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CURSO DE GRADUAÇÃO EM ODONTOLOGIA

DIANA CARLA LIMA DE LACERDA

ANGIOSSARCOMA PRIMÁRIO DE TECIDO MOLE EM CAVIDADE ORAL: UM CASO INCOMUM

Sobral - CE

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Trabalho de Conclusão de Curso apresentado ao Curso de Odontologia da Universidade Federal do Ceará – *Campus* Sobral, como requisito parcial para a obtenção do título de Bacharel em Odontologia.

Orientador: Prof. Dr. Filipe Nobre Chaves

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RESUMO

O angiossarcoma é um tumor maligno raro e agressivo, com prognóstico ruim. Lesões primárias na cavidade oral são extremamente raras. Caracteristicamente, eles têm uma alta taxa de recorrência local e um potencial metastático precoce. O objetivo do presente trabalho é relatar o caso de um homem de 31 anos de idade com angiossarcoma no rebordo alveolar se estendendo ao palato duro, bem como realizar um revisão de literatura. Clinicamente, observaram-se úlceras de bordas elevadas, com características granulomatosas e coloração arroxeada, medindo mais de 24mm. Histologicamente, o tumor consistia em células fusiformes e poligonais contendo núcleos hipercromáticos com nucléolos. Essas células apresentavam-se organizadas em um padrão em forma de stent ou formando numerosas estruturas vasculares de calibres variados. O tumor era invasivo no tecido circundante e a permeação linfovascular foi notada. Imunohistoquimicamente, sendo Grocott negativas, as células tumorais foram positivas para CD34 em vasos e células dispersas, FLI-1 em células fusiformes e marcação Ki-67 maior que 15%, o que suporta o diagnóstico patológico de angiossarcoma. Foram encontradas lesões metastáticas nos membros superiores e face. A terapia proposta é a cirurgia radical, associada à quimioterapia. Para a revisão de literatura, realizou-se uma pesquisa em bases de dados online por artigos publicados nos últimos 10 anos. Devido à raridade, é imprescindível a utilização dos marcadores vasculares, como CD34, CD31 e FLI1, para um correto diagnóstico histológico e adequado planejamento terapêutico.

Palavas-chaves: Cavidade oral. Angiossarcoma. Histopatologia.

ABSTRACT

Angiosarcoma is a rare and aggressive malignant tumor that has a poor prognosis. Primary lesions in the oral cavity are extremely rare (0.0077%). Characteristically, they have a high rate of local recurrence and an early metastatic potential. We aimed to report the case of a 31-year-old male with angiosarcoma in alveolar ridge extending to hard palate as well as literature review. Clinically, there were ulcers with raised borders, with granulomatous characteristics and purplish coloration, measuring more than 24 mm. Histologically, the tumor consisted of spindle and polygonal cells with hyperchromatic nuclei with nucleoli. These cells are sometimes arranged in a stent-shaped pattern or forming numerous vascular structures of varying calibers. The tumor was invasive in the surrounding tissue, and lymphovascular permeation was noted. Immunohistochemically, being Grocott negative, tumor cells were positive for CD34 in vessels and scattered cells, FLI-1 in spindle cells and Ki-67 labeling mair than 15%. A pathological diagnosis of angiosarcoma was made. Metastatic lesions are found in upper limbs and thorax. Radical operation is now planned, associated with chemotherapy. For the review of the literature, an online database search was conducted for articles published in the last 10 years. Because of the rarity, it is essential to use vascular markers, such as CD34, CD31 and FLI1, for one of the histological diagnoses and for internal planning.

Keywords: Oral cavity, Angiosarcoma, Histopathology.

SUMÁRIO

1 CAPÍTULO

Este trabalho está baseado nas normas que regulam o trabalho de conclusão de curso do Curso de Odontologia da Universidade Federal do Ceará - *Campus* Sobral do regimento interno do Curso de Odontologia da UFC - *Campus* Sobral, que regulamenta o formato de artigo em seu Capítulo III, artigo 8º, desde que seja um tema de relevância para Odontologia e siga as normas do periódico selecionado para publicação.

CAPÍTULO 1 – "**Angiossarcoma primário de tecido mole em cavidade oral: um caso incomum**". Diana Carla Lima de Lacerda, Marcelo Bonifácio da Silva Sampieri, Denise Hélen Imaculada Pereira Oliveira, Karuza Maria Alves Pereira, Filipe Nobre Chaves. Este artigo será submetido para publicação no periódico da revista "*Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*" (ISSN: 2212-4403), que possui classificação A2 do Qualis Periódicos na Plataforma Sucupira (CAPES) referente ao presente quadriênio.

