GABRIELA RIBEIRO DE ARAÚJO

LEIOMIOMAS E LEIOMIOSARCOMAS DA REGIÃO ORAL E MAXILOFACIAL: *UM ESTUDO CLINICOPATOLÓGICO E IMUNOISTOQUÍMICO DE UMA SÉRIE DE CASOS*

Faculdade de Odontologia
Universidade Federal de Minas Gerais
Belo Horizonte
2021

Gabriela Ribeiro de Araújo

LEIOMIOMAS E LEIOMIOSARCOMAS DA REGIÃO ORAL E MAXILOFACIAL: *UM ESTUDO CLINICOPATOLÓGICO E IMUNOISTOQUÍMICO DE UMA SÉRIE DE CASOS*

Dissertação 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 Mestre em Odontologia – área de concentração em Estomatologia.

Orientador: Prof. Felipe Paiva Fonseca

Belo Horizonte
2021

Ficha Catalográfica

A663l 2021 T

Araújo, Gabriela Ribeiro de.

Leiomiomas e leiomiosarcomas da região oral e maxilofacial : um estudo clinicopatológico e imunoistoquímico de uma série de casos / Gabriela Ribeiro de Araújo. -- 2021.

59 f. : il.

Orientador: Felipe Paiva Fonseca.

Dissertação (Mestrado) -- Universidade Federal de Minas Gerais, Faculdade de Odontologia.

1. Tumor de músculo liso. 2. Boca. 3. Leiomioma. 4. Leiomiossarcoma. I. Fonseca, Felipe Paiva. II. Universidade Federal de Minas Gerais. Faculdade de Odontologia. III. Título.

BLACK - D047

Elaborada por Sérgio Barbosa dos Santos - CRB 6/3182.

FOLHA DE APROVAÇÃO

Leiomioma e leiomiossarcoma da região oral e maxilofacial: Um estudo clinicopatológico e imunoistoquímico de 27 casos

GABRIELA RIBEIRO DE ARAÚJO

Dissertação submetida à Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em Odontologia, como requisito para obtenção do grau de Mestre, área de concentração Estomatologia.

Aprovada em 19 de julho de 2021, pela banca constituída pelos membros:

Prof(a). Felipe Paiva Fonseca – Orientador
FO-UFMG

Prof(a). Sara Ferreira dos Santos Costa
UFMG

Prof(a). Renata Gonçalves de Resende
Faculdade Padre Arnaldo Jensen

Belo Horizonte, 19 de julho de 2021.

Defesa Homologada pelo Colegiado de Pós-Graduação em Odontologia em 26 / 07 /2021.

Profa. Isabela Almeida Pordeus
Coordenadora do Colegiado de Pós-Graduação
Faculdade de Odontologia

Dedico este trabalho primeiramente a Maria por me conceder o dom da vida. Aos meus pais e irmã que sempre acreditaram no meu potencial e incentivaram minhas escolhas.

AGRADECIMENTO

Primeiramente, agradeço e a Deus e a Maria, por me protegerem e guiarem meu caminho.

Aos meus pais, Maria Lúcia e Roberto, meus maiores incentivadores na vida, agradeço vocês por todo amor incondicional, cuidado e carinho. A minha irmã, Maria Tatiana, e melhor amiga, obrigada por todos os conselhos e por sempre me orientar nas minhas decisões profissionais. Ao Pedro, por valorizar meu potencial e estar sempre ao meu lado com tanta dedicação e amor.

Ao meu orientador, Professor Felipe Paiva Fonseca por todo auxílio e orientação durante a construção desse trabalho, pelos conhecimentos compartilhados ao longo desses dois anos, por todo cuidado e compreensão, e por toda confiança que a mim foi colocada. Tenho uma imensa admiração por todo esforço e sua dedicação na área acadêmica. Um exemplo de pessoa e profissional ao qual me espelho.

A aluna de doutorado, Sara Costa, que desde o início da construção desse trabalho se mostrou disponível, dedicada e parceira, compartilhando de todo seu conhecimento no assunto aqui abordado.

Aos professores da Estomatologia/Patologia Bucal da FAO-UFMG, Maria Cássia Aguiar, Tarcília Silva, Patrícia Caldeira, Sílvia Ferreira, Ricardo Gomez e Ricardo Mesquita. Agradeço por todo conhecimento compartilhado nas aulas, projetos e nas clínicas.

Aos meus colegas e companheiros de pós-graduação, em especial ao Ricardo Correa, Humberto Jácome, Maria Sissa Pereira, Daniela Meirelles, Eustaquio Alexandre, Flavia Leite, Carolina Peres, Isadora Gomes, Taynara Resende e Victor Coutinho pelo aprendizado em conjunto, pela amizade, pareceria, palavras de incentivo e apoio diário. Essa etapa se tornou ainda mais especial na companhia de todos vocês.

Aos meus amigos de infância da caravana Bruna, Gabriela, Guilherme, Juliana, Luisa e Stephanie agradeço por todo carinho e companheirismo. Com vocês a vida se torna mais alegre e cheia de amor.

À Faculdade de Odontologia da Universidade Federal de Minas Gerais pela formação acadêmica.

A todos que, de alguma forma, fizeram a diferença ao longo desse ótimo tempo!

“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 tumores de músculo liso são considerados raros na cavidade oral, com a frequência de leiomioma (LM) e leiomiossarcoma (LMS) oral sendo menor que 1% do total de neoplasias nesta região. Os LMs são caracterizados clinicamente como um nódulo de crescimento lento e assintomático, sendo classificados como angioleiomioma (ALM) e LM sólido. Histologicamente, os LM sólidos apresentam-se como uma proliferação de células fusiformes com citoplasma eosinofílico, formando feixes ou fascículos entrelaçados, enquanto que os ALM são compostos por feixes de células musculares lisas bem diferenciadas em torno de vasos sanguíneos de tamanho variável. A remoção cirúrgica conservadora é o tratamento preconizado e as recorrências são extremamente raras. Já o LMS apresenta-se clinicamente como uma lesão tumoral que exibe um crescimento rápido e localmente destrutivo, exibindo histologicamente um crescimento fascicular de células neoplásicas fusiforme, com figuras de mitose, atipia celular e necrose tecidual. O tratamento mais usado é a excisão cirúrgica radical, frequentemente exibindo recidivas locais e metástases a distância. Devido à longa lista de diagnósticos diferenciais microscópicos destas neoplasias, reações de imunoistoquímica costumam ser fundamentais para o correto diagnóstico. Assim, o objetivo deste estudo foi analisar as características clínicas, histopatológicas e imunoistoquímicas de uma série de casos de LM e LMS afetando a região oral e maxilofacial. Todos os casos diagnosticados como LM e LMS no período de 2000 a 2019, foram recuperados dos arquivos de seis serviços de diagnóstico oral. As características clínicas e demográficas foram obtidas a partir dos registros patológicos dos pacientes, enquanto as características microscópicas e imunoistoquímicas foram revisadas,por pelo menos dois autores simultaneamente, ou repetidas sempre que necessário para confirmação do diagnóstico. Os anticorpos utilizados na imunoistoquimica foram: anti-α-SMA, actina músculo-específica(HHF-35), h-caldesmona e Ki67, entretanto, sempre que necessário, utilizamos S100, desmina e CD34. Foram obtidos 22 casos de LM e cinco LMS. No grupo de LM, houve predomínio do sexo masculino, com média de idade de 45,7 anos. O lábio superior foi o local mais acometido, sendo 18 casos classificados como angioleiomiomas e quatro como LM sólido.O tempo de evolução médio foi de 44.5 meses e 91% dos pacientes foram assintomáticos.Já no grupo LMS houve predomínio do sexo feminino, com média de idade de 47,6 anos. A mandíbula foi o local mais afetado.Todos os pacientes foram sintomáticos, apresentando dor, dormência do lábio inferiror e parestesia do nervo alveolar inferior, com um tempo de evolução variando entre 2-4 mêses. Proliferação difusa de células fusiformes, com necrose e figuras mitóticas, foram achados microscópicos frequentes. LM e LMS foram consistentemente positivos para α-SMA, HHF-35 e h-caldesmona. Concluimos nesse estudo que tanto o LM como o LMS orais são neoplasias raras, sendo que a última geralmente se apresenta como doença metastática. A avaliação histológica de rotina pode ser muito sugestiva para o diagnóstico de LMs orais, mas a imunoexpressão de h-caldesmona é fortemente recomendada para confirmação do diagnóstico de LMS.

Palavras-chave: Tumor de músculo liso. Boca. Leiomioma. Leiomiossarcoma.

ABSTRACT

Leiomyomas and leiomyosarcomas of the oral and maxillofacial region: a clinicopathological and immunohistochemical study of 27 cases

Smooth muscle tumors are considered rare in the oral cavity, with the frequency of leiomyoma (LM) and leiomyosarcoma (LMS) being less than 1% of the total number of neoplasms diagnosed in this region. LM are clinically characterized as a slow and asymptomatic nodule, being classified as angioleiomyoma and solid LM. Histologically, solid LM appear as a proliferation of spindle cells with eosinophilic cytoplasm forming bundles or interlaced fascicles, while angioleiomyomas are composed of bundles of bland, well-differentiated smooth muscle cells and intervening variably sized blood vessels. Surgical removal is the recommended treatment and recurrences are extremely rare. LMS, on the other hand, presents clinically as a tumoral lesion that exhibits rapid and locally destructive growth, histologically showing a fascicular growth of spindle-shaped neoplastic cells, with figures of mitosis, cell atypia and tissue necrosis. The most used treatment is radical surgical excision, often showing local recurrences and distant metastases. Due to the long list of microscopic differential diagnoses of these two neoplasms, immunohistochemistry reactions are usually fundamental for the correct diagnosis. Thus, the aim of this study was to describe in detail the clinical, histopathological and immunohistochemical characteristics of a series of cases of LM and LMS affecting the oral and maxillofacial region. All cases diagnosed as LM and LMS in the period from 2000 to 2019, were recovered from the files of six oral diagnostic services. Clinical and demographic characteristics were obtained from patients' pathological records, while microscopic and immunohistochemistry characteristics were reviewed, by at least two authors simultaneously, and completed when necessary to confirm the diagnosis. Antibodies used in immunohistochemistry were: anti-α-SMA, muscle-specific actin(HHF-35), h-caldesmon and Ki67, however, whenever necessary, we used S100, desmin and CD34. Twenty-two LM and five LMS were obtained in the study. In the LM group, there was a predominance of males, with a mean age of 45.7 years. The upper lip was the most affected site, with 18 cases classified as angioleiomyoma and four as solid LM. The mean evolution time was 44.5 months and 91% of patients were asymptomatic. In the LMS group, there was a predominance of females, with a mean age of 47.6 years. The jaw was the most affected site. All patients were symptomatic, with pain, lower lip numbness and inferior alveolar nerve paresthesia, with evolution time ranging from 2-4 months. Diffuse proliferation of spindle cells, with necrosis and mitotic figures, were frequent microscopic findings. LM and LMS were consistently positive for smooth α-SMA, HHF-35 and h-caldesmon. We concluded in this study that both LM and oral LMS are uncommon neoplasms, the latter usually presenting as a metastatic disease. H&E assessment can be very suggestive for oral LM, but immunohistochemical staining for h-caldesmon is strongly recommended to confirm the diagnosis of LMS.

Keywords: Smooth muscle tumor. Leiomyoma. Leiomyosarcoma. Mouth neoplasms. Case series.

LISTA DE ILUSTRAÇÕES

LISTA DE TABELAS

LISTA DE ABREVIAÇÕES

LM Leiomioma

ALM Angioleiomioma

LMS Leiomiossarcoma

α-SMA Actina de Músculo Liso

HHF-35 Actina Músculo-Específica

H&E Hematoxilina Eosina

OMS Organização Mundial de Saúde

SPSS Statistical Package for the Social Sciences

SUMÁRIO

1 CONSIDERAÇÕES INICIAIS

Os tumores de tecidos moles representam um grupo heterogêneo de neoplasias cuja classificação é baseada em sua histogênese ou diferenciação de tecidos compreendendo neoplasias fibroblásticas / miofibroblásticas, fibrohistiocíticas, vasculares, pericíticas (perivasculares), neurais, adiposas, musculares (lisas ou esqueléticas) e estromais gastrointestinais (FLETCHER 2014; SOLAR e JORDAN, 2011). No geral, os tumores de tecido mole são relativamente incomuns na região de cabeça e pescoço, e os sarcomas nessa região representam apenas 5-10% de todos os casos (FLETCHER, 2002).

Dentre os tumores de tecidos moles, os tumores de músculo liso ocorrem com maior frequência no endométrio, sendo o trato gastrointestinal, a pele e os tecidos subcutâneos outros sítios frequentemente acometidos. A ocorrência na cavidade oral é considerada rara, provavelmente devido à escassez de tecido muscular liso nesta região (SOLAR e JORDAN, 2011; WERTHEIMER-HATCH *et al*., 2000). Acredita-se que os tumores de músculo liso da cavidade oral desenvolvam-se a partir do tecido muscular liso das paredes dos vasos sanguíneos ou das papilas circunvaladas da língua (AMARAPALA e TILAKARATNE, 2006; CASTALDI *et al*., 2006).

