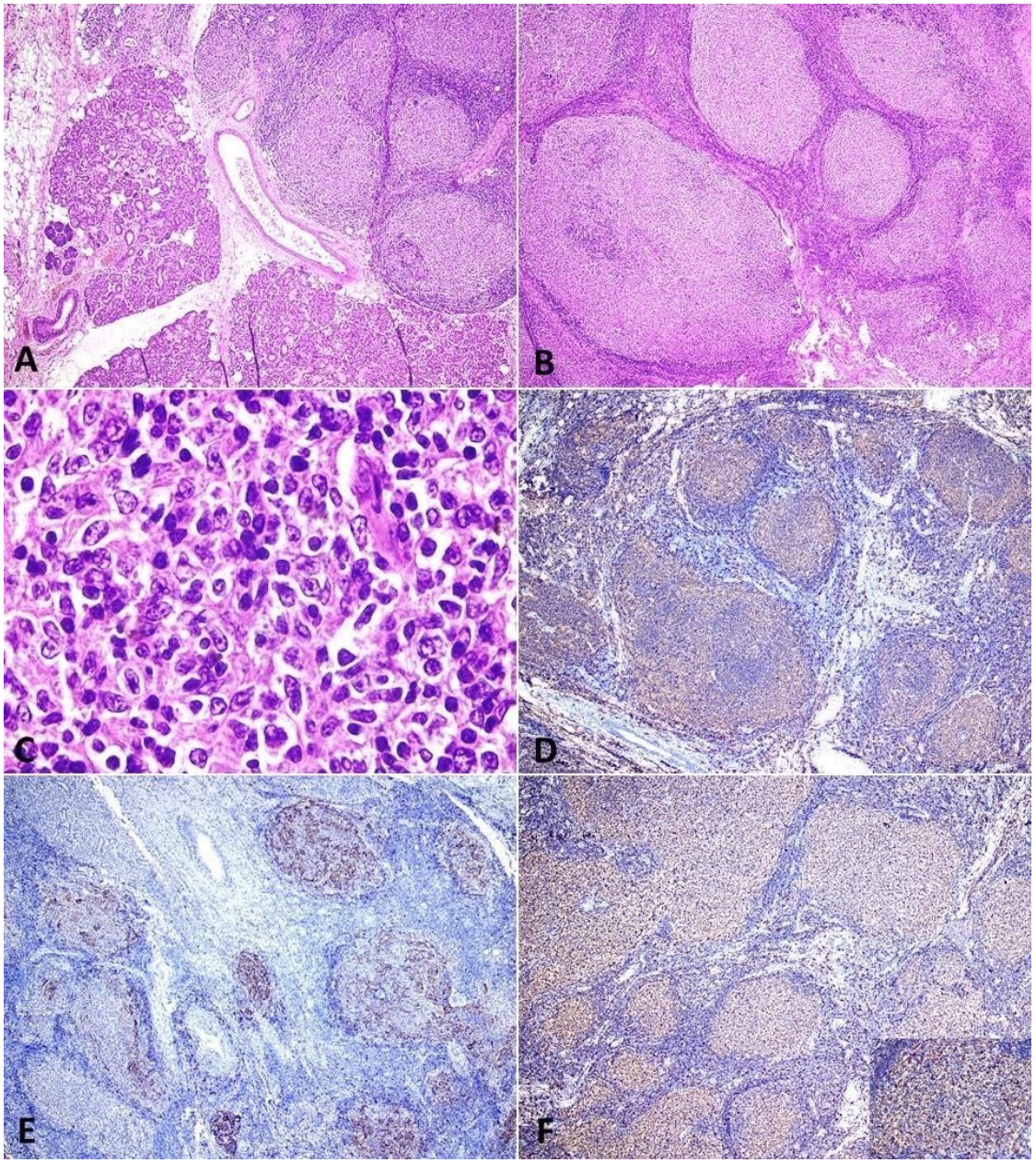

Figure 3. Microscopic features of follicular lymphoma in the sublingual gland. A) The neoplasm exhibited a follicular growth pattern strictly associated with the sublingual gland (H&E; 50x). B) Closely packed neoplastic follicles focally showing a back-to-back pattern(H&E; 100x). C) The neoplastic lymphoid infiltrate was composed predominantly of centrocytes, with several scattered centroblasts leading to the diagnosis of a grade 3A follicular lymphoma (H&E; 400x). D) The neoplastic cells were diffusely positive for CD20 (H&E; 50x) and E) revealed positivity for CD10 (H&E; 50x)and F) Bcl2 proteins in the neoplastic germinal centers [H&E; 100x; higher-magnification in the inset (DAB; 200x)].

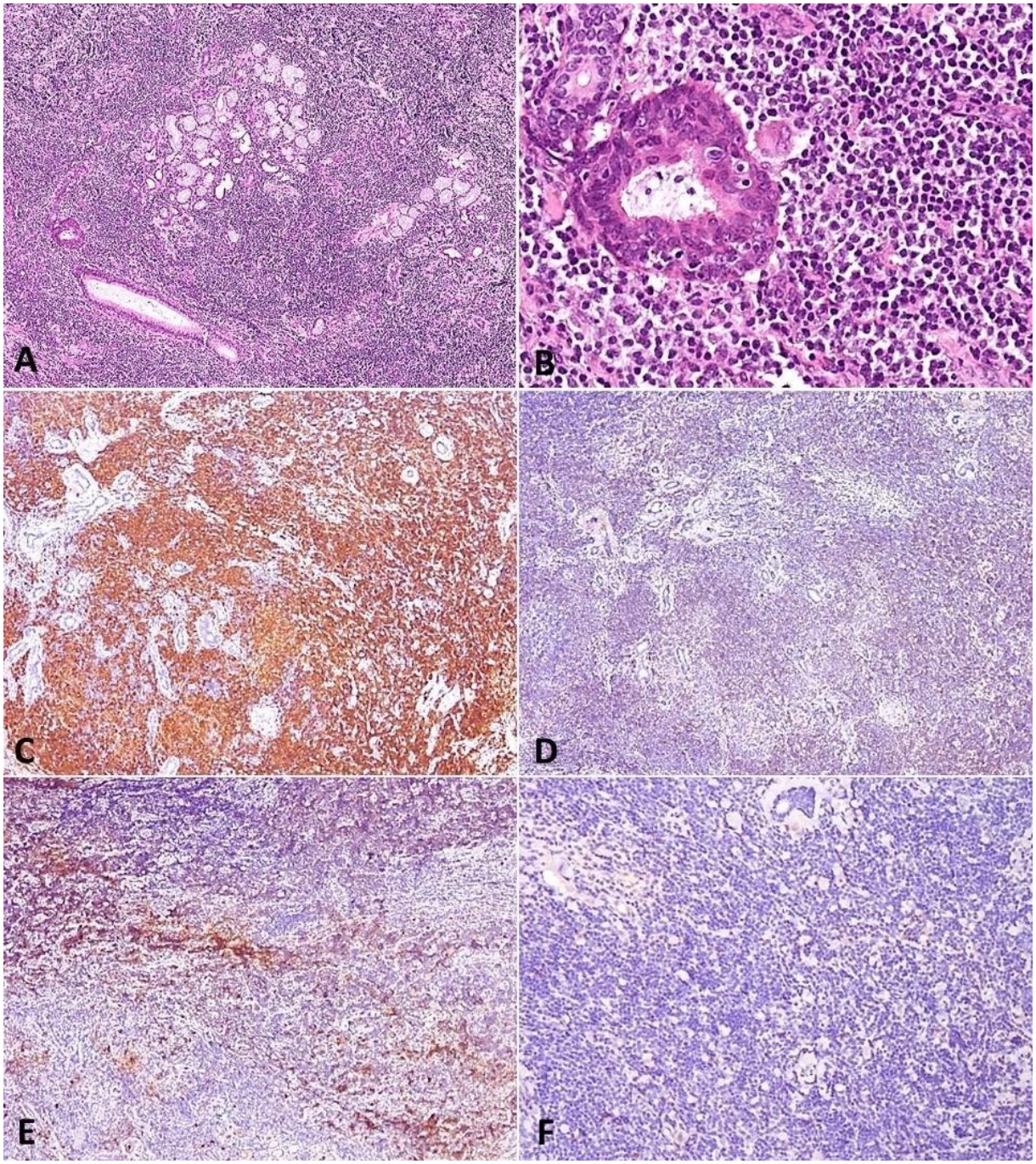

Figure 4. Microscopic findings of MALT lymphoma affecting the sublingual gland. A) A diffuse proliferation of small-to-moderate-sized neoplastic cells with scant cytoplasm (H&E; 100x).B) Presence of neoplastic cells infiltrating glandular structures (H&E; 100x).C) The neoplastic cells were diffusely positive for CD20 (DAB; 100x) and D) negative for CD3 (DAB; 100x). E) Monoclonality for Kappa light chain was observed (DAB; 100x). F) Lambda light chain was negative (DAB; 100x).

4.2 Artigo publicado no periódico *Medicina Oral, Patologia Oral y Cirugia Bucal*

LYMPHOMAS AFFECTING THE SUBMANDIBULAR GLANDS

Lymphomas in the submandibular glands

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Abstract

Background: Lymphomas affecting the submandibular glands are very uncommon and few reports are currently available in the literature. Therefore, the aim of the current study is to describe the clinical and microscopic features of an original series of lymphomas affecting the submandibular glands.

Material and Methods: The pathology files of two institutions were searched for lymphoma cases affecting the submandibular glands. The original hematoxylin and eosin, and immunohistochemical slides were revised by a pathologist for diagnosis confirmation following the revised 4th edition of the World Health Organization classification of tumours of haematopoietic and lymphoid tissues. Clinical data regarding age, sex, clinical manifestation, treatment, follow-up and status at last appointment were retrieved from the patients' medical charts.

Results: During the period investigated, 16 cases were included in the study. Females predominated (10:6) with a mean age of 57.8 years-old. Tumors usually presented as asymptomatic swellings. MALT lymphoma represented the most common subtype, followed by diffuse large B cell lymphoma and follicular lymphoma. Three patients died, one of them affected by plasmablastic lymphoma, one by DLBCL and one by MALT lymphoma.

Conclusion: Low-grade B cell lymphomas predominate in the submandibular glands, but DLBCL and other subtypes may also be rarely diagnosed in this salivary gland.

Key-words: Lymphoma, Salivary gland, Submandibular gland, MALT lymphoma, Follicular lymphoma, diffuse large B cell lymphoma.

Introduction

Non-Hodgkin lymphoma (NHL) is one of the most common human cancers and is characterized by a wide range of clinical manifestations and a complex microscopic classification (1,2). Its incidence showed an increasing trend worldwide from 1990 to 2019 (3). However, the primary involvement of salivary glands is considered very uncommon.

Primary NHL of the salivary gland represent approximately 5% of all extra-nodal non-Hodgkin lymphomas and only 1.7% of all salivary gland tumors (4). Most NHL that occurs in the salivary glands are B-cell lymphomas (5-7) and the submandibular glands are the second most affected major salivary gland after the parotid glands. According to previous small series and individual case reports the most common subtypes affecting the submandibular glands are the marginal zone lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma), follicular lymphoma (FL) and diffuse large B-cells lymphoma (DLBCL) (7-10).

Given the lack of larger series available in the literature, the biological heterogeneity of this group of neoplasms, their unspecific clinical manifestations and because they are very rarely found in the submandibular glands, the diagnosis of lymphomas in this anatomical region remains a challenge, possibly leading to a late diagnosis and an inappropriate management, deserving to be further documented and investigated (10-12). Therefore, the aim of this study was to describe the clinicopathological features of a series of lymphomas affecting the submandibular glands.

Material and methods

Ethics statement

This study was done with approval from the Ethics Committee of the Federal University of Minas Gerais, Brazil (CAAE: 58900722.1.0000.5149). All procedures were in accordance with the ethical standards of the committee for human experimentation (institutional and national) and with the Declaration of Helsinki of 1975, revised in 2008.

Sample and data collection

All cases of lymphomas affecting the submandibular glands were obtained from pathology files of the Getúlio Sales Diagnostics Laboratory (Natal/Brazil) and the Immunohistochemistry Laboratory of the Piracicaba Dental School (University of Campinas) in a time period ranging from January 2003 and December 2019. Lymphoma cases that were known to originate from the neck or from the surrounding lymph nodes that extended and invaded the submandibular glands were not considered in this study. Original H&E-stained histological sections and immunohistochemistry slides were obtained for diagnosis confirmation, which followed the revised 4th edition of the World Health Organization classification for hematopoietic and lymphoid tissue tumors (13). Demographic and clinical data of the cases were obtained from the patient's pathology and/or medical records and comprised gender, age, clinical presentation, follow-up time, status at last follow-up and the possible manifestation of the disease elsewhere in the body.

