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Intraoral epithelioid hemangioendothelioma: A case report and review of the literature

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Abstract

The epithelioid hemangioendothelioma (EH) is an uncommon angiocentric neoplasm of borderline or intermediate malignant potential, between the hemangioma and conventional angiosarcoma. It is characterized by the proliferation of endothelial cells with epithelioid or histiocitoid morphology with vacuolated cytoplasm and occasional eosinophilic spindle cells. Shows potential for local recurrence as well as the ability to metastasize. Rarely affects the oral cavity, it have been described from 1975 until 2008 only 27 oral cases. Morphologically the EHs may be confused with other lesions, from a hemangioma to a squamous cell carcinoma, and thus immunohistochemical analysis is required. This paper reports the clinical and immunohistochemical characteristics of a case of EH in the gingiva of the tooth 35 of a 17 years-old-white-female. We present a review of the clinicopathological and immunohistochemical characteristics of the intraoral epithelioid hemangioendothelioma cases previously reported.

Key words: *Epithelioid hemangioendothelioma, intraoral, vascular neoplasm.*

Introduction

The term hemangioendothelioma was introduced by Borrmann who first proposed the concept of vascular neoplasms with intermediate or low malignant potential (1). Three histological types of hemangioendothelioma are known: kaposiform, hobnail (or Dabska-retiform), and epithelioid (2).

The epithelioid hemangioendothelioma (EH) type

was first described by Weiss and Enzinger in 1982 as a angiocentric neoplasm characterized by neoplastic proliferation of epithelioid or histiocytoid endothelial cells, showing eosinophilic vacuolated cytoplasm, and occasionally, fusiform cells. The cell proliferation can be arranged as short anastomosing cords, solid lobules or lining distinct primitive-appearing vascular channels, with erythrocytes occasionally seen in the lumina.

Frequently, the tumor cells are arranged within a fibromyxoid stroma (3).

This tumor primarily committed to the soft tissues of the extremities (4), cases have been reported in lung, liver, bones, skin and the head and neck region, including the oral cavity (4-6). The EH is rare in the head and neck region and even more rare in the oral cavity, with 27 cases described from 1975 to 2008.

The EHs are usually treated with surgical removal of primary tumors, research the possibility of metastatic lesions and clinical follow-up of the patient due to risk of recurrence (7).

It reported a case of intraoral epithelioid hemangioendothelioma and a literature review is presented focused on clinical-pathological features and immunohistochemistry of the intraoral cases reported in the MEDLINE data base.

Case Report

A 17-year-old white woman, with 1 year history of a lesion in the gingiva after extraction of the 35 tooth, with pink color, exophytic, firm, painless, rapid growth, pediculated, without radiographic appearance and clinical diagnosis of pyogenic granuloma. A incisional biopsy was performed and microscopic examination showed

a fragment of a vascular neoplasia characterized by the proliferation of ovoid and fusiform endothelial cells, with a discrete cellular and nuclear pleomorphism, arranged in nests and cords. Some cells had an abundant eosinophilic cytoplasm and a hyperchromatic nuclei; others, sometimes, showed occasional intracytoplasmic vacuoles (Fig. 1A).

Cell proliferation can be seen scattered in the scanty stroma of lax connective tissue or limiting rudimentary vascular spaces, with erythrocytes occasionally seen in the lumina (Fig. 1B), in addition to areas with mineralized amorphous material between cell proliferation (Fig. 1C). (Table 1) shows the specifications of the antibodies used. Immunopositivity was observed for CD31 (Fig. 1D), CD34 (Fig. 2A), factor VIII-RAg (Fig. 2B), vimentin (Fig. 2C) and focal staining to SMA, mainly in myopericytic cells surrounding the neoplastic cells, showing endothelial differentiation (Fig. 2D). Negativity was observed for EMA, S-100, cytokeratins (AE-1 and AE-3) and CD68.

Based on morphological and immunohistochemical findings, the lesion was diagnosed as epithelioid hemangioendothelioma. The patient is in regular follow-up and 14 months after the surgery, no abnormalities were found on physical examination.