Os leiomiomas (LM) são tumores benignos de músculo liso que afetam preferencialmente os órgãos genitais, pele e trato gastrointestinal, sendo raramente observados na cavidade oral (BADEN *et al.,* 1994; CHERRICK *et al.,* 1973; HACHISUGA *et al.,* 1984; SOLAR e JORDAN, 2011; VEERESH *et al.,* 2013). Em 1964, Hagy e seus colaboradores, realizou uma revisão de literatura e relato de casos sobre LMs, em que descreveu o primeiro caso de leiomioma oral, descrito por Blanc em 1884 (HAGY *et al.*, 1964). Blanc observou o primeiro LM em base da língua na região tonsilar, assintomático, em um homem de 33 anos, que foi submetido a remoção cirúrgica sem recidivas (BLANC, 1884). De acordo com as principais séries atuais disponíveis na literatura, eles são comumente diagnosticados na 4ª e 5ª décadas de vida com uma média de idade variando de 40,6 a 53,6 anos (HUANG e ANTONESCU, 2003; VEERESH *et al.,* 2013). Os estudos anteriores mostram uma distribuição semelhante entre os sexos com uma discreta tendência de ocorrência dos casos de LM em homens (AITKEN-SAAVEDRA *et al.,* 2018; CEPEDA *et al.,* 2008; GUEIROS *et al.*, 2011; IDE *et al.,* 2008). Os locais mais frequentemente acometidos

são os lábios (superior e inferior), seguidos de língua, bochecha, palato mole, palato duro, gengiva e mandíbula (AITKEN-SAAVEDRA *et al.*, 2018; VEERESH *et al*., 2013).

Clinicamente, os LMs orais apresentam-se frequentemente como um pequeno nódulo de crescimento lento, coloração semelhante à mucosa normal ou arroxeado e assintomático; entretanto, alguns podem apresentar sintomatologia dolorosa causando dificuldade de mastigação e deglutição, o que provavelmente está associado com a localização afetada (CHERRICK *et al.,* 1973; VEERESH *et al.,* 2013; WERTHEIMER-HATCH *et al.,* 2000).

Outros tumores benignos de tecido mole, como por exemplo, os neurofibromas, mucocele, variz, processo proliferativo não-neoplásico, neoplasia benigna de glândula salivar e neoplasia mesenquimal benigna, podem apresentar achados clínicos semelhantes ao LM sólido e angioleiomioma. Portanto, a confirmação diagnóstica deve ser estabelecida por meio da avaliação dos achados histopatológicos (VEERESH *et al*., 2013). Microscopicamente, os LMs sólidos apresentam-se como uma proliferação de células com formato fusiforme e citoplasma eosinofílico relativamente abundante, formando feixes ou fascículos entrelaçados. O núcleo das células tumorais é alongado com a terminação achatada semelhante à forma de um charuto. Já os angioleiomiomas são compostos por feixes de células musculares lisas bem diferenciadas em torno de vasos sanguíneos de tamanho variáveis, e são subclassificados em três subtipos histológicos com base em suas morfologias vasculares, sendo eles o sólido, venoso e cavernoso. Tanto o LM sólido quanto o angioleiomioma podem apresentar algumas alterações degenerativas como fibrose, hialinização, calcificação e alteração mixóide. Ao contrário de sua contraparte maligna, figuras mitóticas são extremamente escassas ou estão completamente ausentes em ambos (EI-NAGGA *et al.,* 2017; GOLDBLUM *et al.,* 2008; STOUT, 1937; WHO, 2020).

Uma dificuldade no diagnóstico histológico de LM sólido e angioleiomioma na cavidade oral é que eles podem apresentar características que são compartilhadas com outras lesões. Muitos tumores podem exibir um padrão microscópico semelhante de células fusiformes dispostas em feixes como o miofibroma, tumor solitário fibroso, neurofibroma, schwannoma, dentre outras neoplasias de origem mesenquimal (CEPEDA *et al.,* 2008; DATNM e NEVILLE, 1979; EI-NAGGA *et al.,* 2017; LUACES REY *et al.,* 2007). Portanto, um painel imunoistoquimico contendo actina de músculo

liso (αSMA), calponina, h-caldesmona e desmina é recomendado para confirmação diagnóstica (WHO 2020).

A ressecção cirúrgica é o principal tratamento para os leiomiomas e as recorrências são extremamente raras, apresentando, portanto, um excelente prognóstico (AITKEN-SAAVEDRA *et al*., 2018; CEPEDA *et al.,* 2008; GUEIROS *et al.,* 2011; VEERESH *et al.,* 2013). Até o momento não parece haver exemplos na literatura de LM orais exibindo transformação maligna, entretanto, raros casos de alteração sarcomatosa em LMs foram relatados em dedo (HERREN *et al.,* 1995), retroperitônio (LEE *et al*.,1996) e útero (ROTMENSCH *et al.,* 1993).

O leiomiossarcoma (LMS) é uma neoplasia maligna de músculo liso que representa de 5% a 10% de todos os sarcomas de tecidos moles, sendo extremamente raro na cavidade oral (1%) (KO, 2019; SOLAR e JORDAN, 2011; YAMAGUCHI *et al.,* 2003). Em um estudo realizado no Brasil no período de 2007 a 2016, das 176.537 amostras de lesões orais diagnosticadas nos serviços avaliados, apenas 200 casos (0,11%) de sarcomas orais foram identificados, e 12 casos (6%) foram diagnosticados como LMS (DE CARVALHO *et al.*, 2019).

Considerando-se os poucos casos relatados de LMS orais, observa-se que a idade dos pacientes pode variar dos 7 aos 67 anos, com idade média de 36 anos de idade (KO, 2019). Os casos de LMS orais não apresentam uma nítida predileção em relação ao sexo (VILOS *et al.*, 2005). Clinicamente, o LMS apresenta-se como uma lesão tumoral associada ou não a dor e parestesia, exibindo um crescimento rápido e localmente destrutivo (DRY *et al.*, 2000; ETHUNANDAN *et al.,* 2007; MIZUTANI *et al.*, 1995; VILOS *et al.*, 2005). A maioria dos LMS apresenta dimensão entre 1,5 a 5 cm, sendo casos acima de 5 cm considerados raros (ETHUNANDAN *et al.*, 2007; VILOS *et al.*, 2005). Os sítios mais frequentemente acometimentos são o assoalho de boca, mucosa jugal, língua, mandíbula e maxila (ETHUNANDAN *et al.*, 2007; KO 2019; VILOS *et al.,* 2005).

O diagnóstico é definido após cuidadosa análise microscópica seguida de um detalhado exame imunoistoquímico com o objetivo de confirmar a natureza muscular lisa deste sarcoma (ETHUNANDAN *et al.,* 2007; VILOS *et al.,* 2005). Microscopicamente, o achado típico para LMS é de um crescimento fascicular mal delimitado ou infiltrativo que pode apresentar áreas de necrose tecidual de forma

localizada ou extensa. As células tumorais exibem formato fusiforme, citoplasma bem a moderadamente definido e núcleo oval a alongado com terminação romba. Essas células são arranjadas em fascículos de tamanhos variados que se cruzam perpendicular ou aleatoriamente. A presença de mitose e atipia celular e nuclear são observadas, e em casos mais indiferenciados, podem ser frequentes (ETHUNANDAN *et al.,* 2000; KO, 2019; VILOS *et al.*, 2005).

Ao exame imunoistoquímico, os LMS mostram uma intensa positividade para marcadores miogênicos como actina de músculo liso (αSMA), desmina e actina músculo-específica (HHF-35), sendo negativas para a proteína S100, CD34 e citoqueratinas (ETHUNANDAN *et al.*, 2007; KO, 2019). O diagnóstico diferencial deve incluir outros tumores malignos de células fusiformes como rabdomiossarcoma, fibrossarcoma, assim como carcinomas de células fusiformes e melanomas (VILOS *et al.,* 2005). Além disso, vale ressaltar que os marcadores miogênicos citados também são expressos por miofibroblastos e podem ser observados em casos de miofibrossarcomas. Desta forma, a utilização de h-caldesmona no painel imunoistoquímico é fundamental, uma vez que este marcador é considerado específico de diferenciação muscular lisa, não sendo expresso em lesões miofibroblásticas. Entretanto, muitos dos casos de LMS atualmente disponíveis na literatura não contam com um adequado painel de reações imunoistoquímicas, comprometendo o rigor diagnóstico destas lesões.

O método de tratamento mais usado para LMS na cavidade oral é a excisão cirúrgica radical. A recorrência local e metástases são comuns, com os casos que apresentam envolvimento ósseo (maxila/mandíbula) e aqueles associados a processos metastáticos sendo associados a prognósticos mais desfavoráveis. A estimativa de sobrevida em 5 anos é de aproximadamente 55%, sendo menor para doenças com envolvimento ósseo e metastáticas, de aproximadamente 43% e 19% respectivamente (ETHUNANDAN *et al.*, 2007; KUMAR *et al.,* 2019; VILOS *et al.*, 2005). Os LMS são geralmente considerados resistentes à radioterapia (ETHUNANDAN *et al.,* 2007), enquanto a quimioterapia é usada como modalidade paliativa para lesões inoperáveis e doença metastática (ETHUNANDAN *et al.,* 2007; MONTGOMERY *et al.,* 2002).

Como observado, tanto o LM como o LMS são tumores de tecido mole muito raros na cavidade oral e o diagnóstico pode representar um grande desafio. Sendo assim, o objetivo deste estudo é descrever as características clínicas, histopatológicas e imunoistoquímicas de uma série de casos de LM e LMS da região oral e maxilofacial.

Objetivos da pesquisa

Objetivo geral

Descrever uma série de casos de leiomioma e leiomiossarcoma afetando a região oral e maxilofacial.

Objetivo específico:

a) Avaliar as características clínicas do leiomioma e leiomiossarcoma orais;

b) Descrever as características histopatológicas e imunoistoquímicas do leiomioma e leiomiossarcoma orais.

2 METODOLOGIA EXPANDIDA

Aspectos éticos

Este estudo foi aprovado pelo comitê de ética em pesquisa da Universidade Federal de Minas Gerais (72775717.8.0000.5149).

Delineamento do estudo

É um estudo de série de casos, observacional, retrospectivo (2000-2019) e descritivo.

Seleção dos casos

Foram recuperados de forma retrospectiva todos os casos diagnosticados como LM ou LMS da região oral e maxilofacial disponíveis nos arquivos de patologia dos centros de referência em diagnóstico de doenças orais da Universidade Federal de Minas Gerais (Belo Horizonte / Brasil), da Universidade Estadual de Campinas (Piracicaba / Brasil), da Universidade Federal do Rio de Janeiro (Rio de Janeiro / Brasil), da Universidade Federal do Pará (Hospital Universitário João de Barros Barreto) (Belém / Brasil), do Serviço de Oncologia Dentária do Instituto do Câncer do Estado de São Paulo (São Paulo / Brasil) e da Faculdade de Odontologia da Universidad Nacional de Córdoba (Córdoba / Argentina). Esses casos foram diagnosticados durante um período que varia de 2000 a 2019.

Critérios de elegibilidade

Critérios de inclusão

Foram incluídos neste estudo todos os casos que *1)* apresentavam tecido emblocado em parafina ou lâminas histológicas que permitissem confirmar os

diagnósticos de LM ou LMS; e entre os LMS *2)* foram incluídos apenas os casos que exibiram marcação positiva para h-caldesmona.

Critérios de exclusão

Foram excluídos do estudo *1)* aqueles casos compatíveis com LM ou LMS mas que afetavam outras regiões da cabeça e pescoço que não a cavidade oral e os ossos gnáticos, e *2)* aqueles casos que exibiram marcações imunoistoquímicas incompatíveis com o diagnóstico de neoplasia de músculo liso.

Análise dos dados

Foram analisados todos os dados referentes às informações demográficas, clínicas e histopatológicas.

Dentre as características demográficas, foram avaliadas a distribuição de idade e sexo dos pacientes. Já as características clínicas, foram relatadas as informações referentes ao tamanho da lesão, tendo como referência o maior diâmetro clínico/radiográfico aferido; a localização anatômica; a lesão fundamental; a coloração da lesão; o tempo de evolução; sintomatologia e tipo de tratamento. Além disso, os dados relativos ao acompanhamento, que incluem recorrência e desfecho clínico (paciente afetado por LMS vivo ou morto), também foram avaliados quando disponíveis. Tanto os dados clínicos, como os demográficos coletados dos prontuários físicos e/ou eletrônicos dos pacientes foram tabulados e comparados.

A confirmação do diagnóstico e a descrição histopatológica foram realizadas por meio da análise das lâminas histológicas coradas com 0 por um patologista oral. Da mesma forma, a descrição das características imunoistoquímicas foi feita a partir da análise das lâminas de imunoistoquímica acessíveis. Quando necessário, novas lâminas de H&E e novas reações de imunoistoquímica foram realizadas a partir dos blocos de parafina disponíveis.

As reações imunoistoquímicas foram realizadas usando o método estreptavidina-biotina-peroxidase para confirmação dos diagnósticos. As reações foram realizadas em cortes de 3 µm dos tecidos originais fixados em formalina e preservados em parafina que foram diafanizados com xilol e depois hidratados em

uma série de etanol. A recuperação do antígeno foi realizada e a atividade endógena da peroxidase foi bloqueada com peróxido de hidrogênio a 10% em cinco banhos, cada um com 5 minutos. Após lavagem em tampão PBS (pH 7,4), as lâminas foram incubadas durante a noite com anticorpos primários. Os seguintes anticorpos foram utilizados: anti-α-SMA (clone 1A4; diluição 1: 200; Dako Corp., Carpenteria, CA, EUA), actina músculo-específica (clone HHF35; diluição 1: 400 ; Dako Corp., Carpenteria, CA, EUA), h-caldesmona (clone h-CALD; diluição 1: 100; Medaysis) e Ki67 (clone MIB-1, diluição 1: 100; Dako Corp., Carpenteria, CA, EUA). Além disso, a proteína S100 (clone S100; diluição 1: 500; Dako Corp., Carpenteria, CA, EUA), desmina (clone D33; diluição 1: 100; Dako Corp., Carpenteria, CA, EUA) e CD34 (clone QBEnd / 10; diluição 1: 100; Cell Marque) foram investigados sempre que necessário. Todas as lâminas foram posteriormente expostas ao complexo avidina-biotina-peroxidase (LSAB Kit - DakoCytomation, Carpenteria, CA, EUA), e ao cromógeno tetrahidrocloreto de diaminobenzidina (DAB, Sigma, St. Louis, MO, EUA). Posteriormente foi realizada contra-coloração com hematoxilina de Carazzi. Controles positivos apropriados foram utilizados para cada anticorpo, enquanto o controle negativo foi obtido pela omissão do anticorpo específico primário.