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RELATO DE CASO

ANGIOSSARCOMA PRIMÁRIA DE TECIDO MOLE NA CAVIDADE ORAL: RELATO DE CASO

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1.1 INTRODUÇÃO

O angiossarcoma é um tumor vascular maligno raro e altamente agressivo associado a um prognóstico ruim[1]. Caracteriza-se por uma rápida proliferação de células derivadas do endotélio vascular que delimitam espaços preenchidos por sangue e possuem alto poder de infiltração[2]. Constitui um dos subtipos mais raros de sarcoma[3].

Angiossarcomas tendem a surgir espontaneamente, mas também pode ocorrer em um campo pós-irradiado[4]. Acredita-se que as células progenitoras sejam de origem endotelial[1]. Podem ocorrer em qualquer órgão do corpo, porém o sítio de acometimento mais comum é a pele e tecidos moles superficiais, onde representam 1-2% de todos os sarcomas de tecidos moles[3,5,6]. Na região de cabeça e pescoço, o angiossarcoma cutâneo do couro cabeludo e da face é a forma mais frequente de apresentação[7]. A ocorrência de lesões primárias na cavidade oral é extremamente rara, sendo sua prevalência estimada em 0,14% dos cânceres de cabeça e pescoço e 0,0077% dos cânceres em geral[3].

O diagnóstico do angiossarcoma de tecidos moles é desafiador, face a raridade e semelhança com outras lesões como: hemangioma, hemangiopericitoma, hiperplasia endotelial papilar, hiperplasia angiolinfóide com eosinofilia, granuloma piogênico, sarcoma de Kaposi, melanoma, carcinoma espinocelular e carcinoma de células renais metastático[1,8]. Além disso, essas lesões apresentam uma ampla gama de diferenciação histológica[9]. Dessa forma, o estudo imunohistoquímico para análise da expressão de marcadores vasculares é necessário para discernir o angiossarcoma de outras neoplasias com morfologia similar[4].

Frente a tal situação, o diagnóstico tardio ou até mesmo errôneo é comum[1], piorando o prognóstico e levando ao desenvolvimento até um estágio mais avançado, favorecendo o risco de metástase a distância, a recorrência pós-terapia e uma menor sobrevida[4,7].

O presente relato de caso objetiva demonstrar um angiossarcoma primário em cavidade oral, realizando uma revisão de literatura sobre angiossarcomas primários de tecido mole na cavidade oral associando com o uso de marcadores imunohistoquímico para o diagnóstico.

1.2 RELATO DE CASO

Paciente do sexo masculino, 31 anos de idade, agricultor, etilista e fumante crônico, compareceu ao Ambulatório de Estomatologia da Universidade Federal do Ceará, Campus Sobral, queixando-se de lesão vasculho-hemorrágica em região de palato duro e gengiva maxilar. À oroscopia observaram-se lesões nodulares, granulomatosas com coloração arroxeada, implantação séssil, medindo mais de 24mm (Fig. 1), sem sintomatologia dolorosa, com tempo de evolução de aproximadamente 01 mês e sem fator causal aparente. O paciente não relatou histórico médico importante ou tratamento médico realizado previamente. Para a hipótese diagnóstica inicial de Sarcoma de Kaposi, foram solicitados exames hematológicos, anti-HIV-1 e anti-HCV para confirmação ou descarte da hipótese. A contagem de células do sangue, revelou hemoglobina 12,1 g/dL, linfócitos de 396/mm³ e, plaquetas 424 mil/mm³. A proteína C reativa encontrou-se elevada, estando 21.92 mg/dL. O teste rápido para HIV e sífilis foram negativos. O paciente foi encaminhado para a realização da biópsia incisional em dois sítios (palato duro e rebordo alveolar anterior). Macroscopicamente, os espécimes obtidos consistiam de dois fragmentos de tecido mole com formato e superfície irregulares, consistência fibrosa e coloração acastanhada, medindo 1.4x1.0x0.7cm e 1.3x0.9x0.7cm, respectivamente. Histologicamente, a fotomicrografia exibia abundantes células fusiformes e poligonais, algumas volumosas, contendo núcleos hipercromáticos com nucléolos e pleomorfismo celular e nuclear. Essas células apresentavam-se organizadas em um padrão em forma de stent ou formando numerosas estruturas vasculares de calibres variados (Fig. 2A). O estroma era constituído por tecido conjuntivo fibroso denso mostrando leve infiltrado inflmatório mononuclear. O tumor era invasivo no tecido circundante e a permeação linfovascular foi notada. No estudo imunohistoquimico, sendo Grocott negativas, a marcação de Ki-67 foi maior que 15% (Fig. 2B), as células tumorais foram positivas para CD34 em vasos e células dispersas (Fig. 2C) e FLI-1 em células fusiformes (Fig. 2D). Assim, o