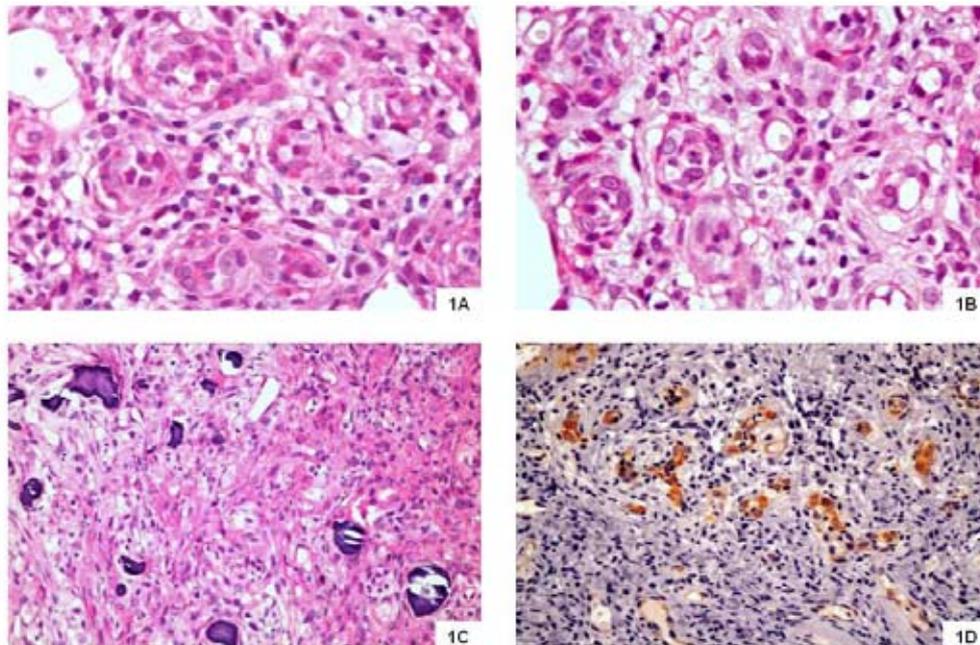


Fig. 1. A. Intense proliferation of neoplastic cells with abundant eosinophilic cytoplasm and hyperchromatic nuclei, and cells with occasional intracytoplasmic vacuoles, H/E – 200x; 1B. Cellular proliferation lining vascular structures, some of which containing erythrocytes and some cells with aspect of "signet ring-like", H/E – 200x; 1C. Amorphous mineralized material suggestive of metaplastic bone formation scattered between the proliferation of spindle and epithelioid neoplastic cells; 1D. Immunopositivity for CD31 in epithelioid-like neoplastic endothelial cells, SABC – 100x.

Table 1. Specifications of the antibodies used.

ANTIBODY	CLONE	SOURCE	DILUTION	ANTIGENIC RETRIEVAL	INCUBATION TIME
CD31	JC/70A	Dako, CA, USA	1:40	Citrato pH 6.0, Pascal	Overnight
CD34	QBEnd-10	Dako, CA, USA	1.50	Tris EDTA pH 9, Pascal	Overnight
Factor VIII	F8/86	Dako, CA, USA	1:400	Citrato pH 6.0, Pascal	30 min
Vimentin	V9	Dako, CA, USA	1:50	Citrato pH 6.0, Pascal	30 min
SMA	α sm-1	Novocastra, London, UK	1:40	Citrato pH 6.0, Pascal	60 min
EMA	E29	Dako, CA, USA	1:40	Sin tratamiento	60 min
S-100	S-100	Dako, CA, USA	1:100	Citrato pH 6.0, Pascal	30 min
Cytokeratins (AE-1/EA-3)	A E - 1 , EA-3	Dako, CA, USA	1:500	Citrato pH 6.0, Pascal	120 min
CD68	KP1	Santa Cruz, CA, USA	1:50	Citrato pH 6.0, Pascal	Overnight