As reações foram avaliadas de forma descritiva por pelo menos dois autores simultaneamente e os diagnósticos finais foram baseados na Classificação mais recente da Organização Mundial de Saúde (OMS) de Tumores de Tecidos Moles e Ósseos (OMS, 2020) e Tumores de Cabeça e Pescoço (El Naggar et al., 2017).

Análise estatística

De acordo com os dados obtidos, a análise estatística descritiva foi realizada após tabulação dos dados, utilizando o programa SPSS (SP SS Inc, Chicago, IL, EUA), versão 22.0.

3 ARTIGO

Os resultados foram escritos em língua inglesa na forma de artigo científico. Artigo submetido e aceito no periódico international *Head and Neck Pathology* (Qualis: B1).

LEIOMYOMA AND LEIOMYOSARCOMA (PRIMARY AND METASTATIC) OF THE ORAL AND MAXILLOFACIAL REGION: A CLINICOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY OF 27 CASES

Gabriela Ribeiro de **Araújo**[1]*, Sara Ferreira dos Santos **Costa**[1]*, Ricardo Alves **Mesquita**[1], Ricardo Santiago **Gomez**[1], Jean Nunes **dos Santos**[2], Hélder Antônio Rebelo **Pontes**[6], Bruno Augusto Benevenuto de **Andrade**[3], Mário José **Romañach**[3], Michelle **Agostini**[3], Pablo Agustin **Vargas**[4,8], Cinthia Verônica Bardalez Lopez de **Cáceres**[4], Alan Roger **Santos-Silva**[4], Ana Carolina Prado **Ribeiro**[5], Thaís Bianca **Brandão**[5], Ramiro Alejandro **Tomasi**[6], Ruth Salomé **Ferreyra**[6], Oslei Paes de **Almeida**[4], and Felipe Paiva **Fonseca**[1,8]

1. Department of Oral Surgery and Pathology, School of Dentistry, Federal University of Minas Gerais, Belo Horizonte/Brazil.
2. Department of Oral Surgery and Pathology, School of Dentistry, Federal University of Bahia, Salvador/Brazil.
3. Department of Oral Diagnosis and Pathology, School of Dentistry, Federal University of Rio de Janeiro, Rio de Janeiro/Brazil.
4. Oral Diagnosis Department (Pathology and Semiology Areas), Piracicaba Dental School, University of Campinas, Piracicaba/Brazil.
5. Dental Oncology Service, Instituto do Câncer do Estado de São Paulo, São Paulo/Brazil.
6. Service of Oral Pathology, João de Barros Barreto University Hospital, Federal University of Pará, Belém/Brazil.
7. Deparment of Pathology, Dental School, National University of Córdoba, Córdoba/Argentina.
8. Department of Oral Biology and Oral Pathology, School of Dentistry, University of Pretoria, Pretoria/South Africa.

* Both authors contributed equally to this study.

Corresponding author:
Prof. Felipe Paiva Fonseca
Department of Oral Surgery and Pathology, School of Dentistry.
Universidade Federal de Minas Gerais
Av. Antônio Carlos, 6627. Belo Horizonte, Brazil. e-Mail:felipepfonseca@hotmail.com

Funding: This study was supported by grants from the São Paulo State Research Foundation (FAPESP 2020/03818-8), the Minas Gerais State Research Foundation (FAPEMIG) and the Coordination for the Improvement of Higher Education Personel (CAPES) (Financial code 001). FPF, RSG, RAM, JSN, PAV and ARSS are research fellows of the National Council for Scientific and Technological Development (CNPq) (Brazil).
No conflict of interest to disclose.

Word count:5397; **Text pages:**12; **Number of figures:** 5; **Number of tables:** 2.

Abstract

Smooth muscle neoplasms represent an important group of lesions which is rare in the oral cavity. Leiomyoma (LM) is benign smooth muscle/pericytic tumor usually presenting as non-aggressive neoplasm, while leiomyosarcoma (LMS)represents its malignant counterpart. The rarity of these lesions, together with its unspecific clinical presentation and a variable histopathological appearance, lead to a broad list of differential diagnoses, hampering their diagnoses. Therefore, in this study we describe the clinical and microscopic features of a series of oral and maxillofacial LMs and LMSs. A retrospective search from 2000 to 2019 was performed and all cases diagnosed as LM and LMS affecting the oral cavity and gnathic bones were retrieved. Clinical and demographic data were obtained from the patients' pathology records, while microscopic features and immunohistochemistry were reviewed and completed when necessary to confirm the diagnoses**.** Twenty-two LMs and five LMSs were obtained. In the LM group, males predominated, with a mean age of 45.7 years. The upper lip was the most affected site, and 18 cases were classified as angioleiomyomas and four as solid LM. In the LMS group, females predominated, with a mean age of 47.6 years. The mandible was the most affected site. Diffuse proliferation of spindle cells, with necrosis and mitotic figures, were frequent microscopic findings. LMs and LMSs were positive for α-smooth muscle actin, HHF-35 and h-caldesmon. In conclusion, oral LM/LMS are uncommon neoplasms with the latter usually presenting as metastatic disease. H&E evaluation may be very suggestive of oral LMs, but h-caldesmon staining is strongly recommended to confirm LMS diagnosis.

Key-words: Angioleiomyoma, Leiomyoma, Leiomyosarcomas, Smooth muscle tumor, oral cavity, Jaw.

Introduction

Soft tissue tumors are relatively uncommon in the head and neck, and sarcomas in this region represent only 5-10% of all cases [1]. Among soft tissue tumors, smooth muscle neoplasms represent an important group of lesions, which mostly affect the endometrium, the gastrointestinal tract, skin and subcutaneous tissues. The occurrence of smooth muscle/pericytic tumors in the oral cavity is very rare, probably due to the scarcity of such components in this anatomic region [2,3], where these tumors are hypothesized to develop from the muscular walls of larger blood vessels or from the circumvallate papillae of the tongue [4,5].

Leiomyomas (LMs) are benign smooth muscle/pericytic tumors that may be diagnosed in the oral cavity and lips usually as non-aggressive neoplasms [6,7]. Although there are several case series describing oral LMs, Silva et al. (2018) demonstrated that this benign tumor accounted for only 0.9% of 790 oral soft tissue neoplasms in a Brazilian study [8]. Therefore, the rarity of this lesion, together with its unspecific clinical presentation and a variable histopathological appearance, may lead to a broad list of differential diagnoses [9-11].

Even rarer than oral LM is its malignant counterpart. Leiomyosarcoma (LMS) represents 5 to 10% of all soft tissue sarcomas, more commonly diagnosed in the uterus, retroperitoneum and intra-abdominal structures [2,12-14]. De Carvalho et al. (2019) recently described the distribution of oral sarcomas in a multi-institutional study from Brazil demonstrating that LMS accounted for 6% of the sample [15], whereas Moreira et al. (2020) found only one oral LMS among 69 head and neck sarcomas also in Brazil [16]. Moreover, although some oral and maxillofacial LMSs have been described in literature, many of these reports lack an appropriate diagnostic documentation and the incidence of oral LMSs might be even lower.

Therefore, in this study we aimed to describe the clinical and microscopic characteristics of a series of 22 LMs and five LMSs affecting the oral and maxillofacial region.

Material and methods

All cases diagnosed as LM and LMS affecting the oral and maxillofacial region were retrieved from six different oral diagnosis services: The Universidade Federal de Minas Gerais (Belo Horizonte/Brazil), the University of Campinas (Piracicaba/Brazil), the Federal University of Rio de Janeiro (Rio de Janeiro/Brazil), the Federal University of Pará (João de Barros Barreto University Hospital) (Belém/Brazil), the Dental Oncology Service of the Instituto do Câncer do Estado de São Paulo (São Paulo/Brazil) and from the School of Dentistry of the National University of Córdoba (Córdoba/Argentina), during a period ranging from January/2000 to December/2019.

The formalin-fixed, paraffin-embedded tissue blocks were obtained and the original or new 3µm thick, H&E-stained slides were reviewed by an oral pathologist. Demographic data and clinical features of all cases were obtained from the patients' records and comprised age and sex of patients, lesion size and location, tumor color, time of duration (months),symptomatology, and treatment modality employed. Follow-up data included information regarding recurrences and patients' status (alive or dead) at last follow-up for those affected by LMS.

Immunohistochemistry was done using the streptavidin–biotin peroxidase complex method to confirm the diagnoses. Briefly, the reactions were done in 3µm sections obtained from the original formalin-fixed, paraffin-embedded tissue blocks that were de-waxed with xylene and hydrated in an ethanol series. The antigen retrieval was done and the endogenous peroxidase activity was blocked using 10% hydrogen peroxide in five baths, 5 minutes each. After washing in PBS buffer (pH 7.4), slides were incubated overnight with the following primary antibodies: monoclonal mouse anti-α-SMA diluted 1:200 (Clone 1A4; dilution 1:200; Dako Corp., Carpenteria, CA, USA), muscle actin (clone HHF35; dilution 1:400; Dako Corp., Carpenteria, CA, USA), h-caldesmon (clone h-CALD; dilution 1:100; Medaysis) and Ki67

(clone MIB-1, dilution 1:100; Dako Corp., Carpenteria, CA, USA). Moreover, S100 protein (clone S100; dilution 1:500; Dako Corp., Carpenteria, CA, USA), desmin (clone D33; dilution 1:100; Dako Corp., Carpenteria, CA, USA), CD34 (clone QBEnd/10; dilution 1:100; Cell Marque) and other complementary markers were investigated when necessary. All slides were subsequently exposed to avidin-biotin complex and horseradish peroxidase reagents (LSAB Kit - DakoCytomation, Carpenteria, CA, USA) and diaminobenzidinetetrahydrochloride (DAB, Sigma, St. Louis, MO, USA), and subsequently counterstained with Carazzi hematoxylin. Appropriate positive controls were used for each antibody, while the negative control was obtained by omitting the primary specific antibody.

The H&E-stained slides and immunohistochemical results were descriptively evaluated and the final diagnoses followed the guidelines of the latest World Health Organization Classification of Soft Tissue and Bone Tumors [6]. In cases with primary sarcoma of the head and neck, CAP/AJCC protocol for the examination of resection specimens of soft tissue tumors is recommended and was also used in this study [12]. Grading and staging is strongly advised for soft tissue sarcomas; however, because the diagnosis of all LMS cases included in this study were based on incisional biopsy samples, some of them relatively small, we did not render a definitive grading for each case, but microscopic findings were detailed provided.

The ethical committee of the Universidade Federal de Minas Gerais approved this study (72775717.8.0000.5149).

Results

Demographic data and clinical features

The demographic data and clinical features of oral LMs are presented in **Table 1**. The patients' age ranged from 28 to 73 years with a mean age of 45.7 ± 13.6 years-old, with the highest frequencies in the fourth and sixth decades of life. LMs were more frequent in men

(1.9:1), but the mean age for women (53.4 ± 15.1) was higher than for men (40.1 ± 9.2). The lesions more commonly affected the upper lip (39.1%) and hard palate (26.1%). While over half of all cases in males occurred in the lip (53%), an anatomic predominance was not observed among females.

All LMs presented as solitary small nodules and just one case had more than 2 cm in its largest diameter. Most of the cases (91.0%) were asymptomatic, with overlying mucosa ranging from normal-colored to reddish or dark bluish (**Figure 1**). The lesions had a mean time of duration of 44.5months (range 2-180months). The most common initial clinical diagnoses included mucocele, varix, reactive proliferative process, benign salivary gland neoplasm and benign mesenchymal neoplasm. All lesions were treated by conservative surgical excision, with no recurrences reported.

The clinical features of five oral and maxillofacial LMSs are shown in **Table 2**. This malignant neoplasm affected 4 women and one man, ranging from 36 to 69 years (mean: 47.6 ± 14.4 years). Two patients presented primary tumors and 3 cases were metastatic diseases occurring in the oral and maxillofacial region from previous retroperitoneal LMS (Cases #2 and #4) and uterine LMS (Case #3). Case #2 also presented other hepatic metastases and the full report of this case is available in Azevedo et al. (2012) [17].

The oral and maxillofacial LMSs presented a tumor size ranging from 1 to 14 cm in their greatest diameter and a history of rapid growth, with duration ranging from 2 to 4 months. Four cases affected the jawbones, 3 the mandible and one the maxilla, while one case affected the gingiva. At extra-oral examination, one case exhibited facial asymmetry with the displacement of the nasal wing and elevation of the inferior eyelid (Case #1). The patients also reported other clinical manifestations like lower lip numbness (Cases #2 and #3) and inferior alveolar nerve paresthesia (Case #5). At intraoral clinical examination, LMSs presented single, well- to ill-defined, non-mobile, sessile, painful swelling with irregular and ulcerated surface

ranging in color from normal to erythematous (**Figure 1**). Regarding the radiographic findings, intraosseous LMSs appeared as radiolucent/hypodense images with ill-defined margins and bone fracture was observed in one case (Case #3) **(Figure 2)**.

Data regarding treatment protocols used were available for two patients with oral and maxillofacial LMS (Cases #1 and #2), both treated by surgical resections. Follow-up information was available for only one patient that died of the disease after 12 months of follow-up.