diagnóstico patológico de angiossarcoma foi feito. Além disso, durante uma sessão de acompanhamento, após 01 mês, observou-se um aumento considerável das lesões intraorais com o aparecimento de lesões metastáticas nos membros superiores e face (Fig. 3). O paciente foi encaminhado ao setor de Oncologia e encontra-se sob tratamento.

1.3 DISCUSSÃO

O angiossarcoma é um tumor mesenquimal maligno originado a partir da diferenciação no endotélio vascular[10]. Considerado altamente agressivo e associado a um mau prognóstico[1], são neoplasias malignas extremamente raras e representam menos de 1% de todos os tumores malignos e entre 1% e 2% dos sarcomas que acometem os tecidos moles[7]. Embora possam surgir em qualquer parte do corpo, 60% surgem na pele ou nos tecidos moles superficiais[1]. Cerca de 50% dos casos são encontrados na região de cabeça e pescoço, afetando predominantemente o couro cabeludo e/ou a face de indivíduos brancos do sexo masculino[4,8].

Dentre os sítios primários de acometimento, os principais são os membros (33-54%), principalmente os inferiores, tórax (30-35%) e região de cabeça e pescoço (11-13%). Pulmão (25%), esqueleto (22%), fígado (16%) e cérebro (11%) estão entre os sítios metastáticos acometidos. O envolvimento da cavidade oral é rara e juntamente com as glândulas salivares, correspondem a 1% dos casos relatados na literatura[9]. Alguns estudos apontam que a língua e a gengiva sejam os sítios mais comuns para a ocorrência[1], como no caso relatado que apresentou lesões primárias em região de palato duro e gengiva maxilar (Tabela 1).

Angiossarcomas orais se apresentam como placas e/ou nódulos azulados ou violáceos, de consistência macia, podendo apresentar sangramento espontâneo, ulceração do epitélio oral e/ou dor em casos mais avançados[6,11]. É visto com uma prevalência igual entre os sexos, apesar de alguns autores sugerirem uma predominância leve pelo sexo masculino na proporção de 2:1[4]. Acomete todas as idades, com pico de incidência na 7º década de vida[3]. Possuem uma alta taxa de recorrência local, disseminam-se amplamente e possuem um potencial metastático precoce[1]. No caso relatado, o paciente acometido era do sexo masculino, com idade jovem de 31 anos, apresentou lesões nodulares, com ulceração, mas sem sintomalogia dolorosa. O potencial invasivo e mestastático ficou evidente a partir do rápido

crescimento das lesões encontradas na cavidade oral e a disseminação para membros superiores e face no período de um mês de acompanhamento.

A etiologia não está completamente definida, podendo surgir espontaneamente ou em associação com algumas condições clínicas, como linfedema crônico e radioterapia prévia[1,7,8]. Toxinas exógenas e mutações nos genes BRCA 1 e BRCA 2 também foram apontados como possíveis fatores predisponentes[8]. Dessa forma, de acordo com os diferentes cenários clínicos aos quais o angiossarcoma pode estar associado, ele pode ser dividido em cinco grupos: associado ao linfedema, induzido por radiação, pós-câncer de mama, de tecidos moles e cutâneo[7].

Histopatologicamente a aparência desses tumores varia muito, podem ser vistos três padrões: angiomatoso, fusiforme ou indiferenciado, variando desde neoplasias bem diferenciadas com vasos anastomosados e bem formados até tumores pouco diferenciados sem atividade vasoativa proeminente, sendo que na maioria das vezes, há uma mistura de padrões e tipos celulares dentro de um mesmo tumor, daí a importância de se utilizar os marcadores[4]. O estudo histológico do caso relatado, mostrou atipias nucleares, invasão do tecido circundate e permeação linfovascular, o que revela sua malignidade. Formação de estruturas vasculares de calibres variados com glóbulos vermelhos em seu interior também foram encontrados, evidenciando sua natureza vascular.