Data analysis

Descriptive analyses were carried out, with continuous variables expressed as mean, standard deviation (SD) and range, while categorical variables were expressed as absolute numbers and percentages. The SPSS software version 22.0 (IBM, Germany) was used for statistical analysis.

Literature review

An electronic search was carried out in December 2022 using the database PubMed/MEDLINE to retrieve all previous reports of lymphomas affecting the submandibular glands that contained individual data available for consultation published from 2001, when the third edition of the WHO classification of hematopoietic and lymphoid tissue tumors was published. The search strategy comprised the following key-words: ("submandibular gland" OR "submandibular glands") AND ("lymphoma" OR “lymphomas”). A manual search on the articles’ references was also performed in order to expand the search. Lymphomas affecting other major salivary glands and those without diagnostic information including histologic and immunohistochemical data, were not included in this review.

Results

A total of 18 lymphoma cases affecting the submandibular glands were identified in the period investigated; however, the histological and/or immunohistochemical slides of two cases were not available for revision and, therefore, were excluded from the study. The clinicopathological data of the 16 cases included in this study are detailed described in **Table 1.** In summary, females predominated (10 cases:6 cases), and a mean age of 57.8 years-old was observed, ranging from 32 years-old to 87 years-old. Tumors presented as asymptomatic unilateral swellings in the submandibular region **(Figure 1)**. Regarding morphological distribution of the cases, MALT lymphoma represented the most frequent histological subtype (7 cases), followed by three cases of DLBCL NOS, 2 cases of follicular lymphomas, one plasmablastic lymphoma and one peripheral T cell lymphoma NOS. Two cases could not be further classified and received the diagnosis of small B cell lymphomas. Five cases were treated by surgery only, while four were treated with different chemotherapeutic schemes. Treatment data was not available for six cases. Follow-up data was available for 12 patients and ranged from 3 to 76 months, with a mean time of 26.4 months. Nine patients were alive free of disease, whereas three patients died (one affected by plasmablastic lymphoma, one by MALT lymphoma and one by DLBCL NOS).

Microscopically, MALT lymphomas were characterized by the proliferation of small to medium-sized neoplastic B cell, with the frequent presence of plasma cells. Monocytoid B cells could be observed in all cases and lymphoepithelial lesions were present in all eight cases **(Figure 2)**. DLBCL NOS was microscopically heterogeneous and characterized be the presence of atypical large B cells with both centroblast and immunoblast features. The two cases of follicular lymphomas were both diagnosed as low-grade subtypes and revealed the presence or poorly defined neoplastic follicles proliferating in the glandular parenchyma **(Figure 3)**. Plasmablastic lymphoma was also comprised by large cells resembling plasmablasts that were positive for EBV detection. The only T-cell neoplasm of this sample represented a PTCL NOS case and exhibited a pleomorphic and heterogeneous microscopic aspect containing small and large cells.

In our literature review 21 articles reporting lymphomas in the submandibular glands could be retrieved, accounting for 30 cases. The clinicopathological data are detailed in **Table 2** and references of this table can be found in **Supplementary**

File 1. Briefly, females predominated (20 females:10 males), with the patients' age ranging from 24 to 75 years, and a mean age of 57.7 years. Most of the lesions presented as a firm, asymptomatic swelling, although discomfort on eating, fever and weight loss were also described. The most common treatment applied was surgery, with eight patients treated with surgery alone; three patients with surgery, chemotherapy and radiotherapy; five with chemotherapy and radiotherapy; six with chemotherapy only; one underwent radiotherapy only and one with surgery and radiotherapy. The information was not available for four patients. Twenty-two patients remained alive at their last follow-up, which ranged from 3 to 120 months. Microscopically, MALT lymphoma and Follicular lymphoma predominated, but DLBCL mantle cell lymphoma, extranodal NK/T-cell lymphoma, Burkitt's lymphoma, and peripheral T-cell lymphoma, not otherwise specified were also described (**Supplementary File 1)**.

Discussion

Non-Hodgkin lymphomas represent a highly heterogeneous group of hematological malignancies that comprise a diverse number of subtypes in the WHO classification of lymphoid tissue tumors (13). They usually affect the lymph nodes, but extranodal manifestations are found in approximately 40% of the cases. The salivary glands is uncommonly affected and the parotid gland is the most involved, especially in patients with Sjögren syndrome (14), while very few cases were reported in the submandibular glands. In this series we demonstrated that MALT lymphoma, DLBCL NOS and follicular lymphoma were the most frequent entities in submandibular glands, similar to our previous study evaluating lymphomas in the sublingual glands (15).

Submandibular glands are located in the submandibular triangle, they have a superficial and a deep lobe separated by the mylohyoid muscle and their main excretory duct, Wharton's duct, measures approximately 5 cm in length and 1.5 mm in diameter and drains inside the oral cavity (16). The submandibular gland is the second largest major salivary gland and its encapsulated tissue is considered a branched tubuloacinar gland composed of mucinous and serous acini, producing most saliva in the unstimulated state and different from parotid glands there is no intraglandular lymph nodes (16,17).

A large number of neoplasms can affect the submandibular glands, accounting for 7% to 11% of all salivary gland tumors and the clinical manifestation of these disorders are usually non-specific, manifesting as asymptomatic swellings (18). Approximately 30% to 54% of these neoplasms are malignant, more often carcinomas, especially adenoid cystic carcinoma, mucoepidermoid carcinoma and carcinoma ex-pleomorphic adenoma (18,19). However, mesenchymal (20) and lymphoid neoplasms (21) can also be found. Moreover, non-neoplastic diseases may also develop in these glands and sialolithiasis is one of the most common pathological conditions, frequently causing painful swellings (22). IgG4-related disease may also manifest in the submandibular glands and it should be considered in the differential diagnosis of lymphomas when this anatomic structure is evaluated for a lymphoid pathological process (23). The use of fine needle aspiration cytology to diagnose submandibular lesions is contributory, and it may aid in the management of the affected patients (19,24).

Only a few lymphoma cases affecting the submandibular glands have been described in the literature, most commonly manifesting as painless swellings in the cervical region. The current study represents one of the largest series described in the literature and we have also observed asymptomatic swellings as the most common clinical presentation of the disease. In accordance to our results, MALT and follicular lymphomas seems to be frequent subtypes in this region, with several cases being previously reported (25,26). However, the occurrence of higher-grade variants, especially DLBCL NOS has already been demonstrated (10,27). In our series, we identified two DLBCB NOS and one plasmablastic lymphoma. So far, we have not been able to find another case of plasmablastic lymphoma in these glands, demonstrating that pathologists must be aware for the occurrence of rare subtypes. Similarly, the presence of T cell lymphomas in submandibular glands is also very rare, with some single reports describing PTCL NOS (28) and FTH (29) lymphomas. In this study we included one case classified as PTCL NOS. The occurrence of these uncommon subtypes affecting the submandibular glands should also consider the possibility of tumor infiltration originating from surrounding lymph nodes that could not be demonstrated by histology analyses.

The diagnosis of a lymphoma in the major glands demands from clinicians a special care for Sjögren syndrome, which increases the risk for the development of hematolymphoid neoplasms (14,25). In this scenario, MALT lymphoma is the most

frequently diagnosed, but its distinction from reactive sialadenitis and follicular lymphomas may be often very difficult, demanding genetic evaluations. The presence of t(14;18)(q32;q21)/*IGH-MALT1* is found in 15% of the cases and, together with the presence of immunoglobulin light chain restriction by immunohistochemistry or in situ hybridization, contributes to confirm the diagnosis of MALT lymphoma (30). Moreover, the use of imaging exams like ultrasound, not only collaborates with the diagnosis of the diseases, but it also represents a useful tool to confirm the involvement of the submandibular glands and to illustrate the limits of the disease, which is especially important considering the presence of various lymph node chains surrounding the gland (24).

As a consequence of a higher predominance of lower-grade B cell lymphomas in submandibular glands, the prognosis of the affected patients is usually favorable, with long survival rates. Depending on the microscopic subtype and also on tumor stage in the moment of diagnosis, treatment comprises surgery, radiotherapy and/or chemotherapy. Different schemes can be applied, but R-CHOP is usually the most used and significantly improved patients' survival (10). In our series three patients passed away, two of them affected by high grade neoplasms, plasmablastic lymphoma and DLBCL NOS, and one affected by MALT lymphoma, who deceased due to another reason not related to the neoplasm.

In conclusion, we demonstrated that submandibular gland is more often affected by low-grade B cell neoplasms like MALT lymphoma and follicular lymphoma, which resembles the results obtained in our previous series of lymphomas affecting the sublingual glands. However, diagnosticians should be aware for high-grade subtypes affecting submandibular glands, especially DLBCL NOS.

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Table 1. Clinicopathologic features of 16 lymphoma cases affecting the submandibular glands.

No.	Sex	Age	Diagnosis	IHC	Treatment	Follow-up (months)	Status
1	F	NS	Small B cell lymphoma	CD20 +, CD3 -, Cyclin D1 -, Bcl2 -, CD23 -, Ki67 85%	NS	NS	NS
2	F	NS	Small B cell lympoma	CD20 +, CD3 -, CD10 +, MUM1 +, Bcl2 +, Bcl6 -, Cyclin D1 -, Ki67 20%	NS	NS	NS
3	F	77	FL	CD20+, CD3-, Bcl2+, Ki67~20%	NS	NS	NS
4	M	52	PBL	CD138+, MUM1 +, LCA -, CD20 –, CD79a –, CD3 –, BCL2 –, BCL6 –, CD30 –, CD246 (Alk1) –, PAX-5 –, Granzyme B –, EBV+, MUM1+, CD10+, Ki67 100%	Surgery	8	Died
5	F	39	PTCL NOS	LCA +, CD20 –, CD45RO +, CD3 +, CD5 +, CD30 –, CD15 –, CD43 –, Cyclin D1 –, BCL2 +, AE1/AE3 –, Ki67 +++	NS	41	Disease-free
6	F	44	MALT	LCA –, CD20+, CD45RO –, CD3 –, CD30 –, CD15 –, CD10 –, CD5 –, Cyclin D1 –, BCL2 +, BCL6 –, AE1/AE3 –, EMA –, CK8/18 –, Vimentin +, Ki67 ++	Surgery	-	Lost
7	M	81	MALT	CD20 +, CD3 –, CD10 +, MUM1 –, BCL2 –, BCL6 +, Ki67 90%	Surgery	76	Disease-free
8	F	52	MALT	CD20 +, CD3 –, CD5 –, CD23 +, CD10 +, Cyclin D1 –, CD43 –, AE1/AE3 –, BCL2 +, BCL6 +, Ki67 20%	NS	21	Disease-free
9	F	87	MALT	CD20 +, CD3 –, CD30 –, CD10 –, CD5 –, Cyclin D1 –, MUM1 –, BCL2 –, BCL6 +, Ki67 90%	NS	54	Died
10	F	46	DLBCL	CD20 +, CD3 –, CD5 –, Cyclin D1 –, CD23 –, CD43 –, CD10 –, BCL2 +, BCL6 –, AE1/AE3 –, Ki67 40%	CHOP	19	Disease-free
11	F	32	FL	CD20 +, CD3 –, CD30 + focal, BCL2 +, BCL6 +, CD10 +, MUM1 +, CD5 –, Cyclin D1 –, Ki67 60%	Surgery	20	Disease-free
12	M	58	DLBCL	CD20 +, CD3 –, CD5 –, Cyclin D1 –, CD23 –, CD43 –, CD10 –, BCL2 +, BCL6 –, AE1/AE3 –, Ki67 85%	Surgery	3	Died
13	F	73	MALT	CD20 +, CD3 –, CD5 –, CD23 +, CD10 +, Cyclin D1 –, CD43 –, AE1/AE3 –, BCL2 +, BCL6 +, Ki67 5%	Rt+CVP	31	Disease-free
14	M	48	MALT	CD20 +, CD3 –, CD10 +, MUM1 –, BCL2 –, BCL6 +, Ki67 10%	Rt+Bd	29	Disease-free
15	M	72	DLBCL	Desmin –, TdT –, CD3 –, CD20 +, CD10 +, BCL2 +, BCL6 –, MUM1 –, CD99 –, Ki67 100%	CHOP	6	Disease-free
16	M	49	MALT	CD20 +, CD3 –, CD30 –, CD10 –, CD5 –, Cyclin D1 –, MUM1 –, BCL2 –, BCL6 +, Ki67 15%	Rt+Bd	9	Disease-free

F=female*; M*=male; *MALT*=mucosa-associated lymphoid tissue; *PL*=plasmablastic lymphoma; *EBV*= Epstein-Barr virus; *T Linf, SOE*= T-cell lymphoma, not otherwise specified; *HL*=Hodgkin lymphoma; *DLBCL*=diffuse large B-cells lymphoma;*FL*=follicular lymphoma; *NS*=not specified. Rituximab (immunotherapy) with bendamustine (Rt+Bd); Rituximab with CVP (Rt+CVP)

Table 2. Clinical and microscopic features of lymphomas affecting the submandibular gland previously published in the literature.