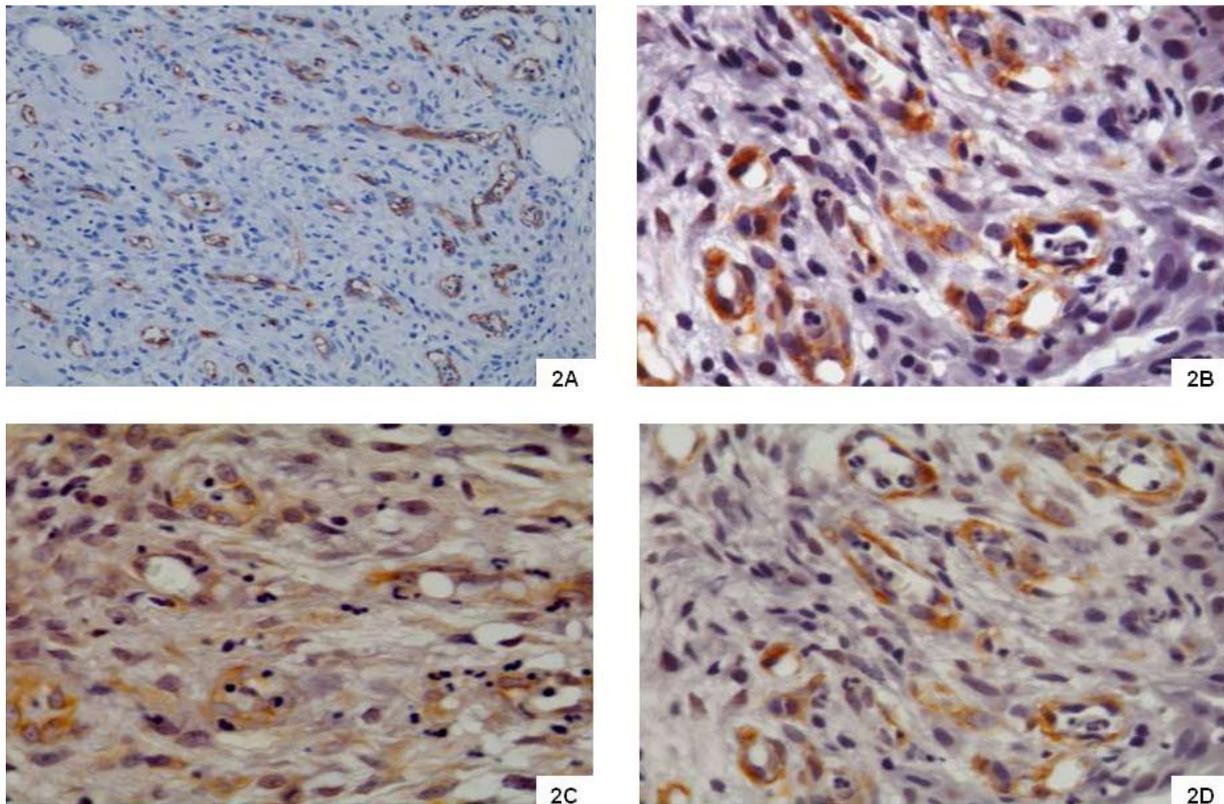


Fig. 2. A. Immunopositivity for CD34 in epithelioid-like neoplastic endothelial cells, SABC-100x; 2B. Cytoplasmic immunostaining for FVIII-RAG, SABC-400x; 2C. Immunostaining for Vimentin, SABC-400x; 2D. Immunostaining for SMA, SABC-400x.

Discussion

The analysis of cases of intraoral epithelioid hemangioma reported in the literature is a relatively difficult task, once the lesion from years ago has received various names, such as “hemangioendothelioma”, “malignant hemangioendothelioma” and “histiocytoid hemangioma” (7-9), thus, the reference point selected for the literature review presented here is the work published in 1975 by Wesley et al. (8), entitled “Primary malignant hemangioendothelioma of the gingiva”, until the most recent reported case by Mohtasham et al. (10).