Uma ampla gama de lesões pode ser considerada no diagnóstico diferencial clínico do angiossarcoma, sendo as mais comuns hemangioma, granuloma piogênico, sarcoma de Kaposi, hiperplasia endotelial papilar e carcinomas[4,7]. Dessa forma, não é possível se fechar o diagnóstico de um angiossarcoma apenas com os achados clínicos, a célula tumoral deve apresentar algum grau de diferenciação vascular, seja em nível microscópico de luz com a identificação de vacúolos intracitoplasmáticos contendo glóbulos vermelhos intactos ou fragmentados, ou por estudo imunohistoquímico, com imunocoloração positiva para

marcadores que indicam que o tumor tem características endoteliais, como FVIII-Rag, CD34 e CD31[1,9].

O angiossarcoma tipicamente expressa marcadores endoteliais que incluem o antígeno relacionado ao fator VIII (FVIII-Rag), as citoqueratinas CD34 e CD31, o marcador de produto de fusão Fli-1, o regulador transcricional ERG e ocasionalmente a proteína podoplanina (D2-40)[3]. O FVIII-Rag está presente nas células endoteliais, no hemangioma e na maioria dos tumores de origem endotelial, como o sarcoma de Kaposi e o angiossarcoma[2]. O CD31 possui expressão membranoplasmática em células endoteliais vasculares não neoplásicas e neoplásicas e tem sido usado como uma ferramenta para identificar a origem vascular de neoplasias, como angiossarcomas, sarcomas de Kaposi e hemangioendotelioma epitelioide[4]. O estudo imunohistoquímico com CD31 também mostrou-se útil para detectar áreas de invasão linfovascular do tumor[1]. A marcação para vimentina e pancitoqueratinas é variado, apesar de a maioria dos tumores de origem mesenquimal exibirem coloração positiva para vimentina e coloração negativa para pancitoqueratinas[10]. Tem sido relatado que a alta sensibilidade e especificidade do Fli-1 é igual ou superior à dos marcadores vasculares estabelecidos[3]. O antígeno do melanoma (HMB45) e a proteína S100 podem ser utilizados para distinguir estes tumores do melanoma maligno, enquanto os marcadores miogênicos (por exemplo, desmina, isoformas de actina, miosina específica de músculo e miogenina) são empregados para o diagnóstico diferencial de sarcomas de origem muscular[4] (Tabela 1).

O tratamento de escolha é a excisão radical, porém, devido à multifocalidade do angiossarcoma e à ausência de margens patológicas bem definidas, o procedimento cirúrgico muitas vezes resulta em recidivas[7]. A radioterapia adjuvante é o tratamento padrão de lesões profundas de alto grau (dois e três)[3]. Entretanto, a combinação com a radioterapia não mostra muita diferença na taxa de sobrevida, uma vez que há a subestimação da extensão periférica da doença[6]. O consenso atual é a utilização de um tratamento combinado, incluindo excisão

da lesão com margens de segurança, mais quimioterapia[4]. A quimioterapia de primeira linha com doxorrubicina ou paclitaxel deve ser comparada com o melhor tratamento de suporte de acordo com as comorbidades e a preferência do paciente[1]. Para doença metastática, o tratamento padrão de primeira linha é a quimioterapia baseada em antraciclinas[3].

1.4 CONSIDERAÇÕES FINAIS

O angiossarcoma é uma neoplasia maligna rara, havendo poucos casos em localização primária intraoral relatados na literatura. O seu diagnóstico definitivo é um desafio, mas essencial para um melhor prognóstico, visto seu caráter agressivo e potencial metastático. Para isso, se faz necessário identificar características histológicas distintas e realizar uma análise imuno-histoquímica da expressão de marcadores endoteliais. Ainda é difícil afirmar qual seria o melhor método de tratamento desses tumores. No entanto, o diagnóstico precoce é essencial e a excisão deve ser realizada o mais rápido possível. Para uma maior segurança, o tratamento pós-operatório, além da cirurgia radical, é necessário.

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FIGURAS

Figura 1: Aspecto das lesões intraorais localizadas em região de palato duro (A) e rebordo alveolar anterior (B).