Authors/Year	Sex	Age	Laterality	Diagnosis	Clinical presentation	Size (mm)	LN	Symptoms	IHC/FISH/ FC/PCR	Treatment	Outcome	Follow up (mo)
Ochoa et al., 2001 (14)	M	65	Right	MALT	Enlargement of a gland mass	30x30	No	No	FC: CD3 14%, CD5 12%, CD7 14%, CD3-8 <1%, CD4 6%, CD8 8%, CD19 83%, CD20 84%, Kappa <1%, Lambda 83%, CD5 <1%, CD10 <1%, CD23 <1%	Surgery	Alive	24
Kojima et al., 2001 (15)	F	50	Left	FL	Firm, tumor	ND	ND	ND	IHC: (+) CD10, BCL2-2, BCL-6 (-) CD5, CD23, cyclin D1, p53, EBER	RT	Alive	120
	F	64	Right	FL	Firm, tumor	ND	ND	ND	IHC: (+) CD10, BCL-6, p53 (-) CD5, CD23, Cyclin D1, BCL-2, EBER	None	Alive	6
Yasumoto et al., 2001 (16)	F	40	Left	Lymphoma	Tumor, partially irregular	40	No	ND	ND	Surgery	ND	ND
	M	68	Left	Lymphoma	Tumor, irregular	40	No	ND	ND	Surgery	ND	ND
	M	73	Left	Lymphoma	Tumor, partially irregular	25	No	ND	ND	Surgery	ND	ND
	F	58	Left	Lymphoma	Tumor, partially irregular	40	No	ND	ND	Surgery	ND	ND
Kojima et al., 2003 (17)	M	48	Right	FL	Tumor	30	ND	No	IHC: (+) CD10, BCL6, CD20, CD79a (-) CD3, CD5, CD21, CD23,	ND	Alive	13

	F	64	Right	FL	Tumor	20	ND	No	CD43, CD45RO, BCL2, Cyclin D1, EBER IHC: (+) CD10, BCL6, CD20, CD79a (-) CD3, CD5, CD21, CD23, CD43, CD45RO, BCL2, Cyclin D1, EBER	ND	Alive	28
	F	68	Right	FL	Tumor	20	ND	No	IHC: (+) CD10, BCL6, CD20, CD79a (-) CD3, CD5, CD21, CD23, CD43, CD45RO, BCL2, Cyclin D1, EBER	ND	Alive	3
Nakamura et al., 2006 (18)	F	45	Left	FL	ND	ND	Yes	ND	IHC: (+) CD79a, CD10, BCL2 (-) CD3, CD5, Cyclin D1 | PCR: monoclonal IgH, (-) BCL-2/IgH	ChT	Alive	120
	F	73	Left	FL	ND	ND	ND	ND	IHC: (+) CD79a, CD10, BCL2 (-) CD3, CD5, Cyclin D1 | PCR: monoclonal IgH, (+) BCL-2/IgH	Observation	Dead	31
	F	39	Bilateral	FL	ND	ND	No	ND	IHC: (+) CD79a, CD10, BCL2 (-) CD3, CD5, Cyclin D1 | PCR: monoclonal IgH,	ChT, RT	Alive	36

	F	66	Left	FL	ND	ND	Yes	ND	(+) BCL-2/IgH IHC: (+) CD79a, CD10 (-) CD3, CD5, Cyclin D1, BCL2 | PCR: monoclonal IgH, (-) BCL-2/IgH	ChT, RT	Alive	56
Mikolaenko et al., 2009 (19)	F	75	Right	MALT	Enlarging ,smoothhomogeneousmass	370x230x160	No	No	IHC: (+) CD19,CD20, CD5 ,CD23 , FMC7, and Surface IgM λ , (-)CD10 and CD11c	Cht	Alive	6
Perera et al., 2010 (20)	F	73	Left	MALT	Mass, firm, non-tender, non-pulsatile, non-fluctuant	15x10	No	No	IHC: (+) CD20, CD79a, BCL2 (-) CD5	Surgery	Alive	24
Movahed et al., 2011 (21)	F	**35**	Right	MALT	Soft andfluctuantswelling	ND	ND	Yes (pain)	IHC: (+) CD20, CD43, (-) CD10, CD5, CD23 and BCL-1	Surgery, Cht,RT	Alive	12
Terada et al., 2012 (22)	F	71	Left	DLBCL	Tumor	60x60x50	No	ND	IHC: (+) CD45, CD20, p53, Ki67 100% (-) CD3, CD30, CD45RO, TdT	ChT, RT	Alive	4
Komatsu et al., 2013 (23)	M	37	Right	Burkitt'slymphoma	Swelling, rapidlygrow	50×36	Yes	Yes (dysphagia)	IHC: (+)CD19 ,CD20, CD10,(-)CD3, CD4, CD8, FISH:(-)EBV, c-myc (+), IgH/MYC (-) IgH/BCL-2 (+)HIV	Cht	Alive	24
Revanappa et al, 2013 (24)	F	73	Bilateral	DLBCL	Diffuse firm swelling, rapidly progressive grow		Yes	Yes (fever, weight loss)	IHC: (+)CD20 ,CD10, CD3, CD5,CD23, Cyclin	ChT, RT	ND	ND

									D1, Ki-67:10-15%			
Shashidara et al., 2014 (25)	F	40	Left	FL	Firmswelling, non tender	90x40	Yes	No	IHC: (+) BCL-2, CD20 (-) CD3	SMG removal	Alive	ND
Chen, 2015 (26)	F	24	Left	MALT	Non-tender mass with rapid enlargement	25x25	No	No	IHC: (+) CD20, BCL2 (-) CD3, CD5, CD10, CD23, CYCLIN D1 | ISH: (-) EBV, IgG4	Surgery	Alive	6
Gorodetskiy et al., 2017 (27)	M	38	Left	PTCL-NOS	Dense mass	ND	Yes	No	NS	ND	Alive	7
Chadha et al., 2017 (28)	F	27	Left	MALT	Swelling	14×11×19	No	No	IHC: (+)CD20, PAX 5, CD79a, CD43, BCL-2, CD23, (-)CD3, CD5, CD10,MUM1, BCL-6, cyclin D1,CD23 and KI-67=10-20%	Surgery and RT	Alive	10
Missaoui et al., 2019 (29)	M	74	ND	ENKTL	Swelling	ND	ND	No	IHC: (+) CD3, CD5, CD56, CD57,LMP-1, CD5,CD23,(-) CD4, CD8, CD20, Granzyme B FISH: (+)EBER	Surgery, ChT, RT	Alive	60
Abukhirian et al., 2020 (30)	M	70	Bilateral	MCL	Firmswelling, graduallygrowing	ND	ND	No	IHC: (+)CD20, CD5, Cyclin D1, (-) CD10, CD3, BCL 6 ,CD23 and Ki-	Cht	Alive	11

Ishibashi et al., 2020 (31)	M	70	Bilateral	MALT	Firm, movable masses	40x20(left), 46x25(right)	No	No	67= 20% IHC: (+) CD79a, CD20, BCL2 (-) CD10, CYCLIN D1, CD5, CD3	ChT	Alive	72
Mnatsakanian et al., 2020 (32)	F	52	Left	MALT	Swelling	15x7x11	Yes	No	ISH: kappa (+), lambda (+) light chain	Surgery, Cht,RT	Alive	ND
Muto et al., 2020 (33)	M	86	Right	FTCL	Palpable elastic hard, movable small mass	25.6x18.2x25.6	No	No	IHC: (+) CD3, CD4, BCL2, CD23, follicular dendritic cell, programmed cell death protein 1, chemokine ligand 13 (-) CD20, CD8, CD10 | ISH: (-) EBER	Surgery	Alive	2
Kushwaha et al., 2021 (34)	F	65	Bilateral	DLBCL	Firm to hard swelling, non-tender, slightly mobile	16x12 (left), 36x32 (right)	No	ND	IHQ: (+) CD45, CD20, CD10, kappa light chain (-) MUM', BCL6, CD5, CD23, CD3 | FC: (+) CD45, CD19, CD20, CD10, CD138, kappa restriction (-) CD8, CD4, CD34, Tdt, CD56	ChT	Dead	ND

F=female*; M*=male*; SMG*=submandibular gland; *MALT*=mucosa-associated lymphoid tissue; *FL*=folicular lymphoma; *DLBCL*=diffuse large B-cells lymphoma *FTCL*=follicular T-cell lymphoma*; ENKTL*= Extranodal NK/T-cell lymphomas, *MCL*=mantle cell lymphoma; *PTCL-NOS*=peripheral T-celll ymphoma, not otherwise specified; *ND*=not described; *IHC*=immunohistochemestry; *FISH*=fluorescence *in situ* hybridization; *ISH=in situ* hybridization; *FC*=flow cytometry *PCR*=polymerase chain reaction; *mo*=months; *RT*=radiotherapy; *ChT*=chemotherapy; LN: Lymph node involvement.

Figures

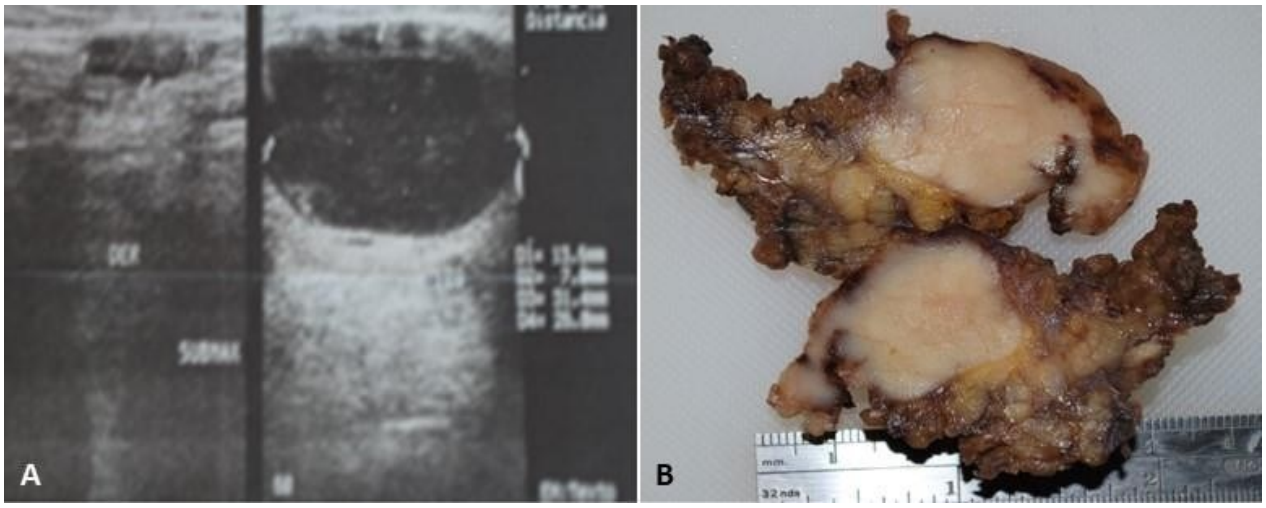

Figure 1. Lymphoma affecting the submandibular gland. **A)** Ultrasonography exam showing a hypoechoic image of a follicular lymphoma involving the submandibular gland. **B)** Gross specimen of the follicular lymphoma affecting the submandibular gland.