Histopathological findings

Grossly, oral LM specimens presented as pinkish to dark bluish, fibrous to rubbery, rounded to oval nodules with smooth to irregular surface. The cut surfaces were homogeneous **(Figure 3)**. On the other hand, oral and maxillofacial LMSs were characterized by irregular-shaped tissues, whitish to brownish with an irregular surface and fibrous consistency.

Oral LMs were usually well-circumscribed often growing in a nodular fashion, although some cases were poorly delimited (Cases #1 and #21). Dilated blood vascular spaces of varying sizes commonly filled by red blood cells were observed in 19 cases (angioleiomyoma). Occasionally, the tumor cells were arranged in concentric rings around the thick muscular walls of the vessels, with vascular spaces that looked compressed and merged into tumor stroma. In contrast, a solid pattern exhibiting small, closely compacted or slit-like blood vascular spaces and larger amounts of spindle tumor cells was observed in 4 cases (Cases #1, #5, #18and #21). LMs were characterized by bundles or fascicles of tumor cells with differentiation towards smooth muscle exhibiting relatively abundant eosinophilic cytoplasm and round to elongated spindle nuclei, often with blunt ends (cigar shaped). The tumor cells were arranged in short to large fascicles perpendicularly to haphazardly or in clusters within a variable fibrous connective tissue stroma. Less common histologic findings included mature lipomatous component (Cases

#2, #14and #16), hemangiopericytoma-like foci (Cases #4 and #13) and myxohyaline degeneration (Case #19) (**Figure 4**). Cellular and nuclear pleomorphism, as well as atypical mitotic figures were absent.

Histopathologically, all five oral LMSs demonstrated an infiltrative or ill-demarcated fascicular growth with focal to extensive necrotic areas, and moderate to poorly differentiated regions**.** The malignant tumor cells were arranged in fascicles of varying size intersecting perpendicularly or randomly, consisting of spindle cells with well to poorly defined eosinophilic cytoplasm and oval to elongated nuclei, also with the blunt-ended (cigar) shape. Mitotic figures were scattered present in four cases and more frequent in one case, and occasional cells showed perinuclear vacuoles **(Figure 5).**

Immunohistochemical findings

Regarding the immunohistochemical findings, LMs exhibited diffuse and strong cytoplasmic positivity for αSMA, calponin, HHF35 and h-caldesmon, while desmin (**Figure 4**) was weaker and diffuse. Tumor cells were negative for S100 and CD34. Regarding LMSs, immunohistochemistry showed positivity for αSMA, h-caldesmon and HHF35 in all five cases. Desmin was also focally observed. Additionally, tumor cells were negative for CD34, S100, MyoD1and cytokeratin. The proliferative index determined by Ki67 expression was very low for LMs with only scattered positive nuclei, whereas LMSs showed very high proliferative indexes (**Figure 5**).

Discussion

Smooth muscle tumors affecting the oral cavity and the jaws are uncommon, more frequently representing benign lesions. Oral and maxillofacial LMSs, although very rare, have been described in the literature, but given the lack of appropriate and well-documented

immunohistochemical investigations in many reports, available data are incomplete. Therefore, in this study we described the clinicopathological features of 22 LMs sand five LMSs following strict diagnostic criteria. LMs presented as benign nodules with different histopathological architectural patterns, whereas LMSs were frequently metastatic diseases with very aggressive clinical behavior and that demanded rigorous histological evaluation and immunohistochemical investigation including h-caldesmon stain for correct diagnosis.

LMs most commonly arise in the soft tissue of female genital tract, skin and gastrointestinal tract [18] only rarely affecting the oral cavity [18-20]. In the mouth there is a slight male predominance, usually affecting adult patients [7,10,21,22]. However, Kim et al (2010) reported a possible congenital LM in the posterior tongue of a 2-months-old infant [23]. In agreement with the literature, our LM series showed a mean age of 45.8 years-old and a similar sex distribution.

Oral LMs usually present as solitary small nodules, which rarely exceed more than 2 cm in the largest diameter, with slow-growing and normal-colored to reddish/bluish surface, which demands from oral diagnosticians that LMs are frequently included in the list of differential diagnoses of many oral benign soft tissue tumors [3, 18, 24]. This indolent behavior was demonstrated by Gueiros et al (2011) [21] and Kim et al (2010) [23] that reported long-standing cases with over 20 years of duration. Moreover, virtually all cases are asymptomatic, although pain and swallowing impairment may be exceptionally reported [3,18]. The lips, tongue, cheek mucosa and palate are the most affected locations [18, 22], but cases in the jaws may rarely occur mostly in the mandible [10,25]. In accordance with these findings, all cases in our series were asymptomatic and the upper lip and the palate were the most affected locations. Given this benign nature, oral LMs are treated conservatively by surgical procedures and recurrences are extremely rare [10,18,21,22].

LMs are characterized by bundles of eosinophilic, blunt-ended (cigar-shaped) spindle cells perpendicularly oriented. Focal degenerative changes, such as fibrosis, calcification, myxoid change and fatty differentiation may occur. Unlike LMS, mitotic figures are rare or absent [4,11,26]. As shown in our series, LMs usually present as angioleiomyomas, which are believed to derive from pericytic cells, showing many vascular spaces surrounded by thick muscular walls [2,6,10]. However, the solid variant is also observed and less common microscopic findings may be found in the oral cavity, including extensive areas of calcification [27,28], presence of granular cells [29] and clear cells [30]. It is important to differentiate oral LMs from other benign spindle cell tumors, such as myofibromas, solitary fibrous tumors, benign fibrous histiocytomas, neurofibromas and schwannomas, some of which may carry an important clinical significance [9-11].

Oral and maxillofacial LMSs are very rare, representing less than 1% of oral sarcomas [2,3,13,31]. However, in a multicenter study developed in Brazil, de Carvalho et al (2019) found that LMSs comprised 6% of the sarcomas in the oral cavity [15]. Recently, Ko (2019) reviewed the clinicopathological features of 29 primary oral LMSs, demonstrating that females were more affected and patients' mean age at diagnosis was 36.7 years [13], although other authors [15,32,33] observed a higher mean age (44-45 years), as also demonstrated in our series (47.6 years-old). In LMS pain is a frequent finding, which was reported by our patients that also complained of chin and lower lip paresthesia. Moreover, LMS affecting the sinonasal tract is also very rare, and in these cases, facial swelling may be found [15, 32-36].

Primary oral LMSs more commonly affect buccal mucosa, tongue, palate and floor of the mouth, while mandibular involvement is unusual, and the lesion size usually ranges from one to 10 cm, as shown in our series [13-15,32,33]. Although our two primary LMSs affected the mandible and the maxilla, after such diagnosis a complete systemic evaluation is mandatory, since metastatic diseases may occur [37,38]. Ko (2019) showed that 10.3% of primary oral

LMSs may develop metastases [13], while Saluja et al. (2019) demonstrated that metastatic head and neck LMSs have a poor prognosis and most of these cases mainly originate from the uterus and retroperitoneum, which is confirmed by our three metastatic diseases that disseminated from these regions [31].

Histopathologically, LMS consists of interlacing fascicles of spindle cells with eosinophilic to pale cytoplasm and oval to elongated hyperchromatic nuclei with a blunt-ended feature. Although LMs and LMSs are usually easily differentiated in the oral and maxillofacial region, in deep soft tissues this distinction can be very difficult. Cytologic atypia, cellularity, pleomorphism, and presence of tumor necrosis are consistent with malignancy, but mitotic activity may be very low [39]. In our five cases, the presence of histopathological findings consistent with malignancy was rapidly observed and facilitated the recognition of the tumor nature, which was further supported by clinical aspects. Nonetheless, other spindle-cell sarcomas must also be considered as differential diagnoses for LMS, including fibrosarcoma, rhabdomyosarcoma, malignant peripheral nerve sheath tumor, spindle cell carcinoma, melanoma and others [13,32,33].

According to the CAP/AJCC guidelines [12] genetic analyses for tumor-specific molecular translocations can be used to help pathologists to classify soft tissue tumors, and LMS is characterized by complex events with frequent deletion of chromosome 1p. Moreover, microscopic grading of LMS is also very important and the French Federation of Cancer Centers Sarcoma Group (FNCLCC) system is one of the most recommended, which combines three microscopic parameters: differentiation, mitotic activity, and necrosis. Although we have described these findings in our series, because we used incisional biopsies to perform the histological investigation of our LMSs, we decided not to render a definitive grading for the cases included, but rather descriptively provide the histological findings.

Although the smooth muscle differentiation should be confirmed with the expression of at least two myogenic markers [11], the most appropriate panel of antibodies remains controversial and many authors have provided incomplete data. In various reports, diagnoses were rendered based on histopathology and positivity for αSMA only, whereas some authors also described positivity for other smooth muscle proteins like desmin, muscle-specific actin (HHF-35) and calponin, combined with negativity to other mesenchymal markers like S100 [13,32]. However, all these smooth muscle markers are also variably expressed in myofibrosarcomas [13,40]. Therefore, because the expression pattern of the above-mentioned myogenic markers are usually not well described or documented and the lack of specificity of these proteins for smooth muscle differentiation, it is possible that some of the previously reported oral LMSs do not show true myogenic differentiation, but rather myofibroblastic.

On the other hand, Ceballos et al. (2000) demonstrated that h-caldesmon would be a reliable marker for differentiating smooth muscle tumors from myofibroblastic neoplasms [40], which was further supported by subsequent studies that investigated tumors from different anatomic locations [41-43], including in the oral cavity [44]. However, Yu et al. (2019) more recently found h-caldesmon expression in gastrointestinal stromal tumors (GIST), slightly decreasing its specificity [45]. Therefore, we understand that the use of h-caldesmon is very important for confirming the diagnosis of oral LMSs and for difficult cases of LMs.

Extensive surgical approaches followed or not by chemotherapy and/or radiotherapy are usually applied for LMSs, but no standard therapeutic scheme is recognized [14,32,33]. Local recurrences occur in approximately 23% of the cases, while metastases are observed in 34% [35]. The overall survival rate of patients affected by oral LMSs ranges from 55% to 61.87% [32,33], but the literature review of Ko (2019) observed a much higher value (94.1%) [13]. The presence of metastatic tumors might significantly impact this rate.

In conclusion, oral LMs are uncommon lesions with innocuous clinical behavior that are usually well suspected under histopathological investigation, while LMSs are aggressive neoplasms whose diagnosis demands the use of an immunohistochemical panel containing h-caldesmon and other myogenic markers which expression pattern must also be considered during pathological interpretation. Moreover, oral LMS diagnosis necessarily requires a systemic evaluation of the patient to rule out a possible metastatic disease.

Declarations

Ethics approval

The questionnaire and methodology for this study was approved by the Human Research Ethics committee of the Universidade Federal de Minas Gerais (72775717.8.0000.5149).

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.

References

1. Fletcher CDM. Distinctive Soft Tissue Tumors of the Head and Neck. *Mod Pathol*. 2002; 15:324–330.
2. Solar AA, Jordan RCK. Soft tissue tumors and common metastases of the oral cavity. *Periodontol 2000*. 2011; 57:177–197.
3. Wertheimer-Hatch L, Hatch GF, Hatch KF, Davis GB; Blanchard DK, Foster RS Skandalakis. Tumors of the oral cavity and pharynx. *World J Surg*. 2000; 24:395-400.
4. Stout AP. Solitary cutaneous and subcutaneous leiomyoma. *Am J Cancer*. 1937; 29:435.
5. Castaldi A, Arcuri T, Carta M, Quilici P, Derchi LE. Primary leiomyosarcoma of the oral tongue: Magnetic resonance and ultrasonography findings with histopathologic correlation. *Acta Radiol*. 2006; 47:514–517.
6. The WHO Classification of Tumours Editorial Board. WHO Classification of Tumours Soft Tissue and Bone Tumours, 5thed. Lyon: IARC Press; 2020.
7. Ide F, Mishima K, Yamada H, Saito I, Horie N, Shimoyama T, Kusama K. Perivascular myoid tumors of the oral region: A clinicopathologic re-evaluation of 35 cases. *J Oral Pathol Med*. 2008; 37:43–49.
8. Silva LAB, Monroy EAC, Serpa MS, Souza LB. Oral benign neoplasms: A retrospective study of 790 patients over a 14-year period. *Acta Otorrinolaringol Esp*. 2018; 70:158-164.
9. Luaces-Rey R, Lorenzo-Franco F, Gómez-Oliveira G, Patiño-Seijas B, Guitián D, López-Cedrún-Cembranos JL. Oral leiomyoma in retromolar trigone. A case report. *Med Oral Patol Oral Cir Bucal*. 2007;12:42–44.
10. Cepeda LAG, Rivera DQ, Rocha FT, Huerta ERL, Sánchez ERM. Vascular leiomyoma of the oral cavity. Clinical, histopathological and immunohistochemical characteristics. Presentation of five cases and review of the literature. *Med Oral Patol Oral Cir Bucal*. 2008; 13:483–488.

11. El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ. World Health Organization Classification of Head and Neck Tumours. 4th edition. Lyon; 2017.

12. College of American Pathologists. AJCC Protocol for the Examination of Resection Specimens from Patients with Soft Tissue Tumors. 8th Edition. 2019.

13. Ko E. Primary oral leiomyosarcoma: A systematic review and update. *J Oral Pathol Med*. 2019; 48:780–787.

14. Yan B, Li Y, Pan J., Xia H., Li L-J. Primary oral leiomyosarcoma: A retrospective clinical analysis of 20 cases. *Oral Dis.* 2010; 16:198–203.

15. de Carvalho WRS, de Souza LL, Pontes FSC, Uchôa DCC, Corrêa DL, de Cáceres CVBL, et al. A multicenter study of oral sarcomas in Brazil. *Oral Dis.* 2019; 26: 43-52.