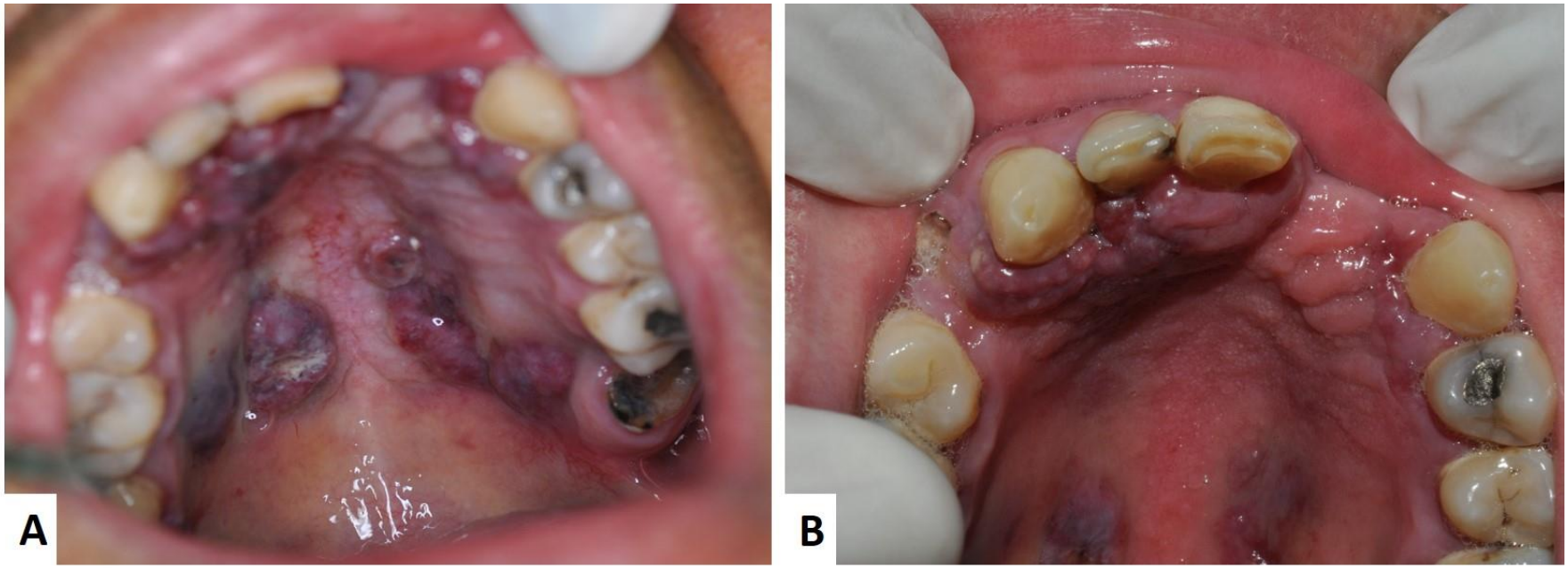


Figura 1: Fotomicrografias da lesão. (A) Presença de atipias celulares, formação de vasos sanguíneos apresentando por vezes células endoteliais sobrepostas dando a impressão de projeção celular para o lúmen (HE 400 x). (B) Imunoexpressão de Ki-67 maior que 15% (LSAB 200x). (C) Expressão positiva e difusa de CD 34 em vasos e células dispersas (LSAB 400x). (D) Expressão positiva e difusa de FLI-1 em células fusiformes (LSAB 200x)