(Table 2) shows the epidemiological data of the EHs reported in the literature in journals indexed in PubMed, including the case reported here. Most cases were clinically diagnosed as benign entities including pyogenic granuloma, fibroma, peripheral giant cell granuloma, peripheral ossifying fibroma, inflammatory fibrous hyperplasia and necrotizing ulcerative gingivitis (11). The case reported here is consistent with the literature, once the hypothesis of clinical diagnosis was pyogenic granuloma. The fact that the majority of EHs are clinically diagnosed as benign lesions has a great relevance, since it is a neoplasm with malignant biological behavior, intermediate between the hemangioma and conventional angiosarcoma, with reported cases displaying aggressive behavior and multiples recurrences (10,12).

It was noted that only 2 cases (7.4%) reported pain associated with the lesion, while the majority had no information about the symptoms, which leads us to infer that they were asymptomatic or that this was not just informed by authors (Table 2). The case reported here was asymptomatic.

The analysis of radiographic features showed that 25.9% of the lesions were associated with resorption or destruction of underlying bone (Table 2), highlighting the need for careful radiographic examination of the lesions to investigate possible alterations of the bone (11). It was not found any radiographic changes in the case reported here.

The malignant potential of the EHs is not well established, however, based on cases reported in the literature, these neoplasms exhibit a biological behavior intermediate between hemangioma and angiosarcoma, as well as potential for recurrence and metastasis (3).

Predictions regarding the biological behavior of EH in the oral region are not entirely possible due to the rarity of the lesion, the lack of agreement relative to terminology and criteria for diagnosis of EH and because of differences in the biologic behavior of these tumors relative to both their anatomic sites and with regard to age of occurrence (6).

Furthermore, EH doesn't show, histopathologically, consistent criteria for predicting their biologic behavior, however, it is reported that the presence of a increased number of mitotic figures and cellular atypia, spindle

tumor cells, metaplastic bone formation, in addition to areas of focal necrosis can be morphological signs of lesions with more aggressive phenotype and consequently more reserved prognosis, with recurrences and regional and/or distant metastasis (1,6,11). The case reported here showed no relevant cellular atypia or mitotic activity, which leads us to suggest that probably could be a lesion with more indolent behavior.

The review of the literature showed that the most prevalent intraoral site for EH was the tongue (7-25.9%), followed by the mandibular gingiva (6-22.2%) and maxillary gingiva (5-18.5%). The size of lesions ranged from 0.2 cm to 7.0 cm, with a mean of 1.7 cm. In the eight reported cases with recurrence (29.6%) (Table 2), it was noted that, in some of them, were multiple recurrences and the recurrent lesions showed a more aggressive appearance of malignancy. These recurrences were more frequent in the maxillary gingiva and buccal mucosa, both with 25.9%, followed by the lower lip, tongue, jaw and maxilla, with 12.9%, respectively. There are no reports of recurrence in mandibular gingiva and this site is the same of the case here reported.

The case reported here agrees with the literature (3) regarding the histomorphological features. The lesion exhibit cells with prominent cytoplasmic vacuoles, which represent primitive-appearing vascular channels; it is reported that these vacuoles are negative for mucin and erythrocytes occasionally seen in the lumina. The EHs can exhibit mineralized material, reported by some authors as metaplastic bone formation, in addition to numerous osteoclast-like giant cells. It reported that the metaplastic bone formation with significant cellular atypia, mitotic activity greater than one per 10 high-power fields, an increased proportion of spindle tumor cells and focal necrosis represent histopathological factors associated with a more aggressive behavior of the lesion (1,13,14).

Due to the predominant morphological characteristics, the EHs can be confused with other lesions including hemangioma to squamous cell carcinoma, therefore, emphasizes the importance of immunohistochemical analysis to establish the definitive diagnosis. In this context, the review of published cases verified that the majority of intraoral EHs lesions were immunoreactive for CD34, CD31, factor VIII-RAg and vimentin, these markers characterize the epithelioid endothelial origin of this entity (Table 3). It is reported that the immunoreactivity for factor VIII-RAg indicates the cytoplasmic luminal features and the epithelial cellular neoplastic nature (11). Furthermore, we agree with the literature that due to the morphological appearance of epithelioid tumoral cells of the EHs an the fact that many lesions are reactive for cytokeratin (AE-1/AE-3), requires a lot of attention from the pathologist, to avoid the risk of misdiagnosed as squamous cell carcinoma (13).