16. Moreira DGL, Silva LP, Morais EF, Queiroz SIML, Santos EM, Souza LB, et al. The occurrence and pattern of head and neck sarcomas: a comprehensive cancer center experience. *European Archives of Oto-Rhino-Laryngology*. 2020; 277:1473–1480.

17. Azevedo RS, Pires FR, Gouvêa AF, Lopes MA, Jorge J. Leiomyosarcomas of the oral cavity: report of a radiation-associated and a metastatic case. *Oral Maxillofac Surg*. 2012; 16(2):227-232.

18. Veeresh M, Sudhakara M, Girish G, Naik C. Leiomyoma: A rare tumor in the head and neck and oral cavity: Report of 3 cases with review. *J Oral Maxillofac Pathol.* 2013; 17:281-287.

19. Baden E, Doyle JL, Lederman DA. Leiomyoma of the oral cavity: A light microscopic and immunohistochemical study with review of the literature from 1884 to 1992. *Eur J Cancer. Part B: Oral Oncol.* 1994; 30:1-7.

20. Ranjan S, Singh KT. Gingival angioleiomyoma-infrequent lesion of oral cavity at a rare site. *J Oral Maxillofac Pathol.* 2014; 18:107-110.

21. Gueiros LA, Romañach MJ, Pires-Soubhia AM, Pires FR, Paes-de-Almeida O, Vargas PA. Angioleiomyoma affecting the lips: Report of 3 cases and review of the literature. *Med Oral Patol Oral Cir Bucal.* 2011; 16.

22. Aitken-Saavedra J, da Silva KD, Gomes APN, Vasconcelos ACU, Etges A, Nóbrega TG, et al. Clinicopathologic and immunohistochemical characterization of 14 cases of angioleiomyomas in oral cavity. *Med Oral Patol Oral Cir Bucal*. 2018; 23:564–568.

23. Kim YH, Jang YW, Pai H, Kim SG. Congenital angiomyoma of the tongue: Case report. *Dentomaxillofac Radiol.* 2010; 39:446-448.

24. Cherrick HM, Dunlap CL, King OH. Leiomyomas of the oral cavity. Review of the literature and clinicopathologic study of seven new cases. *Oral Surg Oral Med Oral Pathol.* 1973; 35:54-66.

25. Liang H, Frederiksen NL, Binnie WH, Cheng YS. Intraosseous oral leiomyoma: Systematic review and report of one case. *Dentomaxillofac Radiol.* 2003; 32:285-290.

26. Goldblum JR, Weiss SW, Folpe AL. Enzinger and Weiss's Soft Tissue Tumors. In: Goldblum JR, Weiss SW, Folpe AL, editors. Leiomyosarcoma. Elsevier Health Sciences; 6 edition; 2008. pp.517-543.

27. Nonaka CFWP, Pereira KMA, Costa-Miguel MC. Oral vascular leiomyoma with extensive calcification areas. *Braz J Otorhinolaryngol.* 2010; 76:539.

28. Montague LJ, Fitzpatrick SG, Islam NM, Cohen DM, Bhattacharyya I. Extensively Ossifying Oral Leiomyoma: A Rare Histologic Finding. *Head Neck Pathol*. 2014; 8:311-316.

29. Bhattacharyya I, Summerlin DJ, Cohen DM, Ellis GL, Bavitz J B, Gillham LL. Granular cell leiomyoma of the oral cavity. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2006;102: 353-359.

30. Darling MR, Wehrli B, Zeligman E, Smillie J, Daley T. Unusual Benign Smooth Muscle Lesions of the Tongue: Review and Report of Two Cases. *Head Neck Pathol.* 2012; 6:121-124.

31. Saluja TS, Iyer JS, Satyendra K. Leiomyosarcoma: Prognostic outline of a rare head and neck malignancy. *Oral Oncol.* 2019; 95:100–105.

32. Ethunandan M, Stokes C, Higgins B, Spedding A, Way C, Brennan P. Primary oral leiomyosarcoma: a clinic pathologic study and analysis of prognostic factors. *Int. J. Oral Maxillofac. Surg.* 2007; 36:409–416.

33. Vilos GA, Rapidis AD, Lagogiannis GD, Apostolidis C. Leiomyosarcoma of the oral tissues: Clinicopathologic analysis of 50 cases. *Int. J. Oral Maxillofac. Surg*. 2005; 63:1461–1477.

34. Mizutani H, Tohnai I, Yambe M, Ueda M. Leiomyosarcoma of the maxillary gingiva: a case report. *Nagoya J Med Sci*. 1995; 58:165-170.

35. Dry SM, Jorgensen JL, Fletcher CDM. Leiomyosarcomas of the oral cavity: An unusual topographic subset easily mistaken for non-mesenchymal tumours. *Histopathology*. 2000; 36:210–220.

36. Chew YK, Noorizan Y, Khir A, Brito-Mutunayagam S. Leiomyosarcoma of the maxillary sinus. Med J Malaysia. 2009;64(2):174-175.

37. Nusrath MA, Kendall CH, Avery CM. Metastatic uterine leiomyosarcoma masquerading as a primary lesion of the masseter muscle. *Int. J. Oral Maxillofac. Surg*. 2006; 35:466–468.

38. Schütz A, Smeets R, Driemel O, Hakim SG, Kosmehl H, Hanken H, et al. Primary and secondary leiomyosarcoma of the oral and perioral region-clinicopathological and immunohistochemical analysis of a rare entity with a review of the literature. *J Oral Maxillofac Surg.* 2013; 71:1132–1142.

39. Brooks JK, Nikitakis NG, Goodman NJ, Levy BA. Clinicopathologic characterization of oral angioleiomyomas. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2002; 94:221-227.

40. Ceballos KM, Nielsen GP, Selig MK, O'Connell JX. Is anti h-caldesmon useful for distinguishing smooth muscle and myofibroblastic tumors? An immunohistochemical study. *Am J Clin Pathol*. 2000; 114:746–753.

41. Perez-Montiel MD, Plaza JA, Dominguez-Malagon H, Suster, S. Differential expression of smooth muscle myosin, smooth muscle actin, H-caldesmon, and calponin in the diagnosis of myofibroblastic and smooth muscle lesions of skin and soft tissue. *Am J Dermatopathol*. 2006; 28:105-111.

42. Robin YM, Penel N, Pérot G, Neuville A, Vélasco V, Ranchère-Vince D, et al. Transgelin is a novel marker of smooth muscle differentiation that improves diagnostic accuracy of leiomyosarcomas: a comparative immunohistochemical reappraisal of myogenic markers in 900 soft tissue tumors. *Mod Pathol.* 2013; 26:502-510.

43. Beck EM, Bauman TM, Rosman IS. A Tale of Two Clones: Caldesmon Staining in the Differentiation of Cutaneous Spindle Cell Neoplasms. *J Cutan Pathol*. 2018; 45:581-587.

44. Pereira de Oliveira DHI, da Silveira EJD, de Souza LB, Caro-Sanchez CHS, Dominguez-Malagon H, Mosqueda Taylor A, et al. Myofibroblastic lesions in the oral cavity: Immunohistochemical and ultrastructural analysis. *Oral Dis*. 2018; 25:174-181.

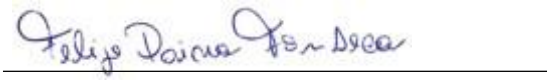
Yu G, Xu J, Jiang L, Cai L, Zohar Y, Wu S, et al. Expression and clinical significance of H-caldesmon in gastrointestinal stromal tumor: is it a specific marker for myogenic differentiation. *Int J Clin Exp Pathol.* 2019;12: 2566–2571.

Compliance with Ethical Standards

Funding: This study was supported by grants from the São Paulo State Research Foundation (FAPESP 2020/03818-8), the Minas Gerais State Research Foundation (FAPEMIG) and the Coordination for the Improvement of Higher Education Personel (CAPES) (Financial code 001). FPF, RSG, RAM, JSN, PAV and ARSS are research fellows of the National Council for Scientific and Technological Development (CNPq) (Brazil).

Conflict of Interest: We state that all authors confirm that they have no potential conflict 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.

Sincerely yours,



Felipe Paiva Fonseca, DDS, PhD.
Depart. Oral Surgery and Pathology, School of Dentistry
Universidade Federal de Minas Gerais
Av. Antônio Carlos, 6627, Pampulha, Belo Horizonte/Brazil.
e-mail: felipepfonseca@hotmail.com

Figures legends

Figure 1. Clinical presentation of smooth muscle tumours of the oral and maxillofacial region. A) LM presenting as a well-defined nodular lesion in the central region of the palate. B) LM showing a superficial elevated mucosa lesion in the left side of the hard palate with a slight bluish appearance. C) LMS demonstrates aggressive clinical behaviour in Case #1 causing a large facial asymmetry in the left side. D) In this same case #1, intra-orally, LMS presented as an ulcerated expansive swelling in the maxilla.

Figure 2. Radiographic findings of oral LMS. A) A localized, single, well-defined, perforating, rounded, measured 4.0 x 3.0 cm, radiolucent image in the posterior region of the mandible, right side, caused by a metastatic LMS, leading to a pathological bone fracture (Case #3). B) Cone bean computed tomography axial image illustrating 6.0cm in the largest diameter, ill-defined, destructive, expansive, heterogeneous, hypodense lesion, involving the left maxillary sinus and the nasal cavity. There was evidence of bone destruction of the lateral, media, anterior and posterior walls of the sinus of the LMS (Case #1). C) Coronal image of Case #1 demonstrating bone destruction all walls and the nasal concha was partially involved. D) Sagittal image of Case #1.

Figure 3. Macroscopic features of oral LM. A) Irregular shape and surface, fibrous tissue showing a whitish to brownish colour. B) A homogeneous whitish cut surface of the lesion. C) A rounded shape and rugged surface, fibrous tissue with a whitish to brownish colour (Case #21) was removed and the overlying mucosa can be seen. D) The homogeneous cut surface can also be found in this case.

Figure 4. Histopathology and immunohistochemical features of oral LM. **A)** An angioleiomyoma showing the presence of irregular blood vessels and demonstrating the proliferation of smooth muscle cells originating from the vascular structures (H&E, 50X magnification). **B)** Solid LM demonstrating hypercellular areas with a fascicular growth pattern (H&E, 50X magnification). **C)** Neoplastic spindle cells with a bland aspect and the so-called cigar-shaped nucleus (H&E, 200X magnification). **D)** Lipomatous component was found in some cases (H&E, 100X magnification. **E)** Tumour cells were positive for h-caldesmon (DAB, 200X magnification) and **F)** Ki67 nuclear staining showed a low proliferative index of tumour cells (DAB, 200X magnification).

Figure 5. Histopathology and immunohistochemical features of oral and maxillofacial LMS. **A)** The presence of tissue necrosis was a common finding in the oral and maxillofacial LMS cases evaluated (H&E, 50X magnification). **B)** Under higher magnification it is possible to illustrate tumour cells showing a fascicular growth pattern (H&E, 100X magnification). **C)**In one of the metastatic LMS it was observed frequent pleomorphic cells with hyperchromatic nuclei (H&E, 100X magnification). **D)** Mitotic figures were found in hypercellular regions (H&E, 200X magnification). **E)** h-caldesmon was strongly positive in all LMS cases (DAB, 100X magnification) and **F)** that also presented a high proliferative index measured by Ki67 expression (DAB, 100X magnification).

Table I. Demographic data and clinical features of the 22 cases diagnosed as oral leiomyomas in the present series.

Case	Age (years)	Sex	Size (cm)	Site	Color	Symptoms	Duration (month)	Treatment
1	34	F	NS	Tongue	NS	NS	NS	Surgical excision
2	40	M	NS	Upper lip	NS	NS	NS	Surgical excision
3	53	M	NS	Upper lip	NS	NS	NS	Surgical excision
4	30	M	NS	Soft palate	NS	NS	NS	Surgical excision
5	32	F	1.5	Gingiva	Reddish	Asymptomatic	NS	Surgical excision
6	54	M	1.2	Upper lip	NS	NS	60	Surgical excision
7	69	F	0.8	Buccal mucosa	NS	NS	NS	Surgical excision
8	45	M	1.5	Lower lip	Purplish	NS	4	Surgical excision
9	NS	M	NS	Hard palate	Bluish	NS	NS	Surgical excision
10	NS	M	NS	Lip	NS	NS	NS	Surgical excision
11	28	M	0.3	Lower lip	Normal	Symptomatic	NS	Surgical excision
12	42	M	1.2	Upper lip	Normal	Asymptomatic	120	Surgical excision
13	59	F	2.0	Buccal mucosa	Normal	Asymptomatic	48	Surgical excision
14	52	F	1.0	Hard palate	Reddish	Asymptomatic	NS	Surgical excision
15	34	M	1.7	Hard palate	Reddish	Asymptomatic	180	Surgical excision
16	33	M	0.6	Hard palate	Bluish	Asymptomatic	NS	Surgical excision
17	44	M	1	Hard palate	Normal	Asymptomatic	NS	Surgical excision
18	34	M	0.4	Lingual frenulum	Normal	Asymptomatic	2	Surgical excision
19	64	F	1	Buccal space	Red	Asymptomatic	5	Surgical excision
20	73	F	0.9	Lower lip	Normal	Asymptomatic	12	Surgical excision
21	56	F	1.5	Tongue	Red	Asymptomatic	2	Surgical excision
22	31	M	3	Buccal mucosa	NS	Asymptomatic	12	Surgical excision

F: Female; M: male; NS: Not specified.

Table II. Demographic data and clinical features of the five oral and maxillofacial leiomyosarcomas included in the present series.