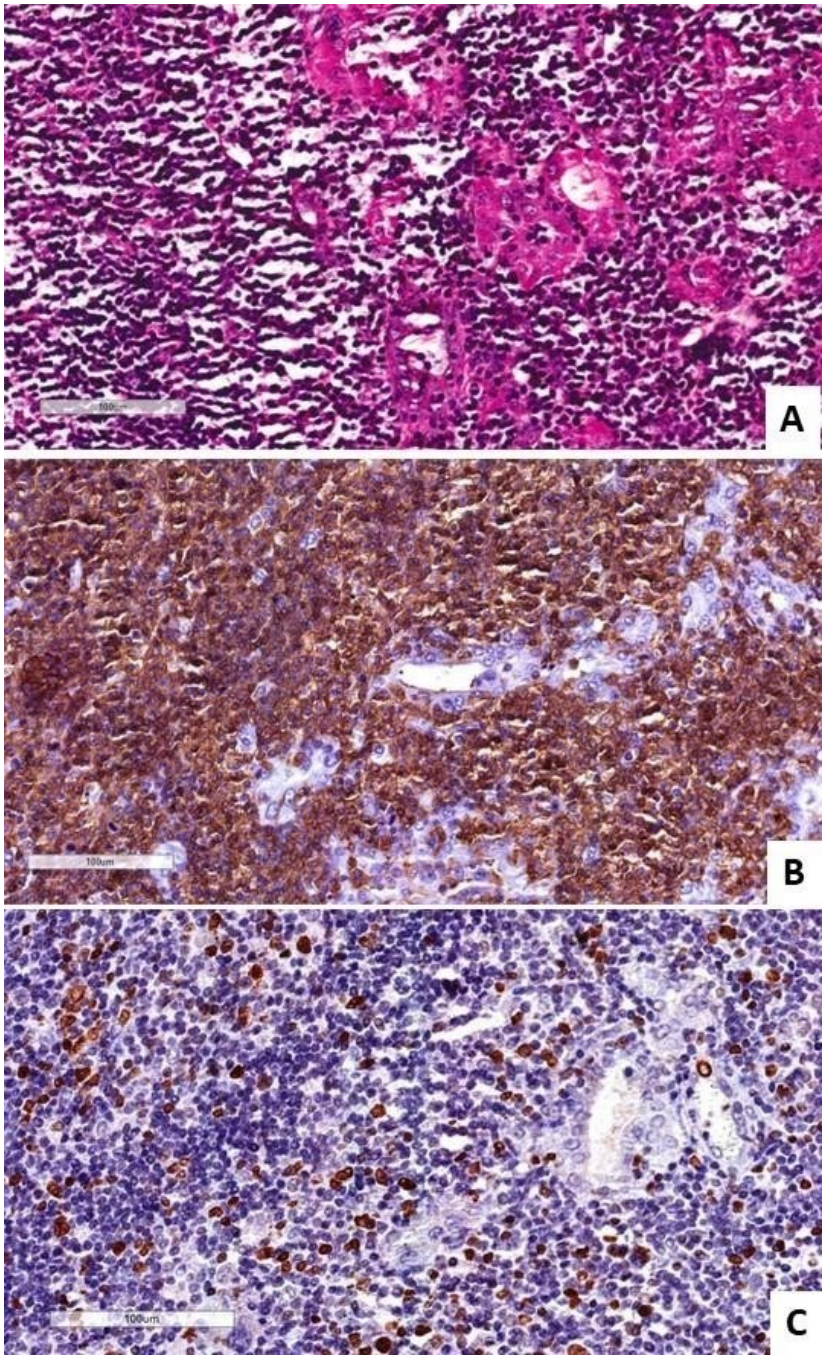

Figure 2. Histopathologic and immunohistochemical features of a MALT lymphoma affecting the submandibular gland. **A)** The presence of lymphoepithelial lesions were found in all tumors investigated (H&E; 100X). **B)** Tumor cells strongly and diffusely expressed CD20, although a variable number of CD3 positive reactive T cells was a common finding (DAB; 100X). **C)** MALT lymphoma exhibited a low proliferative index measured by Ki67 expression (DAB; 100X).

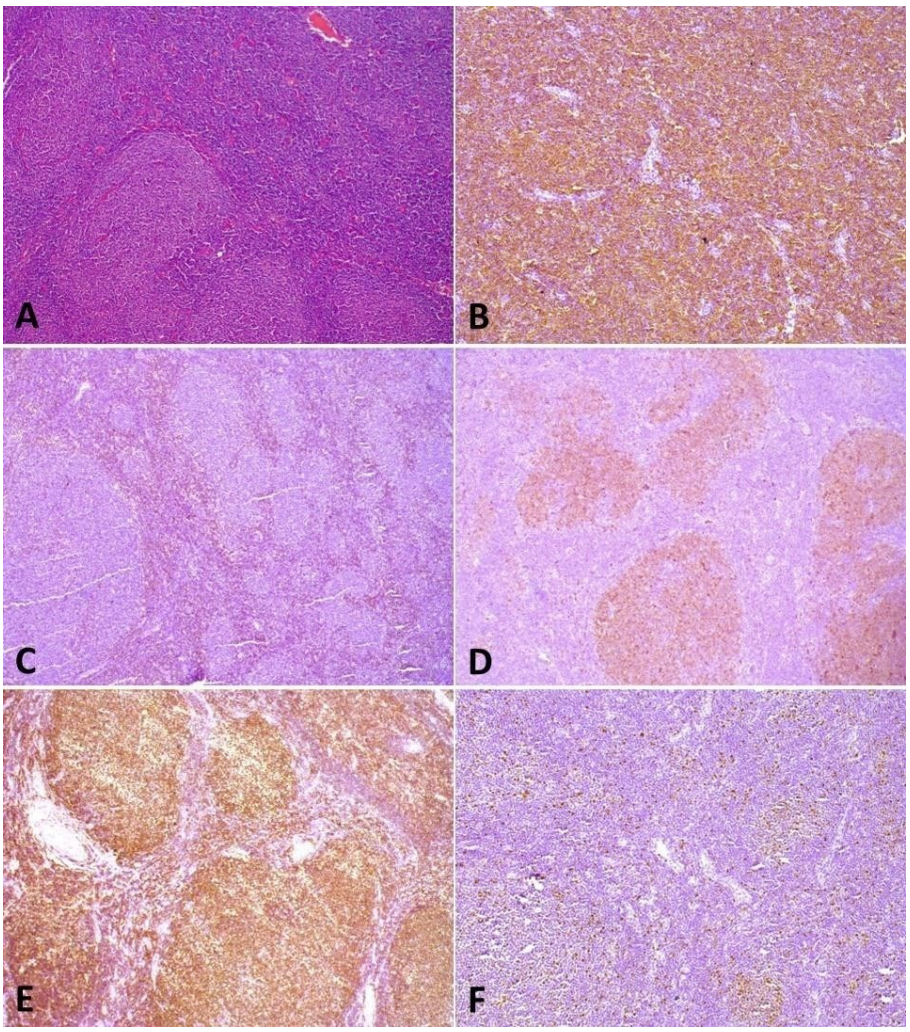

Figure 3. Histopathologic and immunohistochemical features of a follicular lymphoma affecting the submandibular gland. **A)** Presence of neoplastic nodules characterized by variable size and shape, containing centrocytes and fewer than 15 centroblasts per high power field characterizing a low-grade follicular lymphoma (H&E; 100X). **B)** Neoplastic B lymphocytes in the follicles staining positively for CD20 (DAB; 100X), while **C)** the interfollicular regions contained T lymphocytes positive for CD3 (DAB; 100X). **D)** Presence of germinal centers was confirmed by CD10 expression (DAB; 100X). **E)** The expression of the anti-apoptotic protein Bcl2 was observed in the neoplastic germinal center, and also in the neoplastic cells located in the interfollicular region (DAB; 100X). **F)** Proliferative index measured by Ki67 varied, but a higher staining pattern was observed in neoplastic germinal centers (DAB; 100X).

4.3 Artigo em processo de submissão ao periódico *J Oral Diag*

CLINICO-PATHOLOGICAL PROFILE OF NON-HODGKIN LYMPHOMAS AFFECTING THE PAROTID GLANDS

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Abstract

Lymphomas affecting the parotid glands are uncommon, and 79% of all cases are represented by Non-Hodgkin lymphomas (NHL). The aim of this study is to investigate the clinicopathological and immunohistochemical features of a series of lymphomas involving the parotid glands. All cases diagnosed in one pathology service from January 2008 and December 2018 were retrospectively retrieved and the formalin-fixed paraffin-embedded tissue blocks were assessed for diagnostic confirmation. Clinical data were obtained from patients' medical files. We obtained twelve cases of NHL in the parotid glands representing nine MALT lymphomas, two follicular lymphomas (FL), and one diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS). There was a predilection for female sex (10F:2M), and in all cases it was possible to confirm the involvement of the parotid glands by either macroscopic evaluation, imaging studies, or histologic assessment. Clinically, most of the lesions presented as asymptomatic swellings in the parotid region, although associated pain was reported in one case of FL, and three patients with MALT lymphoma had sicca symptoms. In conclusion, NHL affecting the parotid glands are usually of mature B cell lineage, usually representing low-grade subtypes, and frequently simulate other benign or malignant conditions.

Key-words: Lymphoma, MALT lymphoma, follicular lymphoma, Sjögren syndrome, parotid gland.

Introduction

Non-Hodgkin lymphomas (NHL) encompass a wide range of subtypes distinguished by diverse histological, genetic, and clinical features [1]. According to the latest Global Cancer Statistics report, in 2020 NHL accounted for approximately 260,000 deaths worldwide [2]. Lymphomas affecting the parotid glands (PGs) constitute a significant proportion of NHL cases involving salivary glands, estimated at approximately 79% [3].

Unlike other salivary glands, lymphomas affecting the parotid gland can originate not only in the parenchyma, but especially from the intraparotid lymph nodes [4]. Frequently, they manifest as painless swellings without specific symptoms [4,5]; moreover, these parotid lymphomas should be thoroughly assessed and clinically correlated, since they may also represent an indication of Sjögren's syndrome (SS) [6,7]. Patients with SS which may contribute to make marginal zone lymphoma, one of the most prevalent NLH in parotid glands [8]. So, lymphomas arising in the parotids often exhibit a favorable prognosis due to their increased tendency to present as low-grade malignancies [4.]

In the current study, we attempted to investigate the clinicopathological and immunohistochemical features of lymphomas affecting the parotid glands and to compare our results with currently available literature through a literature review.

Material and Methods

Ethics statement

This study was approved by Ethics Committee of the Federal University of Minas Gerais, Brazil (CAAE: 58900722.1.0000.5149). All procedures were in accordance with the ethical standards of the committee for human experimentation (institutional and national) and with the Declaration of Helsinki of 1975, revised in 2008.

Sample and data collection

Lymphomas affecting the parotid glands were obtained from pathology files of the immunohistochemistry Laboratory of the Piracicaba Dental School (University of Campinas) in a period ranging from January 2008 to December 2018. Cases that originate from the neck or the cervical lymph nodes with extension to the parotid glands, and those who without tissue blocks or glass slides available to perform H&E-stained and immunohistochemistry reactions were not included. On the other hand, cases affecting intraparotid lymph nodes and arising in patients diagnosed with Sjogren syndrome were included.

The original H&E-stained histological sections and immunohistochemistry slides were assessed for at least two pathologists and cases classified in accordance to the 4th edition of the World Health Organization guidelines for classification of Tumors of Hematopoietic and Lymphoid Tissues[1]. The clinicopathological data of the cases were obtained from the patient's pathology and/or medical records, and included gender, age, clinical presentation, follow-up time, status at last follow-up and, when possible, information about the primary or disseminated process manifestation of the disease elsewhere in the body.

Data analysis

A descriptive analysis was performed with categorical variables presented as absolute numbers and percentages, while continuous variables expressed as mean, standard deviation (SD) and range. The SPSS software version 22.0 (IBM, Germany) was used for statistical analysis.

Literature review

A review of the literature was performed with an electronic search in August of 2023, using the PubMed/MEDLINE database to retrieve all previous reports of lymphomas affecting the parotid glands that contained individual data available for consultation when the fourth edition of the WHO classification of hematopoietic and lymphoid tissue tumors [1]. The search strategy comprised the following key-words: ("parotid gland" OR "parotid glands") AND

("lymphoma" OR “lymphomas”), and to expand the search, a manual evaluation on the articles’ references was also performed. These articles were included in the app Rayyan (https://www.rayyan.ai/) and three authors reviewed the articles. Lymphomas affecting other major salivary glands and those without data to diagnose were not included in this review.

Results

A total of 15 lymphomas affecting the parotid glands were identified, but three of them were excluded because an accurate diagnosis could not be performed and were descriptively reported as two low-grade small B cell lymphoma and one high grade lymphoma. Out of the remaining 12 cases, nine cases represented MALT lymphoma, two cases follicular lymphomas (FL), and one case as diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS).

The clinicopathological profile of the 12 cases are detailed in **Table 1**. In summary, females were more affected (10 females:2males), with the patients’ age ranging from 32 to 90 years, with a mean age of 53.6 years. Most of the lesions presented as asymptomatic swellings in the parotid region, but pain was reported in one case (8.0%) and three (25.0%) patients had sicca symptoms **(Figure 1)**. Five patients (42.0%) were affected in the right gland, two (17.0%) in the left gland, one (8.0%) was bilateral and one (8.0%) in the intraparotid lymph node. It was possible to confirm the involvement of the parotid glands in all cases by either macroscopic evaluation **(Figure 2)**, imaging studies, or histologic assessment.