Table 2. Clinical and radiographic features of the intraoral EH cases reported in the literature.

	AUTHOR (YEAR)	AGE	SEX	LOCALIZATION	CLINICAL AND RADIOGRAPHIC HISTORY	FOLLOW-UP
1	Wesley et al (1975)	18	F	Mandibular gingiva	Reddish erosive lesion, (34 to 36), bone resorption	2 years SFL
2	Ellis, Kratochvil (1986)	13	F	Maxillary gingiva	Swelling, pink, tooth mobility, 4 years	6 years SFL
3	Ellis, Kratochvil (1986)	4	F	Mandibular gingiva	Tooth mobility, bone resorption	NI
4	Moran et al (1987)	25	F	Palate	Swelling, 1.0 cm, 1 year	21 months SFL
5	de Araujo et al (1987)	4	M	Mandibular gingiva	Swelling, ulceration, tooth mobility, 9 months	NI
6	Marrogi et al (1991)	45	M	Maxillary gingiva	Erythematous lesion, 1.5 cm	3,6 months Rec
7	Marrogi et al (1991)	36	F	Tongue	Painful nodules, 0.2 cm, 2 months	17 months SFL
8	Flaitz et al (1995)	7	F	Mandibular gingiva	Reddish swelling, 1.5 cm, tooth mobility, bone destruction	52 months SFL
9	Hamakawa et al (1999)	76	F	Mandibular anterior region	Submucous swelling, soft, 4.5 cm, bone destruction	6 years SFL
10	Orsini et al (2001)	18	F	Buccal mucosa	Asymptomatic swelling, 1.5 cm, 7 months	9 months Rec
11	Ramer et al (2001)	32	M	Maxilla	Swelling, 3.5 cm	6 months Rec
12	Molina Palma et al (2002)	65	F	Tongue	Swelling, 0.5 cm, 2 months	21 months SFL
13	Machalka et al (2003)	65	M	Jawa	Swelling at the anterior region of jaw, tooth mobility	4.8 years Rec
14	Anderson et al (2003)	18	F	Lower lip	Asymptomatic swelling, 6 months	4 months Rec
15	Chi et al (2005)	28	F	Maxillary gingiva	Purple swelling, 0.6 cm	8 months SFL
16	Chi et al (2005)	23	F	Jaw	2.0 cm, bone destruction	NI
17	Sun et al (2007)	12	M	Maxillary gingiva	Ulcerated swelling, 3.0 cm, 3 months, bone destruction, tooth mobility	6 months SFL
18	Sun et al (2007)	53	M	Buccal mucosa	Swelling, 1.5, 6 months	9 months Rec
19	Sun et al (2007)	17	M	Tongue	Soft swelling, 0.5 cm, 2 months	18 months SFL
20	Sun et al (2007)	52	F	Upper lip	Purple swelling, 2.0 cm, 1 year	3 years SFL
21	Sun et al (2007)	21	M	Tongue	Reddish swelling, 0.5 cm, 2 months	2 years SFL
22	Sun et al (2007)	34	M	Tongue	Swelling, 1.0 cm, 4 months	6 years SFL
23	Sun et al (2007)	11	M	Mandibular gingiva	Painful swelling, 2.0 cm, 1 month, bone destruction, tooth mobility	8 years SFL
24	Sun et al (2007)	46	M	Tongue	Reddish swelling, 1.2 cm	4 months Rec
25	Sun et al (2007)	6	M	Floor of mouth and tongue	Reddish swelling, 7.0 cm, 6 months	2 years SL
26	Mohtasham et al (2008)	9	M	Maxillary gingiva	Ulcerated reddish swelling, asymptomatic, 1.0 cm, 6 months	1 year, Rec
27	Gordón-Núñez et al (2008)	17	F	Mandibular gingiva	Swelling, pink, 2,0 cm, 1 year	9 months, SFL

M: male; F: female; NI: no information; SFL: survival free of lesion; SL: survival with lesion; Rec: recurrence.