Case	Sex	Age (years)	Size (cm)	Site	Occurence	Color	Symptoms	Duration (months)	Treatment	Follow-up (months)	Outcome
1	F	39	>10	Maxilla	Primary	Swelling and facial asymmetry	NS	NS	Surgical excision	NS	NS
2*	M	69	1	Mandible	Metastasis	Swelling with ulcerative regions	Numbness in lower lip	4	Surgical excision	12	Died
3	F	38	4	Mandible	Metastasis	NS	Numbness in lower lip	3	NS	NS	NS
4	F	56	2	Gingiva	Metastasis	Swelling with ulcerative regions	NS	2	NS	NS	NS
5	F	36	14	Mandible	Primary	Swelling and bone destruction	Inferior alveolar nerve paresthesia	NS	NS	NS	NS

M: male; F: female; NS: Not specified *Previously reported case: Azevedo RS, Pires FR, Gouvêa AF, Lopes MA, Jorge J. Leiomyosarcomas of the oral cavity: report of a radiation-associated and a metastatic case. *Oral Maxillofac Surg*. 2012;16(2):227-232. doi:10.1007/s10006-011-0294-5.

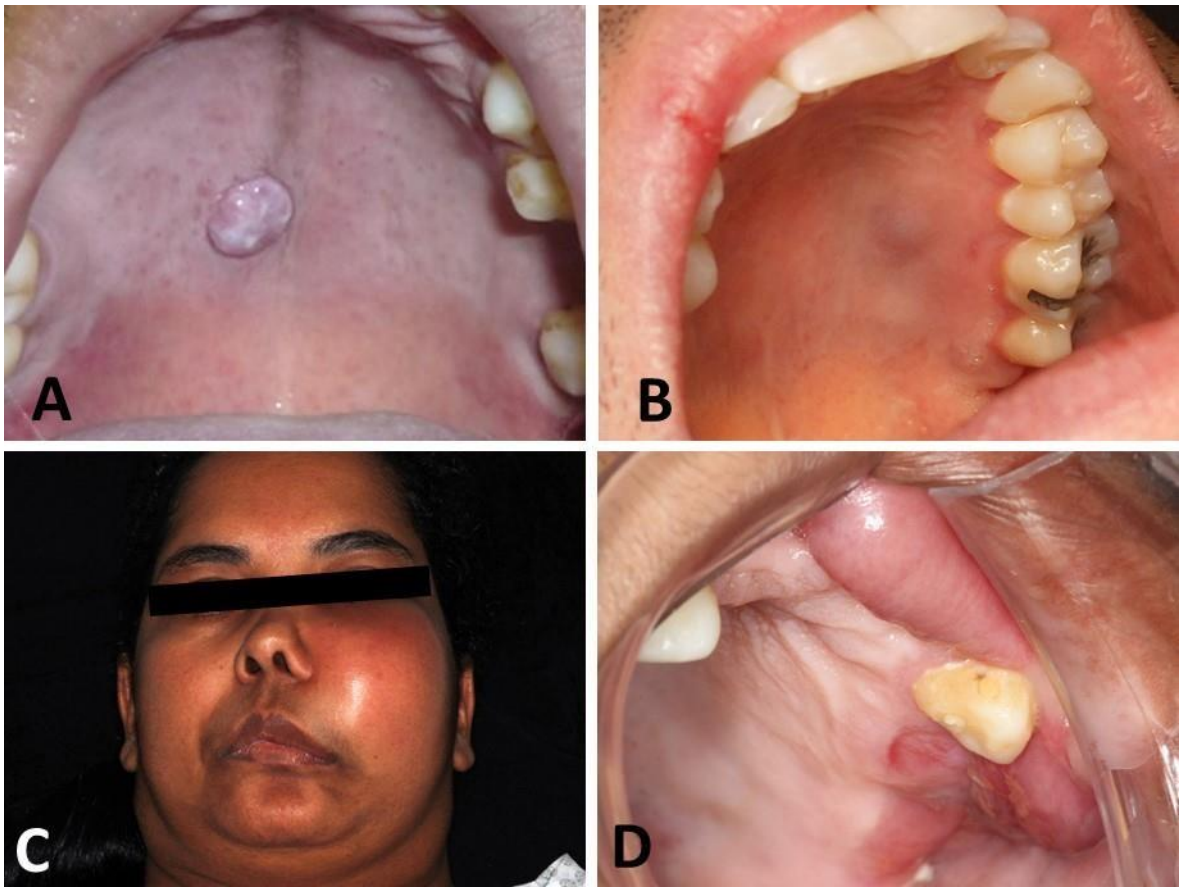


Figure 1. Clinical presentation of smooth muscle tumours of the oral and maxillofacial region. A) LM presenting as a well-defined nodular lesion in the central region of the palate. B) LM showing a superficial elevated mucosa lesion in the left side of the hard palate with a slight bluish appearance. C) LMS demonstrates aggressive clinical behaviour in Case #1 causing a large facial asymmetry in the left side. D) In this same case #1, intra-orally, LMS presented as an ulcerated expansive swelling in the maxilla.

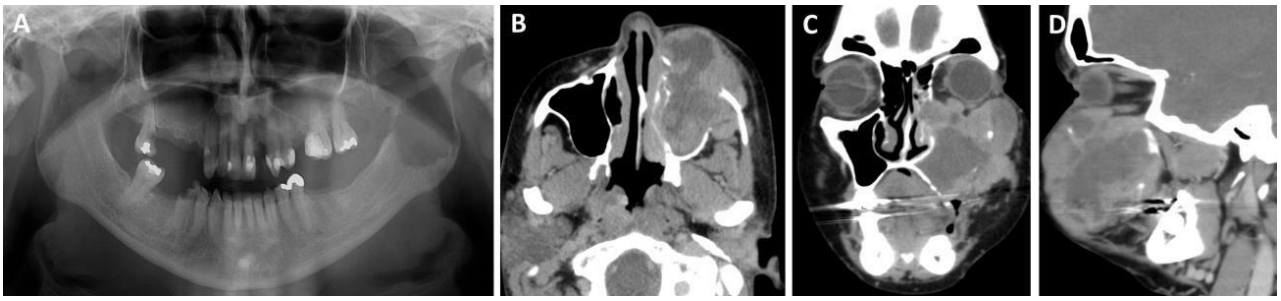


Figure 2. Radiographic findings of oral LMS. A) A localized, single, well-defined, perforating, rounded, measured 4.0 x 3.0 cm, radiolucent image in the posterior region of the mandible, right side, caused by a metastatic LMS, leading to a pathological bone fracture (Case #3). B) Cone bean computed tomography axial image illustrating 6.0cm in the largest diameter, ill-defined, destructive, expansive, heterogeneous, hypodense lesion, involving the left maxillary sinus and the nasal cavity. There was evidence of bone destruction of the lateral, media, anterior and posterior walls of the sinus of the LMS (Case #1). C) Coronal image of Case #1 demonstrating bone destruction all walls and the nasal concha was partially involved. D) Sagittal image of Case #1.

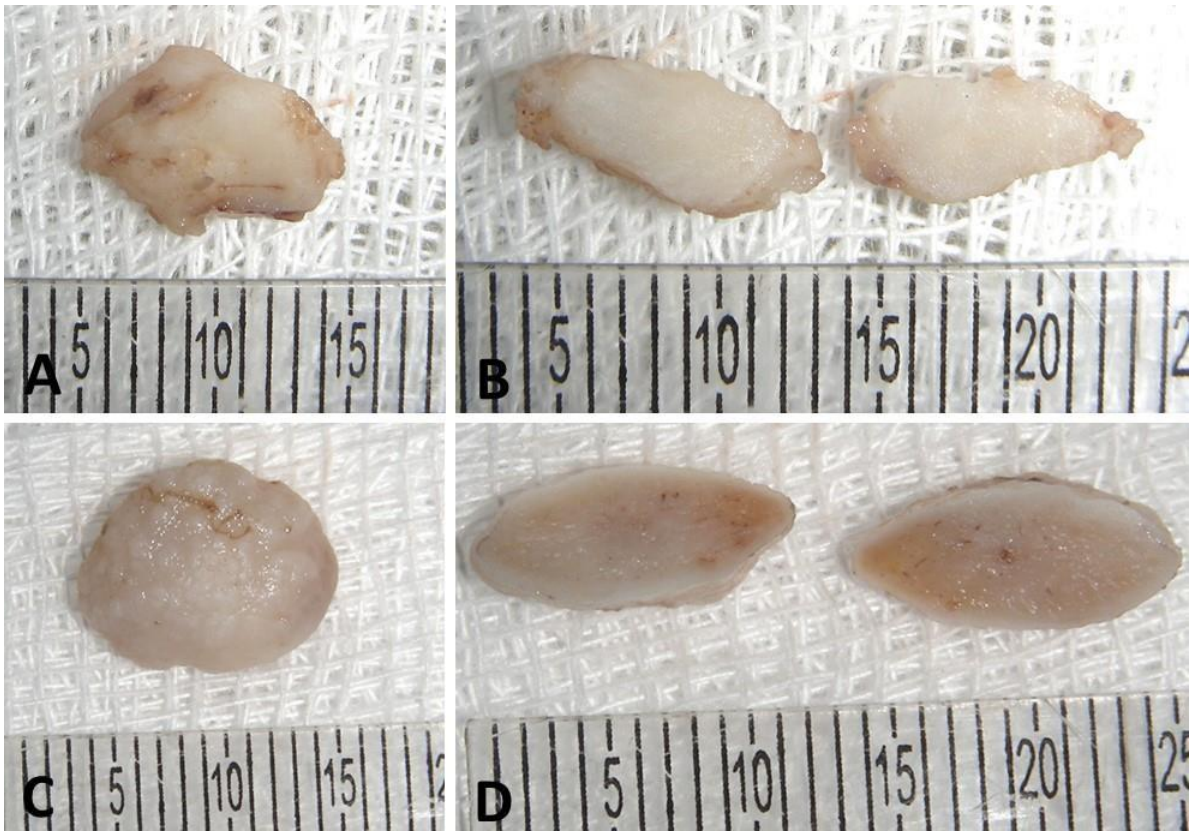


Figure 3. Macroscopic features of oral LM. A) Irregular shape and surface, fibrous tissue showing a whitish to brownish colour. B) A homogeneous whitish cut surface of the lesion. C) A rounded shape and rugged surface, fibrous tissue with a whitish to brownish colour (Case

#21) was removed and the overlying mucosa can be seen. D) The homogeneous cut surface can also be found in this case.

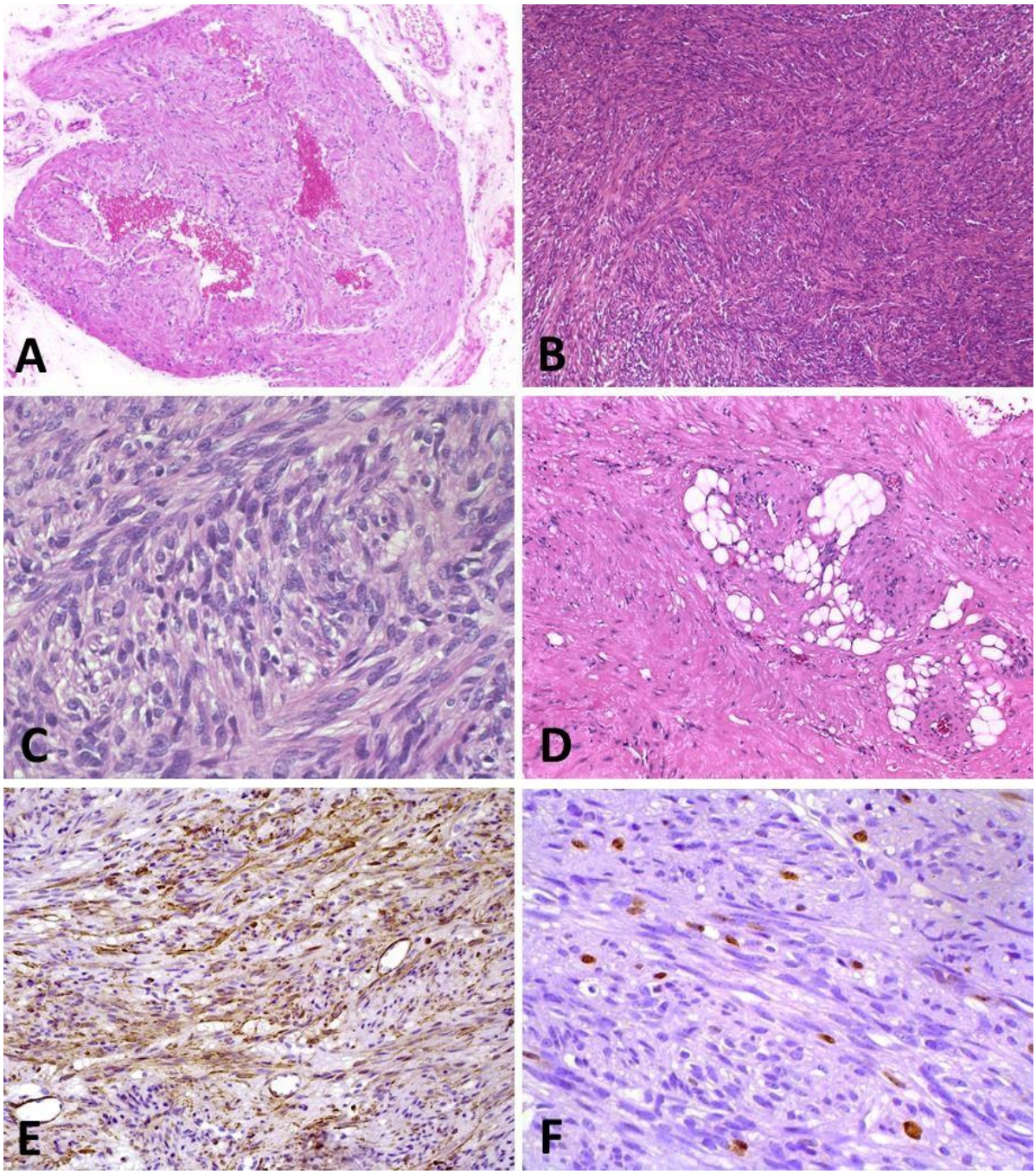


Figure 4. Histopathology and immunohistochemical features of oral LM. **A)** An angioleiomyoma showing the presence of irregular blood vessels and demonstrating the proliferation of smooth muscle cells originating from the vascular structures (H&E, 50X magnification). **B)** Solid LM demonstrating hypercellular areas with a fascicular growth pattern

(H&E, 50X magnification). **C)** Neoplastic spindle cells with a bland aspect and the so-called cigar-shaped nucleus (H&E, 200X magnification). **D)** Lipomatous component was found in some cases (H&E, 100X magnification. **E)** Tumour cells were positive for h-caldesmon (DAB, 200X magnification) and **F)** Ki67 nuclear staining showed a low proliferative index of tumour cells (DAB, 200X magnification).