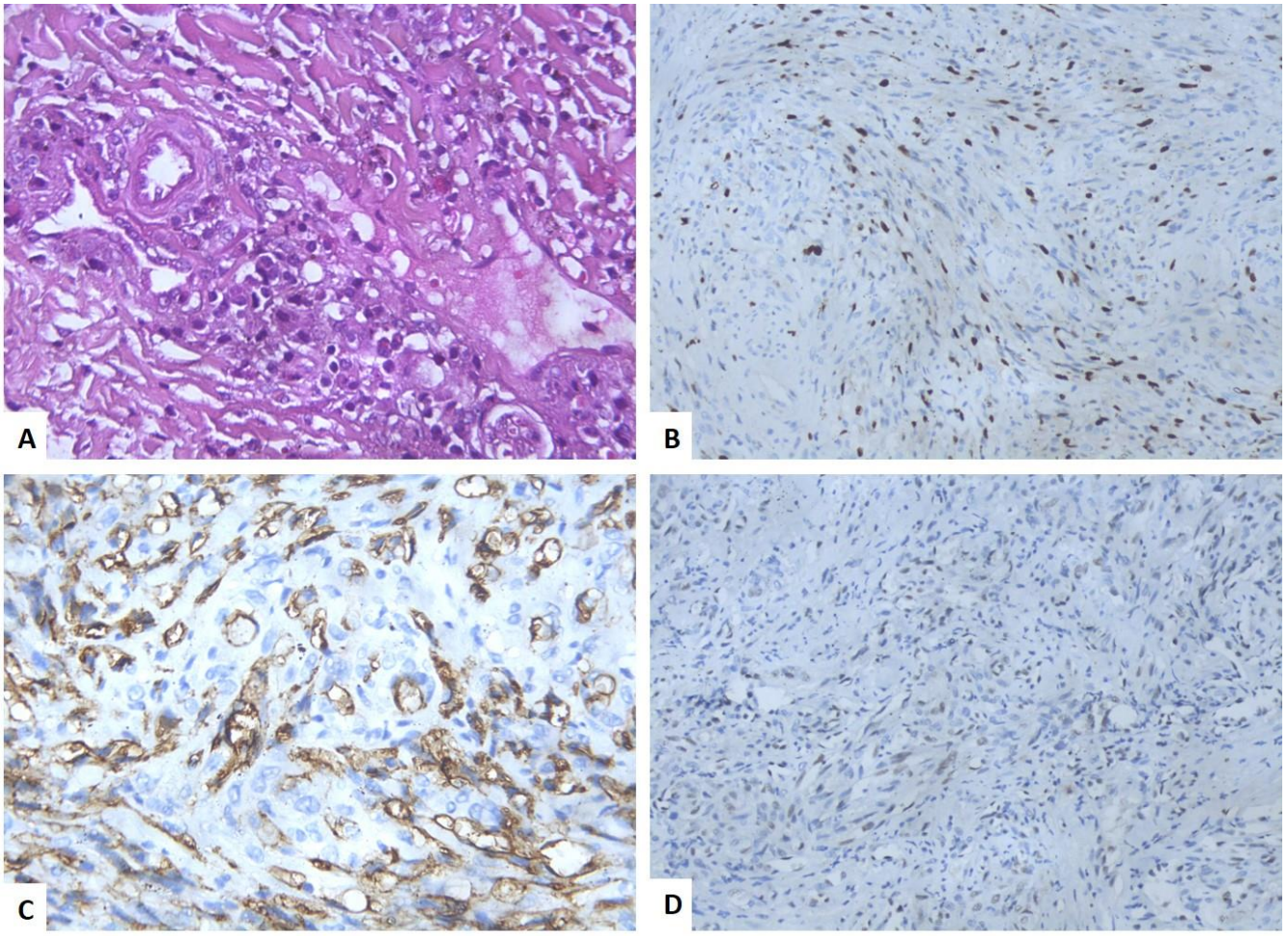
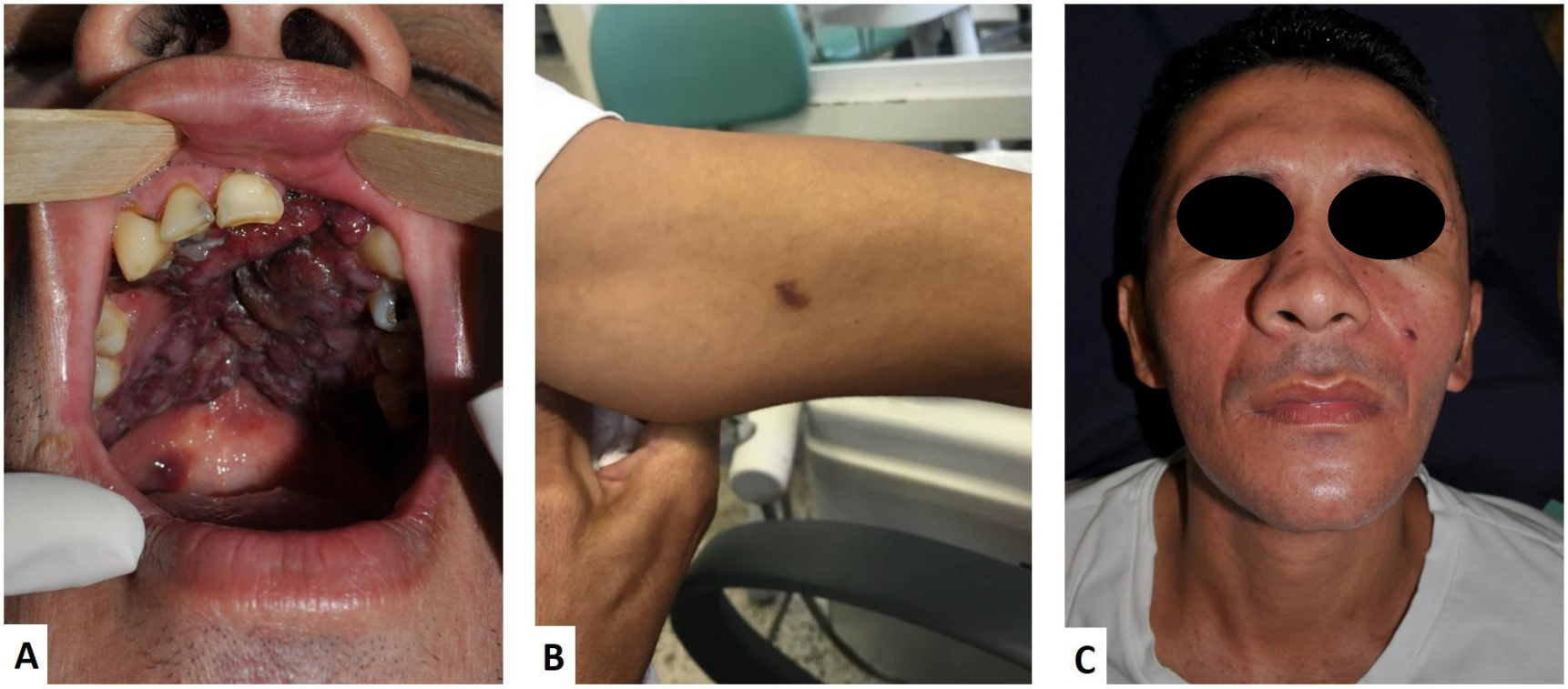