Histologically, MALT lymphoma cases (9 cases, 75%) consisted of a diffuse proliferation of small-to-medium-sized neoplastic B-cells with the presence of lymphoepithelial lesions in different amounts. Some medium-sized cells exhibiting a relatively abundant pale cytoplasm consistent with monocytoid cells were noted. The neoplastic cells diffusely expressed CD20, were negative for CD3, CD5 and Cyclin D1, and a low proliferative rate (Ki67~ 5 to 10%) **(Figure 3)**. AE1/AE3 immunohistochemistry was assessed in MALT lymphoma six (67%) and demonstrated lymphoepithelial lesion. Three (33.0%) patients

affected by MALT lymphoma had clinical signs and symptoms consistent with Sjögren syndrome, and one (11.0%) case was associated with a lymphoepithelial cyst. The two (17.0%) cases of follicular lymphomas exhibited a follicular growth pattern with the neoplastic follicles proliferating in the glandular parenchyma, and one of them was also located in the intraparotid lymph node. They were composed predominantly of centrocytes, with a variable number of centroblasts and both were diagnosed as low-grade subtypes. The neoplastic cells were diffusely positive for CD20, and revealed positivity for CD10, and Bcl2 proteins in the neoplastic germinal centers **(Figure 4)**. The DLBCL, NOS case was microscopically heterogeneous and characterized by a diffuse proliferation of large atypical B-cells with both centroblast and immunoblast features. Immunohistochemically, the neoplastic cells were positive for CD20 and Bcl2, and negative for CD3, Bcl6 and EBER, showing a high Ki67 proliferative index.

In our literature review 15 articles reporting lymphomas in the parotid glands could be retrieved, accounting for 272 cases. The clinicopathological profile of these cases are detailed in **Table 2** and references of this table can be found in Supplementary File 1 (Supplementary file 1). Briefly, females predominated (162 females:82 males), with the patients' age ranging from 15 to 93 years. Most of the lesions presented as a painless hard swelling. The sicca syndrome, manifestation of Sjögren syndrome, arthralgia, fatigue, Raynaud's phenomenon, and fever were also described. Microscopically, MALT lymphoma, FL and DLBCL predominated, but anaplastic large cell lymphoma (ALCL) [9,] adult T-cell leukaemia/lymphoma (ATLL) [9], Burkitt's lymphoma (BL) and small-cell lymphocytic lymphoma (SLL) were also described. The most common treatment applied was surgery, associated with different protocols of radiotherapy and chemotherapy. Only 36 patients died and 240 remained alive at their last follow up.

Discussion

The presence of lymphomas in the salivary glands is uncommon, representing approximately 2% of all salivary gland tumors, and 75% of them occur in the parotid glands, especially in patients with Sjögren syndrome [7,10]. The parotid gland, compared to other major salivary glands, has an important anatomical feature, which is the presence of lymphoid tissue inside of the glandular tissue, that can potentially be involved by reactive, metaplastic or neoplastic lymphoid processes [11]. Considering the low incidence of lymphomas of the salivary glands and their unspecific clinical manifestations, the diagnostic process is very complex and these neoplasms may simulate the clinical manifestation of many other entities, like benign salivary gland tumours, making their final diagnosis very difficult. In this series of 12 cases, we demonstrated that the most common entities were MALT, followed by FL and DLBCL, NOS;, most often manifesting as asymptomatic swellings, which is in accordance with previous studies (Supplementary File 1).

It is known that the risk of occurrence of MALT is significantly increased in the context of Sjögren syndrome, an autoimmune disorder that more often affects the lacrimal and salivary glands, and predisposes patients to develop NHL [12,13].It is believed that the parotid glands patients with Sjögren syndrome have a microenvironment that plays a pathogenetic role in the final step of primary Sjögren syndrome-related lymphomagenesis [7,14,15,16]. Although any lymphoma subtype can develop in the parotid glands of Sjögren syndrome patients, it is well known that MALT is the most frequent subtype [17,18],as illustrated in our study where all three patients diagnosed with Sjögren syndrome were affected by MALT lymphoma.

The clinical manifestations of lymphomas in the parotid glands are very unspecific, with most of the cases associated with expansive swelling, more often asymptomatic, although pain and paresthesia may occur, especially in higher grade subtypes. In patients diagnosed with Sjögren syndrome, parotid swelling has been considered a very early and important key predictor of neoplastic development, and the disease should be assessed for the possibility of a

lymphoma [7]. Moreover, some studies demonstrated a correlation between the duration of parotid gland swelling and the risk of lymphoma diagnosis, reporting that the increase in time make the risk of lymphoma diagnosis to increase significantly [7]. Therefore, a careful evaluation of parotid gland swelling should be conducted, and even more cautiously when patients already have the diagnosis of Sjögren syndrome; in the meanwhile, when patients are diagnosed with lymphomas in the salivary glands, diagnosticians should investigate the possibility of a Sjögren syndrome scenario which could not have been established so far.

Although the definitive diagnosis of lymphomas in the parotid glands relies on the microscopic and immunohistochemical examination of the surgical specimen, there seems to be some advantages of performing ultrasound-guided salivary gland fine needle aspiration biopsy, especially in Sjögren syndrome individuals [19,20]. This diagnostic approach allows for an exploratory microscopic investigation even in the absence of an evident parotid gland swelling [21], representing a minimally invasive technique with a satisfactory initial diagnostic predictability [22]. Although the definitive diagnose and subclassification of lymphoma type normally depend on the histopathological examination of the surgical specimen.

The treatment for lymphomas in parotid glands dependents on the microscopic diagnosis, tumor grade and clinical stage, more often consisting of surgery, radiotherapy, chemotherapy, and immunotherapy alone or in combination. In localized diseases the neoplasms may be successfully treated by more conservative approaches [23], although this type of treatment is considered more effective for low-stage, low-grade indolent forms of lymphomas [24]. Most of the cases in our literature review were affected by FL and MALT lymphomas and several of them were treated only with radiotherapy (Supplementary File 1).

The prognosis of patients affected by lymphomas in the parotid glands is usually good, with the prognosis of patients affected by MALT lymphomas is usually the most favorable among the lymphoma subtypes described in the literature [25,26]. The risk of death associated with

a parotid gland lymphoma is directly impacted by older age, higher grade tumors and advanced stage neoplasms [25]. In our literature review, it was observed that deaths were strongly associated with higher grade diagnoses like ATLL, DLBCL and mantle cell lymphoma (MCL) (Supplementary file 1).

In conclusion, we observed that lymphomas of the parotid glands represent a challenging diagnostic that can frequently simulate both benign or malignant conditions. Therefore, a careful evaluation of all parotid swellings, specially in patients with Sjögren syndrome, is mandatory to provide an accurate diagnosis for affected patients, which should be systematically evaluated to rule out a disseminated disease.

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Supplementary File 1:

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Table 1. Clinicopathological profile of 12 non-Hodgkin lymphoma cases affecting the parotid glands.

No.	Sex	Age	Diagnosis	Side	Sjögren Syndrome	Immunohistochemistry
1	M	NS	FL	Left	Unknown	CD20+, CD3+, Bcl2+, CD23+, Ki67~30%
2	F	32	MALT	Right	Unknown	CD3+, CD8+, CD10–, Bcl2+, CD43–, CD79a+, CD138+, VS38C+, AE1/AE3+**, EBER r–, Ki67~5%
3	F	58	DLBCL	Right	Unknown	LCA+, CD3–, CD20+, CD23–, CD138–, EMA-, Kappa+, Lambda–, Cyclin D1–, Bcl2+, Bcl6 –, CD10+, TDT–, EBER–, Ki67 ~5%
4	F	35	MALT	Left	Unknown	CD3–, CD20+, CD138+, MUM1+, AE1/AE3+*, Ki67~5%
5	F	90	MALT	Right	Unknown	CD3–, CD20+, CD5–, CD10–, CD43+, CD79a+, Bcl2+, Cyclin D1–, AE1/AE3+*, Ki67~5%
6	M	61	FL	NS	Unknown	LCA+, CD3–, CD20+, CD43+, CD79a+, Bcl2+, Ki67~35%
7	F	69	MALT	NS	Unknown	LCA+, CD3–, CD20+, CD5–, CD10–, CD43–, Cyclin D1–, Bcl2+, Ki67~5%
8	F	81	MALT	Bilateral	Unknown	CD3–, CD20+, CD5–, CD10–, AE1/AE3+*, Ki67~25%
9	F	49	MALT	NS	Yes	CD3–, CD20+, CD10–, AE1/AE3+*, Ki67~10%
10	F	67	MALT	Right	Yes	CD3-, CD20+, CD10-, CD23-, Cyclin D1- Ki67~5%
11	F	44	MALT	Right	Unknown	CD3–, CD20 +, CD10– , CD30–, CD68+, AE1/AE3+*, Bcl2 +, CD18–, Ki67~10%
12	F	58	MALT	NS	Yes	LCA+, CD3–, CD20+, CD5–, CD23–, CD68–, CD79a+, Bcl2+, Cyclin D1–, TDT–, Ki67~5%

F=female*; M*=male; *MALT*=mucosa-associated lymphoid tissue; *EBV*= Epstein-Barr virus; *DLBCL*=diffuse large B-cells lymphoma; *FL*=follicular lymphoma; *NS*=not specified; *AE1/AE3 was imunopositive in lymphoepithelial lesion.

Table 2. Clinicopathological profile of 272 lymphoma cases affecting the parotid glands and reported in literature from 2008 to 2024.

Study/Year	Cases per study	Sex	Age	Laterality	Diagnosis	Clinical presentation	Lymph node involvement	Symptoms/medical history	IHC/FISH/FC/PCR	Treatment	Outcome	Follow (mo)
Miyagi T et al., 2009	3	M	59	ND	ALCL	Homogeneous masses; ill-defined borders, enhancement (CT)	ND	No	(+): CD30, CD45RO (weakly) / (-): CD3, CD20, EMA, S100, keratin, HAM45	CHOP + RT	Alive	65
		F	57	ND	ATLL		ND	No	(+): CD45RO	CHOP	Dead	8
		F	88	ND	ATLL		Yes	No	(+): CD45RO	CHOP-like chemotherapy + RT	Dead	4
Alvarez-Buylla Blanco M et al., 2010	8	F: 5 M: 3	~74 (52-85)	Left: 87,5%	LGBL	Painless hard mass (more frequent) average size of 2,8cm	3 cases	SS	ND	R-CHOP, RT	Alive: 87.5 %	At least 21
					HGBL			ND	high grade B NHL: (+) CD20, CD79,	R-CHOP, RT		
					HGBL			Waldenstrom disease	CD3, ⅔ CD5, ⅔ CD43, ⅔ Bcl2	R-CHOP		
					HGBL			orbit and lip NHL		R-CHOP, RT		
					MALT			Hashimoto's thyroid	B MALT NHL: (+) CD20,	R-CHOP		
					MALT			ND	CD79, ⅓ CD43	No		
					MALT			ND		No		
					FL			ND	ND	R-CHOP		
Nassie DI et al., 2010	13	M	54	Bilateral: 1	Mixed B-cell lymphoma	painless mass	9 cases	Painless; Sistematic findings on PET-CT: 5	Diagnosis on the basis of histologic and immunohistologic consistent with lymphoma	Chlorambucil, RT	Alive	108
		F	43	Unilaterally: 12	Marginal B-cell					CHOP, RT	Alive	120
		M	46		LBCL					CHOP, RT	Alive	108
		F	76		LBCL					COP	Dead	36
		M	53		FL					ND	Alive	120

		F	70		FL					Chlorambucil	Alive	84
		M	75		T cell Rich B-cell Lymphoma					CHOP	Dead	108
		M	83		LBCL					R-CHOP	Alive	48
		M	76		BL					ND	Alive	36
		M	54		LGBL					R-CHOP + RT	Alive	24
		F	50		Mixed B-cell Lymphoma					ABVD + RT	Alive	36
		M	73		LBCL					CHOP + RT	Alive	12
		F	72		FL					No	Alive	12
Pollard RP et al., 2011	35	F	68	ND	MALT	PGS	Locally disseminated: 5	SS, Arthralgia, arthritis	IHC was performed for at least CD3, CD5, CD20, CD79a, CD10, BCL6, and cytoplasmic immunoglobulins (kappa, lambda, IgM, IgG, and IgA). PCR: 21/35. All 21 cases revealed a dominant and reproducible monoclonal population of B cells in 1 or more framework PCR reactions.	Watchful waiting, Surgery	Alive	153
		F	77			ND	Disseminated disease: 4	SS, Arthralgia, Fatigue		Watchful waiting	Dead	109
		F	61			PGS		SS		Surgery	Alive	141
		M	33			PGS		SS, Arthritis, fatigue		Surgery + R-CP	Alive	124
		F	55			ND		SS, Arthralgia, arthritis		Watchful waiting	Alive	128
		F	28			PGS		SS, Arthralgia, arthritis, RP		Surgery + RT	Alive	102
		F	64			PGS		SS, Arthralgia, arthritis, fatigue		Watchful waiting	Alive	108
		F	36			PGS		SS, Arthralgia, fatigue, RP, fatigue		Rituximab, CYC	Alive	91
		M	62			ND		SS, Arthralgia, fatigue		Rituximab	Alive	78
		F	54			PGS		SS, Fatigue, vasculitis, pulmonary		RT + CYC	Alive	153