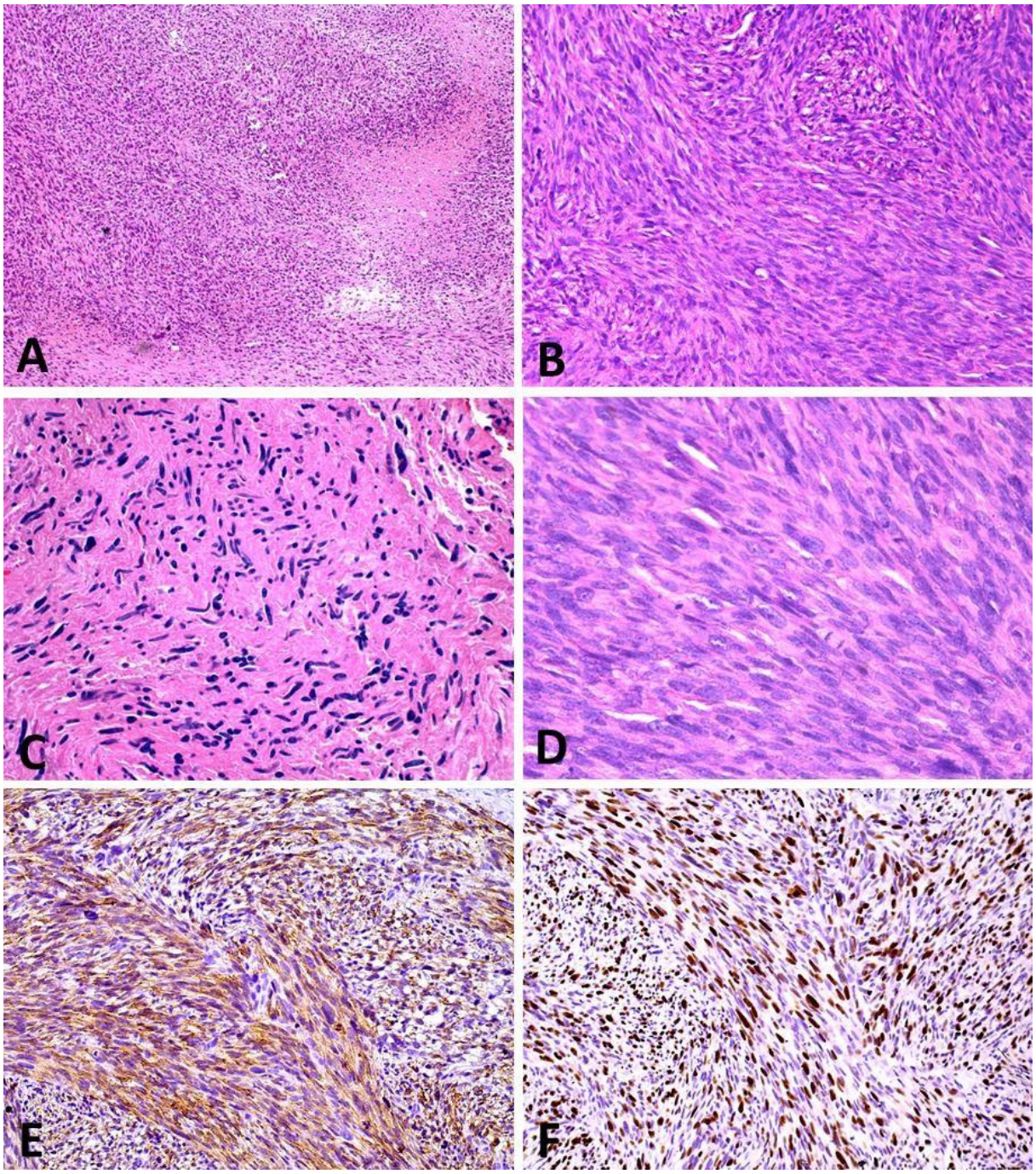


Figure 5. Histopathology and immunohistochemical features of oral and maxillofacial LMS. **A)** The presence of tissue necrosis was a common finding in the oral and maxillofacial LMS cases evaluated (H&E, 50X magnification). **B)** Under higher magnification it is possible to illustrate tumour cells showing a fascicular growth pattern (H&E, 100X magnification). **C)**In one of the metastatic LMS it was observed frequent pleomorphic cells with hyperchromatic nuclei (H&E, 100X magnification). **D)** Mitotic figures were found in hypercellular regions (H&E, 200X magnification). **E)** h-caldesmon was strongly positive in all LMS cases (DAB, 100X magnification) and **F)** that also presented a high proliferative index measured by Ki67 expression (DAB, 100X magnification).

5 CONSIDERAÇÕES FINAIS

Neste estudo, 22 casos de LM e cinco casos de LMS afetando a cavidade oral e os ossos gnáticos foram avaliados. Concluimos que os LMs orais são lesões incomuns com comportamento clínico inócuo que geralmente são bem diagnosticados na investigação histopatológica de rotina, enquanto os LMSs orais são neoplasias agressivas cujo diagnóstico exige o uso de um painel imunoistoquímico contendo h-caldesmona e outros marcadores miogênicos cujo padrão de expressão deve ser considerado durante interpretação patológica. Por fim, foi observado que o diagnóstico de LMS oral exige necessariamente uma avaliação sistêmica do paciente para descartar uma possível doença metastática.

REFERÊNCIAS

AITKEN-SAAVEDRA, J., DA SILVA, K. D., GOMES, A. P. N., VASCONCELOS, A. C. U., ETGES, A., NÓBREGA, T. G., & TARQUINIO, S. B. C. Clinicopathologic and immunohistochemical characterization of 14 cases of angioleiomyomas in oral cavity. **Medicina Oral Patologia Oral y Cirugia Bucal**, 23(5), e564–e568, 2018.

AMARAPALA H, TILAKARATNE WM. Leiomyosarcoma of the oral cavity: report of seven cases and review of literature. **Oral Oncol Extra,** 42, 14–17, 2006.

BADEN, E., DOYLE, J. L., & LEDERMAN, D. A. Leiomyoma of the oral cavity: A light microscopic and immunohistochemical study with review of the literature from 1884 to 1992. **European Journal of Cancer**. Part B: Oral Oncology, 30(1), 1–7, 1994.

BLANC E. Travaux originaux. **Gaz Hebd Med Chir**., 21, 611,1884.

BROOKS JK, NIKITAKIS NG, GOODMAN NJ, LEVY BA. Clinicopathologic characterization of oral angioleiomyomas. **Oral Surg Oral Med Oral Pathol Oral Radiol Endod.** 94:221-7, 2002.

CASTALDI, A., ARCURI, T., CARTA, M., QUILICI, P., & DERCHI, L. E. Primary leiomyosarcoma of the oral tongue: Magnetic resonance and ultrasonography findings with histopathologic correlation. **Acta Radiologica**, 47(5), 514–517, 2006.

CEPEDA, L. A. G., RIVERA, D. Q., ROCHA, F. T., HUERTA, E. R. L., SÁNCHEZ, E. R. M. Vascular leiomyoma of the oral cavity. Clinical, histopathological and immunohistochemical characteristics. Presentation of five cases and review of the literature. **Medicina Oral, Patologia Oral y Cirugia Bucal,** v. 13(8), p. 483–488, 2008.

CHERRICK HM, DUNLAP CL, KING OH. Leiomyomas of the oral cavity. Review of the literature and clinicopathologic study of seven new cases. **Oral Surg Oral Med Oral Pathol.** 35:54-66, 1973.

DATNM, D. D., & NEVILLR, B. W.Short communications & case reports Oral leiomyoma. . **Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology,** v.47,n.4, p. 343–348, abril 1979.

DE CARVALHO, W. R. S., DE SOUZA, L. L., PONTES, F. S. C., UCHÔA, D. C. C., CORRÊA, D. L., DE CÁCERES, C. V. B. L., PONTES, H. A. R. A multicenter study of oral sarcomas in Brazil. **Oral Diseases,** v.200, p.1–10, Jul. 2019.

DRY, S. M., JORGENSEN, J. L., & FLETCHER, C. D. M. Leiomyosarcomas of the oral cavity: An unusual topographic subset easily mistaken for nonmesenchymal tumours. **Histopathology**, v.36(3), p.210–220, 2000.

EI-NAGGAR A.K., CHAN J.K.C., GRANDIS J.R., TAKATA T., SLOOTWEG P.J. WHO Classification of Head and Neck Tumours (4th edition). **IARC**: Lyon. 2017.

ETHUNANDAN M, STOKES C, HIGGINS B, SPEDDING A, WAY C, BRENNAN P. Primary oral leiomyosarcoma: a clinic pathologic study and analysis of prognostic factors. **Int J Oral Maxillofac Surg**, v.36, p 409–416, 2007

FLETCHER C.D.M. Distinctive Soft Tissue Tumors of the Head and Neck. **Modern Pathology**, v. 15, p. 324–330, 2002.

FLETCHER C.D.M, JO VY. WHO classification of soft tissue tumours: an update based on the 2013 (4th) edition. **Pathology,** v. 46, p. 95–104, 2014.

GAGNIER JJ, KIENLE G, ALTMAN DG, MOHER D, SOX H, RILEY D; CARE GROUP. The CARE guidelines: consensus-based clinical case report guideline development. **J Clin Epidemiol,** v.67, p 46-51, Jan. 2014.

GOLDBLUM J. R., WEISS S. W., FOLPE, A.L. Benign tumors of smooth muscle. In:GOLDBLUM J. R., WEISS S. W., FOLPE, A.L.Enzinger and Weiss's Soft Tissue Tumors. 6 ed. Elsevier Health Sciences, cap. 17, p.517-543, 2008.

GUEIROS, L. A., ROMAÑACH, M. J., PIRES-SOUBHIA, A. M., PIRES, F. R., PAES-DE-ALMEIDA, O., & VARGAS, P. A. Angioleiomyoma affecting the lips: Report of 3 cases and review of the literature. **Medicina Oral, Patologia Oral y Cirugia Bucal,** v.16(4), 2011.

HACHISUGA T, HASHIMOTO H, ENJOJI M. Angioleiomyoma. A clinicopathologic reappraisal of 562 cases. **Cancer,** v. 54, p 126-30, 1984.

HAGY D M, HALPERIN V, WOOD C. Leiomyoma of the oral cavity: Review of the literature and report of a case. **Oral Surg Oral Med Oral Pathol**, v. 17, p. 748-55, 1964.

HERREN DB, ZIMMERMANN A, BU¨CHLER U. Vascular leiomyoma in an index finger undergoing malignant transformation**. J Hand Surg**., v. 20B, p.484-7,1995.

HUANG, H. Y., & ANTONESCU, C. R. Sinonasal smooth muscle cell tumors: A clinicopathologic and immunohistochemical analysis of 12 cases with emphasis on the low-grade end of the spectrum. **Archives of Pathology and Laboratory Medicine,** v.127(3), p.297–304, 2003.

IDE, F., MISHIMA, K., YAMADA, H., SAITO, I., HORIE, N., SHIMOYAMA, T., & KUSAMA, K. Perivascular myoid tumors of the oral region: A clinicopathologic re-evaluation of 35 cases. **Journal of Oral Pathology and Medicine**, v. 37(1), p. 43–49, 2008.

KO E. Primary oral leiomyosarcoma: A systematic review and update. **J Oral Pathol Med**., v.48, p.780-787, Apr. 2019.

KUMAR, P., SURYA, V., URS, A. B., AUGUSTINE, J., MOHANTY, S., & GUPTA, S. Sarcomas of the Oral and Maxillofacial Region: Analysis of 26 Cases with Emphasis on Diagnostic Challenges**. Pathology and Oncology Research,** v.25(2), p.593–601, 2019.

LEE JM, BAUMGARTNER FJ, SHELLANS S, BUTLER J, FRENCH S. Degeneration and sarcomatous transformation of a retroperitoneal leiomyoma. **Eur J Surg**.,v.162, p.337-40, 1996

LUACES REY, R., LORENZO FRANCO, F., GÓMEZ OLIVEIRA, G., PATIÑO SEIJAS, B., GUITIÁN, D., & LÓPEZ-CEDRÚN CEMBRANOS, J. L. Oral leiomyoma in retromolar trigone. A case report. **Medicina Oral, Patologia Oral y Cirugia Bucal,** v. 12(1), p. 42–44, 2007.

MIZUTANI H, TOHNAI I, YAMBE M, UEDA M. Leiomyosarcoma of the maxillary gingiva: a case report. **Nagoya J. Med. Sci**.,v. 58, p.165±170, 1995.