Figura 3. Aparência clínica após 01 mês de acompanhamento. (A) Aumento de tamanho considerável das lesões intraorais. (B, C) Lesões extraorais localizadas nos membros superiores e face, respectivamente.



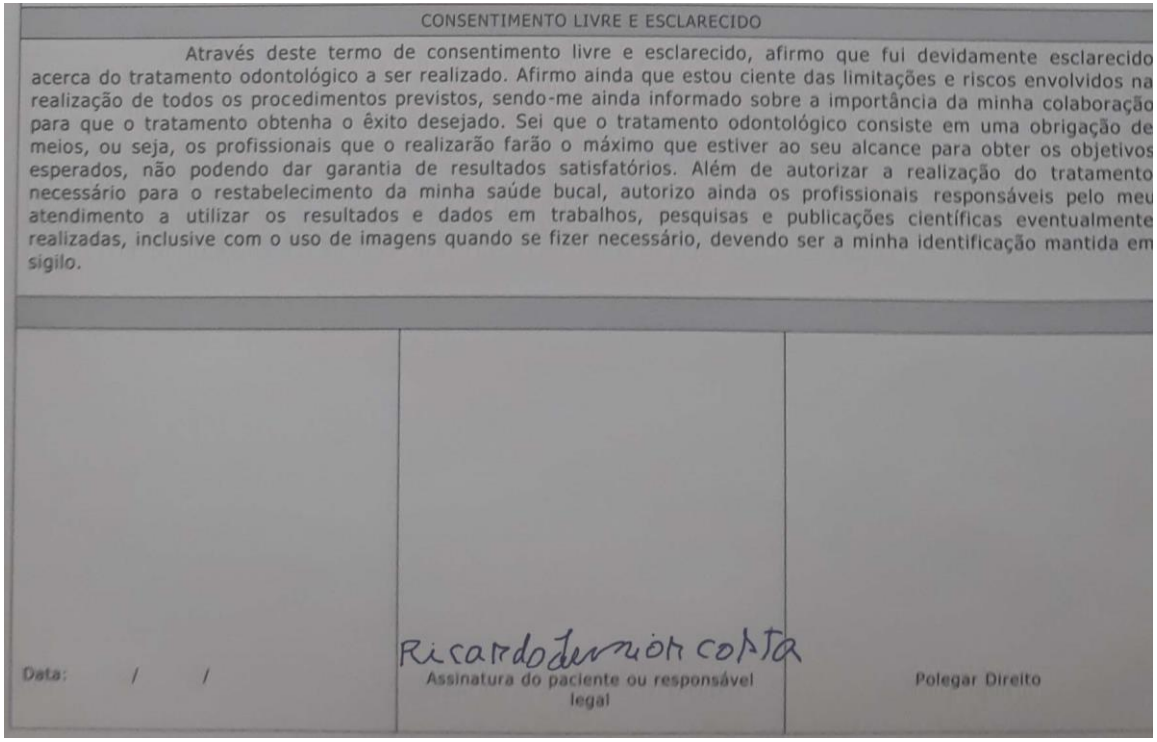
TABELAS

Tabela 1. Sítios de localização intraoral e uso de marcadores imunohistoquímicos em Angiossarcomas orais nos últimos 10 anos.