			, hepatic and renal involvement			
		PGS				
F	48		SS	Rituximab	Alive	141
		PGS				
F	72		SS, Arthralgia, fatigue	Rituximab	Alive	75
		PGS				
F	50		SS, Arthritis, fatigue, RP, vasculitis and esophageal involvement	Rituximab	Alive	66
		PGS				
F	43		SS, Arthritis, fatigue, RP	Rituximab	Alive	70
		PGS				
F	57		SS, Fatigue	Surgery + RT	Alive	100
		ND				
F	43		SS, Fatigue	Rituximab	Alive	94
		ND				
F	76		SS, Arthralgia, RP	Rituximab	Alive	83
		ND				
F	58		SS, Fatigue	Rituximab	Alive	64
		PGS				
M	36		SS, Fatigue	Rituximab	Alive	67
		PGS				
F	57		SS, Fatigue	Watchful waiting	Alive	64
		PGS				
F	67		SS, Fatigue, RP	Rituximab	Alive	57
		ND				
F	51		SS, Arthralgia, fatigue	Rituximab	Alive	58
		PGS				
F	57		SS, Fatigue	Surgery + RT + R-CP	Alive	85
		PGS				
F	68		SS, Arthralgia	Watchful waiting	Alive	75
		PGS				
F	41		SS, Arthralgia, fatigue	Watchful waiting	Alive	53
		PGS				
F	65		SS, Fatigue	R-CP	Alive	49
		PGS				
F	72		SS, Fatigue, RP	Watchful waiting	Alive	46
		PGS				
F	64		SS, Fatigue, vasculitis,	R-CP	Alive	50

								pulmonary and esophageal involvement, polyneuropathy				
		F	76			PGS		SS, Arthritis, RP		R-CP + RT	Alive	47
		F	65			PGS		SS, Arthralgia		Watchful waiting + RT	Alive	50
		F	60			ND		SS		R-CP	Alive	36
		F	85			PGS		SS, Fatigue		R-CP	Alive	28
		F	42			PGS		SS		Watchful waiting	Alive	28
		F	54			PGS		SS, Arthralgia		R-CP	Alive	26
		F	37			PGS		ND		Rituximab	Alive	16
Troch M et al., 2011	28	F	75	Left: 17	MALT	Unilateral or bilateral swelling: 26	ND	CREST Syndrome	All cases: light chain restriction and CD20+, CD5-, CD10-, cyclin D1-	Bortezomib	Dead	ND
		M	46	Right: 4			ND	SS		RT	Alive	10
		F	31	Bilateral			ND	SS; Involvement of thymus		R-CHOP	Alive	ND
		M	66	Bilateral			Yes	SS		Oxaliplatin	Dead	15
		F	63	Left: 17 Right: 4			Yes	SHARP Syndrome; Lung involvement		R-CHOP	Alive	10
		F	40	Bilateral			ND			RT	Alive	ND
		M	65	Left: 17 Right: 4			ND	Orbit and kidney involvement		R-CHOP	Alive	ND
		M	61				ND	SS		Wait and see	Alive	ND
		F	47	Bilateral			ND	SS		RT	Alive	ND
		F	36	Left: 17			ND	SS		Surgery	Alive	10
		F	46	Right: 4			ND	Polymyalgia Rheumatica		RT	Alive	29
		F	69	Bilateral			ND	ND		RT	Dead	18

		F	42	Left: 17			ND	SS		RT	Alive	91
		F	54	Right: 4			Yes	ND		Wait and see	Alive	ND
		F	51				ND	SS		COP	Dead	51
		F	54				ND	SS		R-CHOP	Alive	ND
		M	31				ND	Hashimoto Thyroids		Surgery	Alive	18
		F	50				ND	ND		Surgery	Alive	ND
		F	35				ND	ND		Surgery	Alive	13
		F	62				ND	ND		MCP	Alive	48
		M	48				Yes	SS		MCP	Alive	ND
		F	39				ND	SS		Bortezomib	Alive	ND
		F	50				ND	SS		Surgery	Alive	ND
		M	35				Yes	ND		RT	Alive	27
		F	56				ND	ND		RT	Alive	55
		F	36	Bilateral			ND	SS		2-CdA	Alive	ND
		F	53	Bilateral			ND	ND		Wait and see	Alive	ND
		M	49	Left: 17 Right: 4			Yes	SS		RT	Alive	ND
Zenone T, 2012	2	F	56	Left	DLBCL	Enlarged left neck gland and large left neck mass;	ND	pSS	ND	chemotherapy + rituximab + localized radiation therapy	Dead	69
		F	42	Bilateral	MALT	Painful bilateral PGS	Yes	pSS, palpable purpura and hypothyroidism related to Hashimoto's thyroiditis CT: heterogeneous hypertrophy	ND	Rituximab	Alive	26
	8	F	60		MALT	Parotid swelling	ND	pSS	ND	Surgery	Alive	73

Risseladа AP et al., 2013		F	63		MALT	Parotid swelling	ND	pSS	ND	Wait-and-see	Alive	59
		F	59		MALT	Parotid swelling	ND	pSS	ND	Wait-and-see	Alive	30
		F	56		MALT	Small, hard node in parotid gland	ND	pSS	ND	Surgery	Alive	27
		M	59		MALT	Parotid swelling	Yes	pSS	ND	Chemotherapy + Rituximab	Alive	180
		F	52		MALT	Parotid swelling	ND	pSS, night sweats	ND	Chemotherapy + rituximab	Alive	9
		F	45		MALT	Parotid swelling	ND	pSS	ND	Rituximab	Alive	62
		F	54		MALT	Parotid swelling	ND	pSS	ND	Surgery	Alive	84
Wyss E et al., 2013	28	14 F 14 M	Mean age: 66 (28 - 93)	Left: 18 Right: 7 Bilateral: 2	FL	Progressing parotid mass: 27 Painless: 21 Left hard palate ulceration: 1	6 cases	Pain: 7 Induration: 6 Dysesthesia: 5 Sicca symptoms: 5 Trismus: 1	ND	RT + COPM	Alive	39
					FL				ND	Lateral parotidectomy + RT	Alive	114
					FL				ND	R-COP	Alive	30
					FL	No symptoms		SS: 4	ND	Lateral parotidectomy; watch and wait	Alive	8
					FL	-			ND	RT + Rituximab	Alive	21
					FL	-			ND	Rituximab	Dead	16
					FL	-			ND	Lateral parotidectomy; RT + Chlorambucil + prednisone + rituximab	Dead	63
					FL	-			ND	R-CHOP	Dead	4
					FL	-			ND	Total parotidectomy; RT + R-CHOP; R-Gemcitabine; Etoposide + ifosfamid (Holoxan); ESAP	Dead	127
					FL	-			ND	RT, CYC + Epirucibin +	Alive	210

					vinscritine (Oncovin) + Predinisone		
		MALT	-	ND	Lateral parotidecto my; Patient refused further therapy	Alive	43
		MALT	-	ND	Lateral parotidecto my; RT	Alive	146
		MALT	-	ND	RT + CHOP + Rituximab	Dead ***	13
		MALT	-	ND	RT	Alive	51
		MALT	-	ND	Lateral parotidecto my; Rituximab	Alive	30
		MALT	-	ND	RT + Chlorambuc il + Prednisone	Alive	75
		MALT	-	ND	Chorambuci l + Prednisone	Dead	87
		MALT	-	ND	Lateral parotidecto my; ND	Dead ***	0
		MALT	-	ND	Total parotidecto my; No therapy, palliative with carcinoma	Dead ***	24
		DLBCL	-	ND	Lateral parotidecto my; R-CHOP	Alive	17
		DLBCL	-	ND	Lateral parotidecto my; RT + R-CHOP	Alive	31
		DLBCL	-	ND	Chlorambuc il + prednisone; Rituximab; CYC + Chlorambuc il + Prednisone + Rituximab	Alive	72
		DLBCL	-	ND	CYC + Epirucibin + vinscritine (Oncovin) + Predinisone	Dead ***	37
		MCL	-	ND	Total parotidecto	Alive	23

										my; R-CHOP		
					MCL	-			ND	R-COP	Dead	21
					Nodular lymphocyte-predominant Hodgkin lymphoma	-			ND	RT + CYC + vincristine (Oncovin) + Procarbazine (Natulan)	Alive	53
					Extraosseous Plasmacytoma	-			ND	RT	Alive	59
					Chronic Lymphocytic Leukemia	-			ND	Total parotidectomy + Neck dissection; RT for carcinoma; watch and wait for CLL	Alive	22
Shum JW et al., 2014	3	F	53	Left	MALT	Growing mass	No	SS, Hashimoto thyroiditis	(+) CD20, CD19, CD22, CD23, CD52, Ki67~10 to 30%	RT	Alive	60
		M	53	Right	FL	Parotid swelling	Yes	No	(+) CD20, CD10, BCL2, Ki67~15 to 60%	R-CHOP + maintenance rituximab	Alive	24
		M	53	Right	FL	Mass in the preauricular region	No	No	(+) CD10, CD20, BCL2, BCL6	R-CHOP + RT	Alive	12
Yaprak N et al., 2015	8	2 M 6 F	mean age 46.6	4 right; 4 left	3 LGBL; 2 MALT; 2 HL; 1 HGBL	ND	ND	ND	ND	ChT/ChT+RT	ND	Range 7 to 108
Lieder A et al., 2017	19				1 HL; 9 FL; 7 marginal zone lymphoma; 2 NHL	84% Painless preauricular swelling	No	16% pain	ND	ChT/RT	2 Dead; 16 Alive	At least 72
Zhang Y et al., 2018	17	5 M 12 F	Mean age 47	11 right; 2 left; 4 bilateral	MALT	Diffused enlargement	ND	7 SS; 1 SS + Hashimoto thyroiditis	(+) CD20, CD43, CD79a, CK (-) CD3, lambda, kappa	Total/parcial excision, 4 surgery+ChT; 1 surgery+RT	17 Alive	Average: 53

Tesher MS et al., 2019	2	F	15	Left	MALT	Parotid swelling	ND	Fever, sore throat, headache, celiac disease, SS	(+) CD43	Rituximab, methylprednisolone, hydroxychloroquine	Alive	>36
		M	15	Right	MALT	Parotid swelling	ND	Left ankle pain, stiffness, dry mouth, dry eyes, SS	(+) CD20 (-) CD43, CD3	Parotidectomy; rituximab, bendamustine, hydroxychloroquine	Alive	24
Wang J et al., 2020	31	10 M 21 F	Mean age 64	27 Unilateral, 4 Bilateral	18 MALT, 7 DLBCL, 6 FL	Nodule or mass	9 cases	24 Painless, 5 Spontaneous pain, 1 Facial paralysis, 5 SS, 1 Rheumatoid arthritis	MALT (+) CD20, CD43, PAX-5 | DLBCL (+) CD20, MUM-1, PAX-5 | FL (+) CD20, CD10, Bcl6	6 Tumor resection, 3 surgery+RT, 14 surgery+ChT, 3 surgery+RT+ChT, 4 ChT, 1 RT+ChT	14 Dead, 17 Alive	Range 29 to 92
Mantsopoulos K et al., 2021	67	33 M 34 F	Mean age 61.4		6 HL, 21 MZL (12/21 MALT), 19 FL, 17 DLBCL, 2 MCL, 1 BL, 1 SLL	ND	10 cases	12 SS (patients with MALT), 3 with B symptoms		13 Parotidectomy, 31 surgery+RT, 21 surgery+RT+ChT, 2 ND	ND	Range 20 to 158

F=female*; M*=male*; SMG*=submandibular gland; *ALCL*=Anaplastic Large Cell Lymphoma; *ATLL*=Adult T-cell Leukaemia/Lymphoma; *MALT*=mucosa-associated lymphoid tissue; *FL*=follicular lymphoma; *LGBL*=Low Grade B-cell Lymphoma; *HGBL*=High Grade B-cell Lymphoma; *DLBCL*=diffuse large B-cells lymphoma; *FTCL*=follicular T-cell lymphoma*; ENKTL*= Extranodal NK/T-cell lymphomas, *MCL*=mantle cell lymphoma; *LBCL*: Large B-cell Lymphoma; *PTCL-NOS*=peripheral T-cell lymphoma, not otherwise specified; *HL*=Hodgkin lymphoma; *MZL*=marginal zone lymphoma; *BL*=Burkitt lymphoma; *SLL*= Small-cell lymphocytic lymphoma; *ND*=not described; *IHC*=immunohistochemestry; *FISH*=fluorescence *in situ* hybridization; *ISH*=*in situ* hybridization; *FC*=flow cytometry; *PCR*=polymerase chain reaction; *mo*=months; *RT*=radiotherapy; *ChT*=chemotherapy; *PGS*=parotid gland swelling; *SS*=Sjogren Syndrome; *RP*=Raynaud's phenomenon; *CYC*=cyclophosphamide; *R-CP*=rituximab with cyclophosphamide and prednisone; *Locally disseminated*=lymphoma localized in 1 or more salivary glands (unilateral or bilateral) with 1 or more enlarged regional lymph nodes (> 1 cm); *Disseminated disease*=localization of lymphoma in 1 or more salivary glands (unilateral or bilateral) with 1 or more enlarged distant lymph nodes (> 1 cm), and/or bone marrow, spleen, liver, or other extranodal site than the salivary gland, or localization of lymphoma in multiple extranodal; *MCP*=mitoxantrone, chlorambucil, prednisolone; *R-CNOP*=rituximab, cyclophosphamide, mitoxantrone, vincristine, prednisolone; *2-CdA*=2-chlorodeoxyadenosine; *COPM*=cyclophosphamide, vincristine (Oncovin), prednisone, rituximab (MabThera); *ESAP*=etoposide/ methylprednisolone (Solumedrol)/cytarabine (Ara C)/cisplatin