MONTERO LUIS, Á., PÉREZ AGUILAR, D., & LÓPEZ MARTÍN, J. A. Multidisciplinary management of soft tissue sarcomas. **Clinical and Translational Oncology,** v.12(8), p.543–553, 2010.

MONTGOMERY E, GOLDBLUM JR, FISHER C. Leiomyosarcoma of the head and neck: a clinicopathological study. **Histopathology,** v.40, p.518–525, 2002 19

MORIMOTO N. Angiomyoma (vascular leiomyoma): A clinicopathological study. **Med J Kagoshima Univ**, v. 24, p.663-83, 1973.

ROTMENSCH J, BOSNYAK S, MONTAG A. Malignant transition of uterine leiomyomata **Int J Gynecol Obstet**., v.42, p.47-9,1993.

SOLAR AA, JORDAN RCK. Soft tissue tumors and common metastases of the oral cavity. **Periodontol 2000,** v.57(1), p.177-197, 2011.

STOUT, A.P.: Solitary cutaneous and subcutaneous leiomyoma. **Am. J. Cancer** , v.29, p.435, 1937

SUMIDA T., OTAWA N., KAMATA Y., YAMADA T., UCHIDA K., NAKANO H., … MORI, Y. A clinical investigation of oral sarcomas at multi-institutions over the past 30 years. **Anticancer Research,** v. 35(8), p.4551–4556, 2015.

The WHO Classification of Tumours Editorial Board. WHO Classification of Tumours Soft Tissue and Bone Tumours, 5thed. Lyon: IARC Press; 2020.

VEERESH M, SUDHAKARA M, GIRISH G, NAIK C. Leiomyoma: A rare tumor in the head with review**. J Oral Maxillofac Pathol.**, v.17, p.281-7. 2013.

VILOS GA, RAPIDIS AD, LAGOGIANNIS GD, APOSTOLIDIS C. Leiomyosarcoma of the oral tissues: clinicopathologic analysis of 50 cases. **J Oral Maxillofac Surg**., v. 63, p.1461–1477, 2005

WERTHEIMER-HATCH L, HATCH GF, HATCH KF, DAVIS GB; BLANCHARD DK, FOSTER RS et al. Tumors of the oral cavity and pharynx. **World J Surg**., v.24, p.395-400, 2000.

YAMAGUCHI S, NAGASAWA H, SUZUKI T, IWAKI H, AMAGASA T. Sarcomas of the oral and maxillofacial region: a review of 32 cases in 25 years. **Clin Oral Invest .,** v. 8, p.52-55, 2004.

ANEXO A - Aprovação do comitê de ética em pesquisa

UNIVERSIDADE FEDERAL DE MINAS GERAIS

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ANÁLISE MICROSCÓPICA DAS LESÕES MESENQUIMAIS BENIGNAS DA CAVIDADE ORAL

Pesquisador: Felipe Paiva Fonseca

Área Temática:

Versão: 1

CAAE: 72775717.8.0000.5149

Instituição Proponente: UNIVERSIDADE FEDERAL DE MINAS GERAIS

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.314.137

Apresentação do Projeto:

As neoplasias benignas da cavidade oral que se originam de estruturas mesenquimais são incomuns e usualmente apresentam-se como nódulos de crescimento lento e comportamento indolente, apesar de poderem ocasionalmente representar a manifestação oral de uma doença sistêmica (ex.: miofibromatose, neurofibromatose). O diagnostico microscópico destas lesões também representa um desafio, haja vista que a maioria destas lesões compartilha um padrão histológico composto predominantemente pela proliferação de células fusiformes. Desta forma, a melhor compreensão a cerca das suas características epidemiológicas, clínicas e microscópicas, poderá contribuir para o melhor reconhecimento destas entidades e com o manejo clínico dos pacientes afetados. Assim, o presente estudo se propõe a investigar a distribuição destas lesões mesenquimais benignas da cavidade oral, descrevendo suas principais características clínicas e microscópicas. Para isto, serão recuperados de forma retrospectiva dos arquivos da área de Patologia da Faculdade de Odontologia da Universidade Federal de Minas Gerais 50 casos diagnosticados como tumor fibroso solitário, miofibroma, histiocitoma fibroso benigno, neuroma traumático, tumor de células granulares, schwannoma, neurofibroma, neuroma encapsulado em paliçada, perineurioma, leiomioma e rabdomioma, no período de janeiro de 2000 a maio de

Endereço: Av. Presidente Antônio Carlos,6627 2º Ad SI 2005
Bairro: Unidade Administrativa II **CEP:** 31.270-901
UF: MG **Município:** BELO HORIZONTE
Telefone: (31)3409-4592 **E-mail:** coep@prpq.ufmg.br

2016. As lâminas coradas em hematoxilina e eosina serão revisadas por dois observadores conjuntamente para confirmação dos diagnósticos e as informações acerca do perfil imunoistoquímico, quando disponíveis, serão coletadas dos laudos microscópicos de cada caso. Os dados clínicos referentes a sexo, idade e localização das lesões serão recuperados das fichas de solicitação de exame histopatológico. Os achados microscópicos
serão apresentados de forma descritiva e correlacionados com os achados imunoistoquímicos disponíveis e com as informações clínicas coletadas.

Objetivo da Pesquisa:

Hipótese:

O perfil de distribuição epidemiológica, apresentação clínica e aspectos microscópicos das neoplasias mesenquimais benignas da cavidade oral auxiliam no seu diagnóstico e favorecem o manejo clinico dos pacientes.

Objetivo Primário:

Avaliar as características epidemiológicas, clínicas e microscópicas das lesões mesenquimais benignas da cavidade oral.

Avaliação dos Riscos e Benefícios:

Riscos:

Uma vez que as biópsias e cirurgias foram realizadas independentemente e previamente ao planejamento desta pesquisa, sendo os blocos de parafina coletados de forma retrospectiva de arquivos a partir da autorização dos participantes, espera-se que apenas a identificação do sujeito represente um potencial risco ou desconforto ao mesmo. Para minimizar este possível desconforto, destacamos que os dados de identificação dos
participantes ficarão sob a guarda restrita dos pesquisadores durante a realização da pesquisa, na Faculdade de Odontologia da UFMG (Belo Horizonte – MG), sendo de cunho confidencial e seu nome não será divulgado.

Benefícios:

Não haverá benefício direto ao sujeito, uma vez que as biópsias e cirurgias foram realizadas independentemente da pesquisa e anterior a ela. Com relação aos benefícios científicos, essa pesquisa gerará um maior conhecimento a cerca das características epidemiológicas, clínicas e microscópicas das neoplasias benignas mesenquimais da cavidade oral.

Comentários e Considerações sobre a Pesquisa:

Pesquisa relevante para a área de Patologia Oral / Estomatologia.

Término previsto para 31/12/2019.

Considerações sobre os Termos de apresentação obrigatória:

Foram inseridos os seguintes documentos:Informações Básicas do Projeto; Lattes do pesquisador responsável; Folha de Rosto; Declaração de Instituição e Infraestrutura (carta de anuência); Parecer consubstanciado aprovado pela Câmara Departamental; TCLE; Projeto de pesquisa detalhado.

Em relação ao TCLE:

- sugiro que seja reformulado com uma linguagem mais acessível aos participantes da pesquisa leigos; por exemplo, não há necessidade de descrever metodologia da pesquisa no TCLE;
- numerar as páginas;
- quando os autores citam "Forma de contato com os pesquisadores" e ao final do TCLE, explicitar que o contato do participante com o COEP-UFMG deverá acontecer somente em casos de dúvidas quanto aos aspectos éticos da pesquisa;
- sugiro substituir o termo "sujeito" por participante;
- ao final da segunda página, em "garantia de sigilo", substituir o termo "cópia" por via, a fim de garantir a originalidade do documento;

Conclusões ou Pendências e Lista de Inadequações:

Somos favoráveis à aprovação do projeto " ANÁLISE MICROSCÓPICA DAS LESÕES MESENQUIMAIS BENIGNAS DA CAVIDADE ORAL " do (a) pesquisador(a) responsável Prof.(a) Dr (a.) " Felipe Paiva Fonseca ".

Considerações Finais a critério do CEP:

Tendo em vista a legislação vigente (Resolução CNS 466/12), o COEP-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 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_952425.pdf	02/08/2017 14:11:07		Aceito

UNIVERSIDADE FEDERAL DE MINAS GERAIS

Continuação do Parecer: 2.314.137

Outros	lattes_felipe.pdf	02/08/2017 13:24:22	Felipe Paiva Fonseca	Aceito
Folha de Rosto	folha_de_rosto.pdf	02/08/2017 13:23:16	Felipe Paiva Fonseca	Aceito
Declaração de Instituição e Infraestrutura	carta_anuencia.jpg	02/08/2017 11:07:52	Felipe Paiva Fonseca	Aceito
Outros	parecer.jpg	02/08/2017 11:06:04	Felipe Paiva Fonseca	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.doc	28/06/2017 11:16:22	Felipe Paiva Fonseca	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_Lesoes_Mesenquimais_Orais.doc	28/06/2017 10:58:17	Felipe Paiva Fonseca	Aceito
Outros	72775717parecerassinado.pdf	05/10/2017 10:38:47	Vivian Resende	Aceito
Orçamento	72775717aprovacaoassinada.pdf	05/10/2017 10:38:53	Vivian Resende	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

BELO HORIZONTE, 05 de Outubro de 2017

Assinado por:
Vivian Resende
(Coordenador)

Endereço: Av. Presidente Antônio Carlos,6627 2º Ad SI 2005
Bairro: Unidade Administrativa II **CEP:** 31.270-901
UF: MG **Município:** BELO HORIZONTE
Telefone: (31)3409-4592 **E-mail:** coep@prpq.ufmg.br

ANEXO B – Artigo publicado no periódico

Artigo publicado no periódico *Head and Neck Pathology* (Qualis: B1).

DOI: https://doi.org/10.1007/s12105-021-01336-2

Head and Neck Pathology
https://doi.org/10.1007/s12105-021-01336-2

CASE REPORTS

Leiomyoma and Leiomyosarcoma (Primary and Metastatic) of the Oral and Maxillofacial Region: A Clinicopathological and Immunohistochemical Study of 27 Cases

Gabriela Ribeiro de Araújo[1] · Sara Ferreira dos Santos Costa[1] · Ricardo Alves Mesquita[1] · Ricardo Santiago Gomez[1] · Jean Nunes dos Santos[2] · Hélder Antônio Rebelo Pontes[3] · Bruno Augusto Benevenuto de Andrade[4] · Mário José Romañach[4] · Michelle Agostini[4] · Pablo Agustin Vargas[5,8] · Cinthia Verônica Bardalez Lopez de Cáceres[5] · Alan Roger Santos-Silva[5] · Ana Carolina Prado Ribeiro[6] · Thaís Bianca Brandão[6] · Ramiro Alejandro Tomasi[7] · Ruth Salomé Ferreyra[7] · Oslei Paes de Almeida[5] · Felipe Paiva Fonseca[1,8]

Received: 24 March 2021 / Accepted: 18 May 2021

Abstract
Smooth muscle neoplasms represent an important group of lesions which is rare in the oral cavity. Leiomyoma (LM) is benign smooth muscle/pericytic tumor usually presenting as non-aggressive neoplasm, while leiomyosarcoma (LMS) represents its malignant counterpart. The rarity of these lesions, together with its unspecific clinical presentation and a variable histopathological appearance, lead to a broad list of differential diagnoses, hampering their diagnoses. Therefore, in this study we describe the clinical and microscopic features of a series of oral and maxillofacial LMs and LMSs. A retrospective search from 2000 to 2019 was performed and all cases diagnosed as LM and LMS affecting the oral cavity and gnathic bones were retrieved. Clinical and demographic data were obtained from the patients' pathology records, while microscopic features and immunohistochemistry were reviewed and completed when necessary to confirm the diagnoses. Twenty-two LMs and five LMSs were obtained. In the LM group, males predominated, with a mean age of 45.7 years. The upper lip was the most affected site, and 18 cases were classified as angioleiomyomas and four as solid LM. In the LMS group, females predominated, with a mean age of 47.6 years. The mandible was the most affected site. Diffuse proliferation of spindle cells, with necrosis and mitotic figures, were frequent microscopic findings. LMs and LMSs were positive for α-smooth muscle actin, HHF-35 and h-caldesmon. In conclusion, oral LM/LMS are uncommon neoplasms with the latter usually presenting as metastatic disease. H&E evaluation may be very suggestive of oral LMs, but h-caldesmon staining is strongly recommended to confirm LMS diagnosis.

Keywords Angioleiomyoma · Leiomyoma · Leiomyosarcomas · Smooth muscle tumor · Oral cavity · Jaw

✉ Felipe Paiva Fonseca
felipepfonseca@hotmail.com

[1] Department of Oral Surgery and Pathology, School of Dentistry, Federal University of Minas Gerais, Belo Horizonte, Brazil

[2] Department of Oral Surgery and Pathology, School of Dentistry, Federal University of Bahia, Salvador, Brazil

[3] Service of Oral Pathology, João de Barros Barreto University Hospital, Federal University of Pará, Belém, Brazil

[4] Department of Oral Diagnosis and Pathology, School of Dentistry, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

[5] Oral Diagnosis Department (Pathology and Semiology Areas), Piracicaba Dental School, University of Campinas, Piracicaba, Brazil

[6] Dental Oncology Service, Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil

[7] Deparment of Pathology, Dental School, National University of Córdoba, Córdoba, Argentina

[8] Department of Oral Biology and Oral Pathology, School of Dentistry, University of Pretoria, Pretoria, South Africa

Published online: 09 June 2021