Autor/ Ano	Idade/ Sexo	Localiz.	M. vascular endotelial	M. mesenquimal	M. Epitelial
Arribas-Garcia et al. 2008	15/M	Lábio	FVIII- Rag (-) / CD31 (+) / CD34 (+)	-	-
Driemel et al. 2008	63/M	Gengiva maxilar	FVIII- Rag (+) / CD31 (+) / CD34 (+)	-	E- caderina (-)
Mucke et al. 2010	72/M	G. maxilar e mandibular	FVIII- Rag (-) / CD31 (+) / CD34 (-)	-	CK 45(-) / CK18 (-) / EMA (-)
Suzuki et al. 2011	69/F	Gengiva maxilar	FVIII- Rag (-) / CD31 (+)	-	-
Terada, 2011	54/M	Mucosa jugal	FVIII- Rag (-) / CD31 (+) / CD34 (+)	Vimentina (+)	CK 18 (-) / CK20 (-) / EMA (-)
Terada, 2011	77/M	Gengiva Mandibular	FVIII- Rag (+) / CD31 (+) / CD34 (+)	Vimentina (+)	-
Sumida et al. 2012	55/F	Gengiva mandibular	FVIII- Rag (+) / CD31 (+)	Vimentina (+)	-
Olson et al. 2012	11/F	Língua	CD31 (+) / CD34 (+)		AE1/AE3 (-)
M. Nagata et al. 2014	55/M 64/M 78/F	Gengiva mandibular Gengiva maxilar Língua	CD 34 (+) FVIII-RAg (+) / CD31 (+) / CD34 (+) FVIII-RAg (-) / CD31 (+) / CD34 (-)	- Vimentin (-) Vimentin (-)	EMA (+) / AE1/AE3 (-) AE1/AE3 (-) AE1/AE3 (+)
Doeuk et al. 2014	46/F	Ramo da mandibula esquerdo	FVIII-RAg (+) / CD31 (+) / CD34 (+).		AE1 / AE3 (-)
Evan B. Rosen et al. 2015	76/M	Palato duro e mole	-	-	-
Fomete et al. 2015	35/M	Mucosa Jugal	-	-	-
Hunasg et al. 2016	30/F	Gengiva anterior mandibular	FVIII-RAg (+) / CD31 (+) / CD34 (+)	-	-
Chamberland et al. 2016	83/M	Gengiva maxilar	CD31 (+) / CD34 (+)	-	EMA (+) / Pancitoqueratina e P63 (+)
Pratik B. Patel et al. 2017	57/M	Base da língua	CD31 (+) / Erg9 (+)	-	-
CASO RELATADO	31/M	Rebordo Alveolar e Palato Duro	CD34 (+) / FLI -1 (+)	-	-

ANEXO

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO



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APÊNDICE

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The *Oral Medicine Section* aims to publish a broad range of original articles that help clinicians understand more thoroughly the pathobiology, etiology, diagnosis, prevention, and management of oral conditions related to underlying medical conditions, including diseases of the head, neck, and oral mucosal structures, orofacial pain conditions, salivary gland disorders, and taste disorders. The section also seeks research regarding the dental management of persons with medical problems and/or complicated medical conditions.

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The *Oral and Maxillofacial Pathology Section* encourages the submission of original articles of high scientific quality that investigate the pathogenesis, diagnosis, and management of diseases affecting the oral and maxillofacial region. Submitted manuscripts may summarize findings from clinical, translational, or basic research in the broad field of oral and maxillofacial pathology but must contribute substantively to the body of knowledge in this field and should be of obvious clinical and/or diagnostic significance to the practicing oral and maxillofacial pathologist. Areas of focus may include the investigation of disease pathogenesis, the diagnosis of disease using microscopic, clinical, radiographic, biochemical, molecular, or other methods as well as the natural history and management of patients with various conditions of the head, neck, and oral mucosal structures. Diagnostic accuracy studies should conform to the principles of the STARD document http://www.stard-statement.org. Articles presenting

novel and reproducible research that introduce new knowledge and observations are especially encouraged. This section also welcomes the submission of topical review papers on relevant subjects.

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The section also seeks extensive case series representing various expressions of particular conditions, descriptions of innovative imaging technique applications to these series, and description of novel imaging features to assist imaging specialists develop clinical protocols and interpretive knowledge based on multiple observations. Only papers contributing substantively to the body of knowledge in oral and maxillofacial imaging and performed with scientific rigor will be considered. These papers should assist clinicians in developing evidence-based practice and provide improved clinical decision-making regarding the performance of specific techniques and interpretation of resulting images affecting the oral and maxillofacial region. Diagnostic accuracy studies should conform to the principles of the STARD document http://www.stard-statement.org).

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