Figures

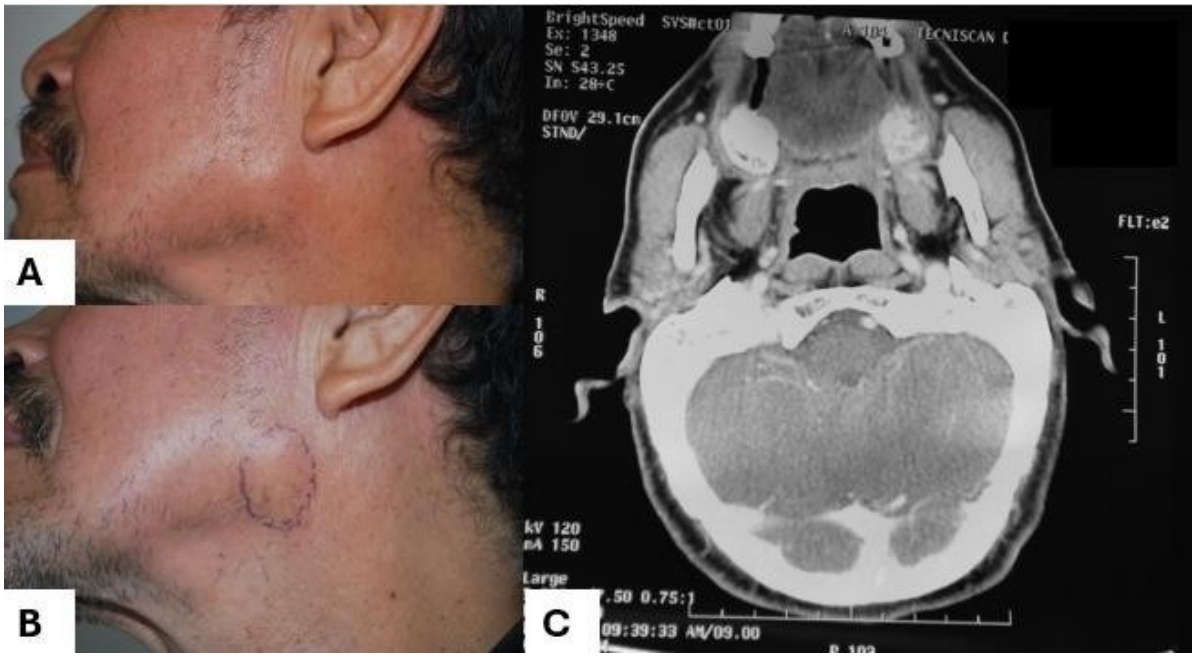

Figure 1. Clinical presentation of lymphomas affecting the parotid gland. A-B) Follicular lymphoma lymphoma in a 61-year-old-man presenting with a pain swelling in parotid gland (Case #6), C) and in the axial section of the tomography we can observe a bilateral increase in volume of the parotid gland and the presence of necrosis (Case #6).

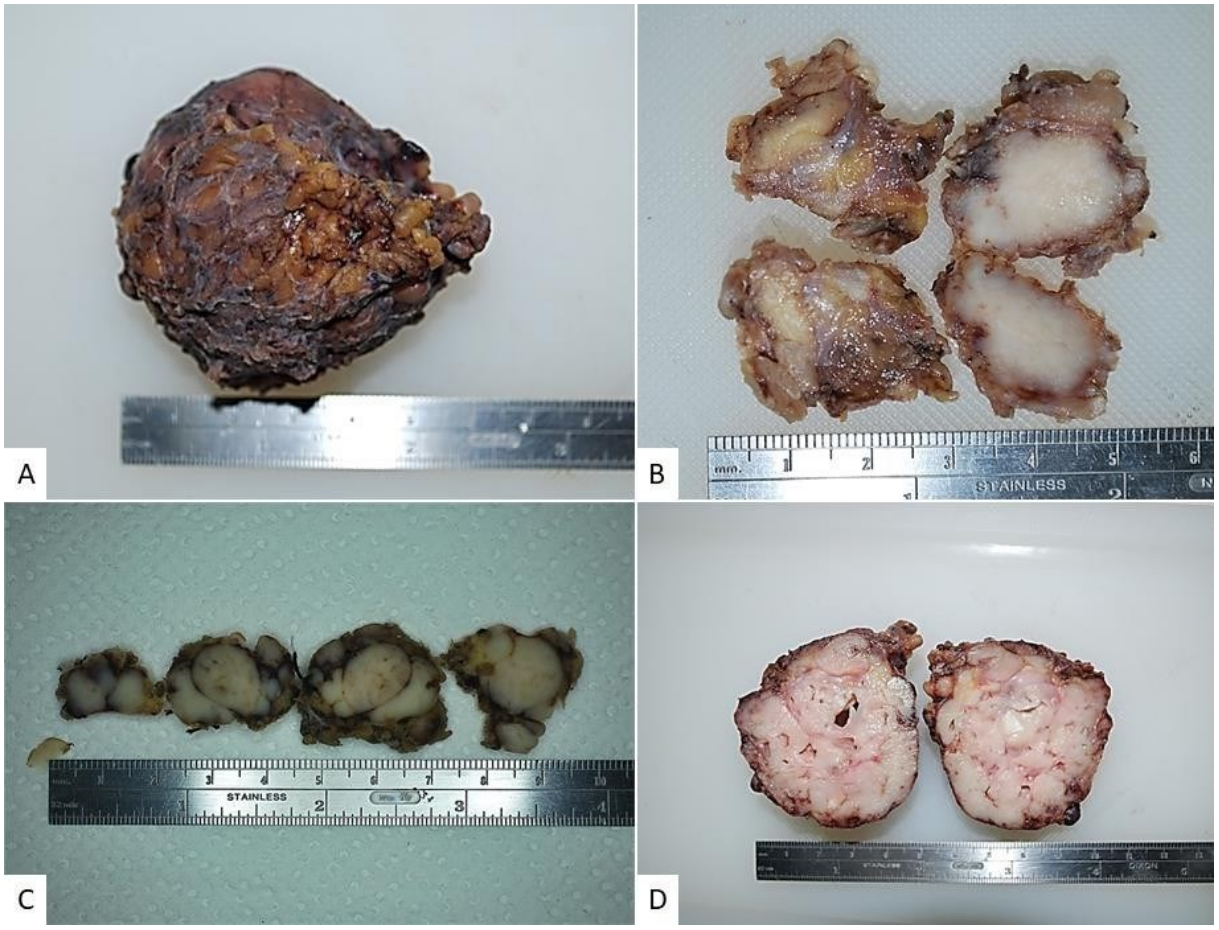

Figure 2. Gross specimen evaluation of lymphomas affecting the parotid gland (PG). A) Surgical specimen of MALT lymphoma in right parotid gland presented with an irregular shape and surface, with a brown color (case #2). B) Surgical specimen of a Follicular lymphoma lymphoma affecting the intraparotid lymph node in a PG with an irregular shape and smooth surface, with a whitish color on cut section (case #6). C) Surgical specimen of MALT lymphoma in right parotid gland with patient with Sjögren's syndrome. The tumor presented with an irregular shape and smooth surface, with a whitish-to-brown color on cut section (case #10). D) Surgical specimen of DLBCL, NOS in right parotid gland with an irregular shape and surface, with a whitish-to-red color on cut section (Case #3).

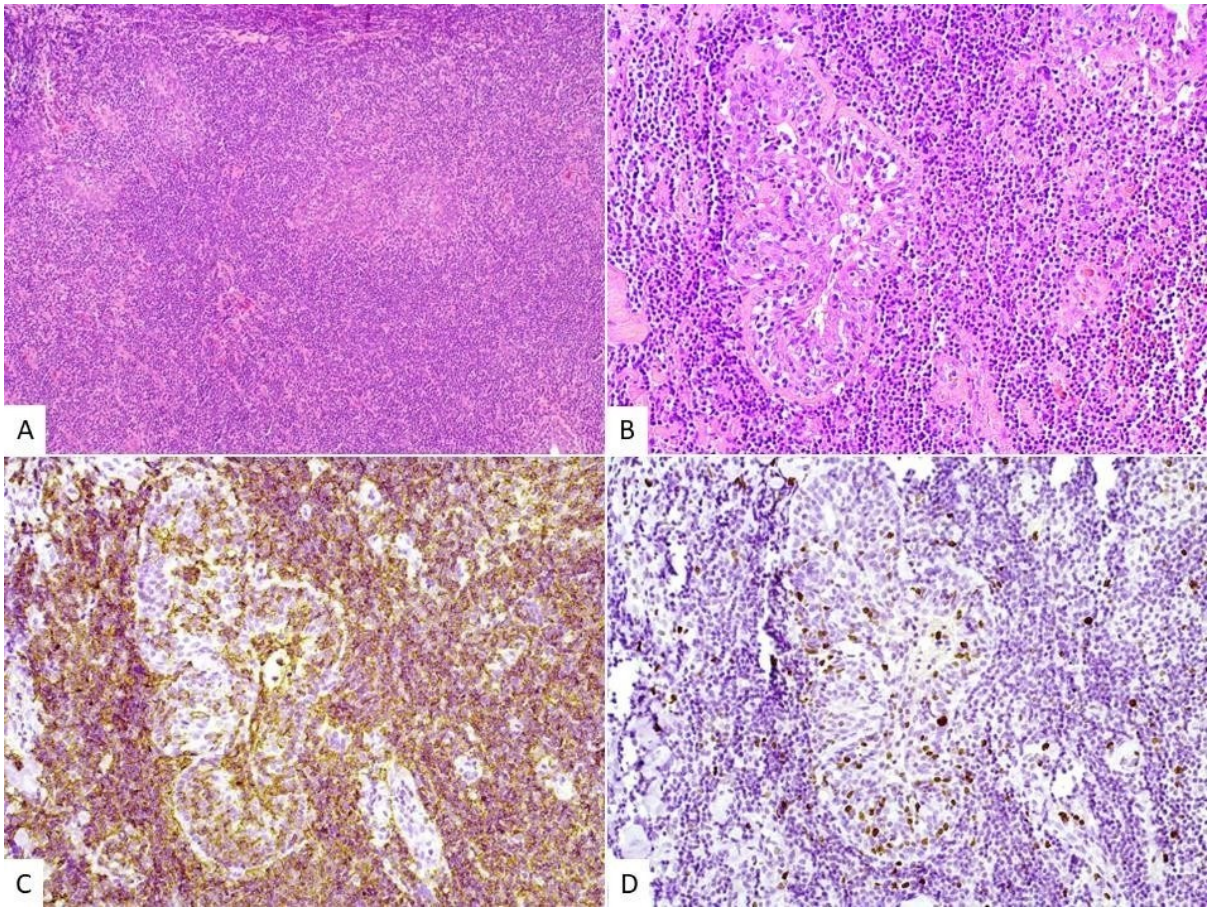

Figure 3. Microscopic findings of MALT lymphoma affecting the parotid gland (case #4). A) A diffuse proliferation of small-to-moderate-sized neoplastic cells with scant cytoplasm (H&E; 100 ×). B) Presence of neoplastic cells in glandular structures with lymphoepithelial lesions (H&E; 200 ×). C) The neoplastic cells were diffusely positive for CD20 (DAB; 200 ×) and D) Ki-67 with index of ~5%(DAB; 200 ×).

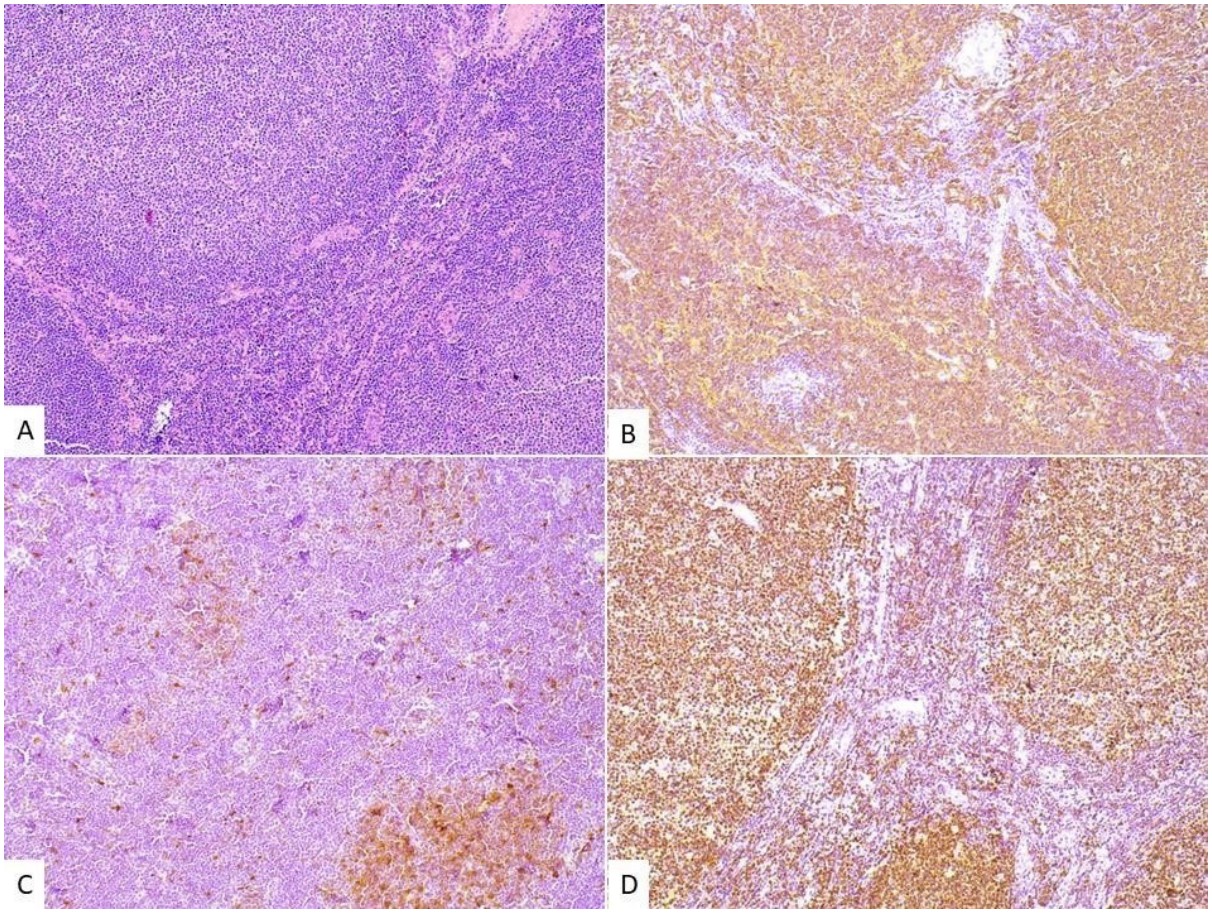

Figure 4. Microscopic features of follicular lymphoma in the parotid gland . A) The neoplasm exhibited a follicular lymphoma growth pattern with follicles focally showing a back-to-back pattern (H&E; 100 ×). B) The neoplastic cells were diffusely positive for CD20 (100x), and C) revealed positivity for CD10 (100x) and D) Bcl2 proteins in the neoplastic germinal centers (100x).

6 CONSIDERAÇÕES FINAIS

Os linfomas que envolvem as glândulas submandibulares, sublinguais e parótidas são incomuns e mais frequentemente correspondem a neoplasias de células B de baixo grau, como o linfoma folicular e o linfoma MALT. No entanto, atenção deve ser dada aos subtipos de alto grau que afetam estas glândulas, especialmente ao LDGCB SOE. Além disso, o diagnóstico diferencial destas neoplasias em relação às neoplasias de glândulas salivares merece especial atenção. Pacientes com diagnóstico de linfomas em glândulas salivares maiores, em especial aqueles afetados pelo linfoma MALT devem ser avaliados quanto a presença da Síndrome de Sjögren. Finalmente, pacientes com diagnóstico de linfoma envolvendo as glândulas sublinguais, submandibulares e parótidas devem passar por uma avaliação sistêmica criteriosa para determinar se a doença se trata de uma neoplasia primária ou disseminada.

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UNIVERSIDADE FEDERAL DE

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ANEXO 1

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação das manifestações clínicas e microscópicas dos linfomas em glândulas salivares maiores

Pesquisador: Felipe Paiva Fonseca

Área Temática:

Versão: 1

CAAE: 58900722.1.0000.5149

Instituição Proponente: UNIVERSIDADE FEDERAL DE MINAS GERAIS

Patrocinador Principal: FUND COORD DE APERFEICOAMENTO DE PESSOAL DE NIVEL SUP

DADOS DO PARECER

Número do Parecer: 5.508.097

Apresentação do Projeto:

Os linfomas correspondem a um grupo de lesões que se desenvolvem de linfócitos em diferentes estágios de maturação, representando o terceiro grupo de neoplasias malignas mais comum na região de cabeça e pescoço após o carcinoma de células escamosas e as neoplasias de glândulas salivares. As glândulas salivares maiores representam o terceiro sítio extranodal mais acometido pelo linfoma na região da cabeça e pescoço; entretanto, ainda são considerados muito raros, representando aproximadamente1,7–3,1% de todas as neoplasias das glândulas salivares, acometendo a maioria dos casos as glândulas parótidas (79%), seguidas pelas glândulas submandibulares (18%) e sublinguais(1%). O linfoma do tecido linfoide associado à mucosa (MALT), o linfoma folicular (FL) e o linfoma difuso de grandes células B (DLBCL) costumam ser os subtipos mais diagnosticados nas glândulas maiores, e a frequência destas neoplasias está associado com a ocorrência simultânea de condições sistêmicas que predispõem ao desenvolvimento de neoplasias linfoides como a Síndrome de Sjögren. Entretanto, a literatura sobre linfomas em glândulas maiores permanece muito escassa e impede que conheçamos de forma apropriada as características destes pacientes. Assim, o objetivo deste estudo é avaliar as manifestações clínicas e microscópicas dos linfomas em glândulas salivares maiores. Para isto, serão recuperados de forma retrospectiva dos arquivos de patologia de duas instituições todos os casos diagnosticados como linfomas acometendo estes sítios anatômicos. Os dados clínicos referentes ao sexo, idade, localização, apresentação clínica e ocorrência de síndrome de Sjögren

serão coletados dos exames anatomopatológicos.
Novos cortes histológicos serão revisados e correlacionados com dados de exames imunoistoquímicos para confirmação dos diagnósticos. Os resultados obtidos serão avaliados de forma descritiva, para Doutorado.

Objetivo da Pesquisa:

Hipótese:
Os linfomas não Hodgkin do tipo folicular, MALT, difuso de grandes células B sem outras especificações e de células do manto são os subtipos de linfomas que mais afetam as glândulas salivares maiores

Objetivo Primário:

Caracterizar os aspectos clinicopatológicos dos linfomas que se manifestam nas glândulas salivares maiores.

Objetivo Secundário:

Determinar os subtipos mais comuns de linfomas em glândulas salivares maiores;Investigar as características clínicas dos linfomas em glândulas salivares maiores; Avaliar as características histopatológicas e imunoistoquímicas dos linfomas em glândulas salivares maiores.Investigar de forma comparativa as características clínicas e microscópicas dos linfomas em função de cada tipo de glândula salivar maior

Avaliação dos Riscos e Benefícios:

Critério de Inclusão:

Serão incluídos todos os casos que tiverem lâminas histológicas e/ou blocos de parafina que permitam a confirmação do diagnóstico de acordo com os critérios de Classificação de Neoplasias Hematolinfoides da Organização Mundial da Saúde (OMS) (GASCOYNE et al. 2017).

Critério de Exclusão:

Serão excluídos todos os casos de linfomas que acometam outras localizações da região de cabeça e pescoço, e os casos diagnosticados em glândulas salivares menores.

Riscos:

A pesquisa não vai trazer desconfortos ou riscos previsíveis direto ao participante, mas uma possível perda da confidencialidade pode ocorrer.

Dessa forma iremos abordar técnicas para minimizar esse
risco. Benefícios:

Não haverá benefícios diretos para o individuo envolvido na pesquisa visto que as amostras dos participantes já foram coletadas no momento do diagnostico, sendo assim eles já foram

UNIVERSIDADE FEDERAL DE MINAS GERAIS

(Continuação do Parecer: 5.508.007)

diagnosticados e tratados. Entretanto, a pesquisa auxiliará futuros pacientes no diagnóstico mais preciso e precoce dos linfomas em glândulas salivares maiores, auxiliando em tratamentos mais rápidos e, consequentemente, melhores taxas de sobrevida.

Comentários e Considerações sobre a Pesquisa:

Pesquisa relevante para o conhecimento dos linfomas

Considerações sobre os Termos de apresentação obrigatória:

1. Folha de rosto preenchida e assinada.
2. Aprovação Ad referendum do Colegiado de pós-graduação da Faculdade de Odontologia da UFMG
3. C0-participantesUNICAMP,UFPA,RN
4. Viabilidade financeira e cronograma
5. Instrumentos de coleta de dados
6. Projeto completo
7. TCLE como carta convite, resguardando a confidencialidade dos dados, o anonimato, o direito à recusa, e desistir do projeto a qualquer momento sem qualquer prejuízo. Foi informado sobre a metodologia, o objetivo e o armazenamento de 05 anos dos dados, salvaguardando a sua consulta. Esclarece que não haverá qualquer forma de pagamento, mas disponibiliza apoio em caso de gerar algum risco à integridade física, mental ou de qualquer outra natureza ao participante. Consentimento para registro de áudio, vídeo, imagens. Dados do pesquisador e do COEP relatados
8. Termos de constituição de biorepositório, para armazenamento de dados biológicos, conforme a Resolução 411/2011.

Recomendações:

- Retirar a logomarca da UFMG e da Faculdade de Odontologia no início do TCLE.

Conclusões ou Pendências e Lista de Inadequações:

Pelo apresentado , somos pela aprovação do projeto.

Considerações Finais a critério do CEP:

Tendo em vista a legislação vigente (Resolução CNS 466/12), o CEP-UFMG recomenda aos Pesquisadores: comunicar toda e qualquer alteração do projeto e do termo de consentimento via emenda na Plataforma Brasil, informar imediatamente qualquer evento adverso ocorrido durante o

UNIVERSIDADE FEDERAL DE MINAS GERAIS

continuação do Parecer: 5.508.097

desenvolvimento da pesquisa (via documental encaminhada em papel), apresentar na forma de notificação relatórios parciais do andamento do mesmo a cada 06 (seis) meses e ao término da pesquisa encaminhar a este Comitê um sumário dos resultados do projeto (relatório final).

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1949211.pdf	20/05/2022 15:54:07		Aceito
Outros	DADOS.docx	20/05/2022 15:52:02	GABRIELA RIBEIRO DE ARAUJO	Aceito
Solicitação registrada pelo CEP	cep.pdf	20/05/2022 15:49:46	GABRIELA RIBEIRO DE ARAUJO	Aceito
Solicitação Assinada pelo Pesquisador Responsável	Pesquisador.pdf	20/05/2022 15:42:43	GABRIELA RIBEIRO DE ARAUJO	Aceito
Folha de Rosto	Folha.pdf	20/05/2022 15:35:51	GABRIELA RIBEIRO DE ARAUJO	Aceito
Outros	RN.pdf	20/05/2022 15:35:19	GABRIELA RIBEIRO DE ARAUJO	Aceito
Outros	UNICAMP.doc	20/05/2022 15:35:03	GABRIELA RIBEIRO DE ARAUJO	Aceito
Outros	UFPA.doc	20/05/2022 15:34:50	GABRIELA RIBEIRO DE ARAUJO	Aceito
Outros	UFMG.pdf	20/05/2022 15:22:03	GABRIELA RIBEIRO DE ARAUJO	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.docx	20/05/2022 15:17:29	GABRIELA RIBEIRO DE ARAUJO	Aceito
Declaração de Instituição e Infraestrutura	Declaracao.pdf	20/05/2022 15:15:40	GABRIELA RIBEIRO DE ARAUJO	Aceito
Projeto Detalhado / Brochura Investigador	Projeto.docx	20/05/2022 15:14:41	GABRIELA RIBEIRO DE ARAUJO	Aceito
Declaração de Manuseio Material Biológico / Biorepositório / Biobanco	Biorrepositorio.docx	20/05/2022 15:13:56	GABRIELA RIBEIRO DE ARAUJO	Aceito

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Continuação do Parecer: 5.508.097

Situação do Parecer:
Aprovado
Necessita Apreciação da CONEP:
Não

BELO HORIZONTE, 04 de Julho de 2022

Assinado por:

Críssia Carem Paiva Fontainha
(Coordenador(a))

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