A variable immunohistochemical expression to SMA for intraoral EHs has been observed previously (12,15,16) (Table 3). In the case reported here the immunoreactivity for this marker was focally, as evidenced at times immunoreactivity in myopericities cells surrounding the neoplastic cells, showing the endothelial differentiation of these. The nuclear transcription factor Fli-1, a specific marker for Ewing's sarcoma and primitive

neuroectodermal tumor, has been sensitive to vascular lesions, including EH (15).

Considering the intermediate malignant potential of the EH, wide local excision was the mode of choice in most cases reported in the literature (6,11,15,17), it was observed that conservative procedures such as curettage may favor the recurrence of the lesions (18). Under this, after established a diagnosis of EH the correct treatment should al-

Table 3. Immunohistochemical analysis of the intraoral EH cases reported in the literature.

	AUTHOR (year)	CD34	CD31	CD68	Factor VIII-RAg	VIMENTIN	SMA	S-100	EMA	AE-1/ AE-3	Flt-1	VEGF
1	Ellis, Kratochvil (1986)				+							
2	Ellis, Kratochvil (1986)				+							
3	Moran et al (1987)				+							
4	Flaitz et al (1995)				+							
5	Hamakawa et al (1999)	+			+	+		-	-	-		
6	Orsini et al (2001)				+							
7	Ramer et al (2001)	+			+							
8	Molina Palma et al (2002)		+		+							
9	Machalka et al (2003)	+	+	-	+	+	+	-	-	-		
10	Chi et al (2005)	-	+	-				-	-	-	+	
11	Chi et al (2005)	+	+	-				+	-	-	+	
12	Sun et al (2007)	+			+	+	+	-	-	+		
13	Sun et al (2007)	+			+	+	+	-	-	+		
14	Sun et al (2007)	+			+	+	+	-	-	+		
15	Sun et al (2007)	+			+	+	+	-	-	-		
16	Sun et al (2007)	+			+	+	+	-	-	-		
17	Sun et al (2007)	+			+	+	+	-	-	-		
18	Sun et al (2007)	+			+	+	+	-	-	-		
19	Sun et al (2007)	+			+	+	+	-	-	-		
20	Sun et al (2007)	+					+	-	-	-		
21	Mohtasham et al (2008)	+	+									
22	Gordón-Núñez et al (2008)	+	+	-	+	+	+	-	-	-		

(+) Immunopositivity, (-) Immunonegativity.

ways be the total surgical removal of the lesion and follow-up, to avoid the risk of permanence of neoplastic material and consequently recurrence. Therapeutic modalities as chemo and / or radiotherapy have been suggested for the treatment of EH, but without satisfactory results.

Among the 27 cases of intraoral EHs reported in the literature, including the case of this paper was observed that 23 cases (85.2%) had clinical follow-up information. Most of the patients (15-55.6%) survive free of evidence of lesion. On the other hand, 8 lesions (29.6%) recurred locally and fortunately was not registered a local or distant metastasis, nor death associated with lesions (Table 2). These data reinforce the less aggressive nature of the intraoral EHs when compared with those who commit other regions of the body.

The differential diagnosis of EH with another entities that occurs at the oral cavity may be assisted by certain clinical, histopathological, biochemical and/or immunohistochemistry. In this context, relates that epithelioid hemangioma, for example, is an lesion that usually exhibits cells with voluminous and eosinophilic cytoplasm, may be associated with lymphadenopathy and eosinophilia with elevated IgE and unlike the HE, epithelioid hemangiomas are located superficially, multilobular, not exhibit endothelial cells, cells with intracytoplasmic vacuoles, atypia, mitosis and necrosis (11). The association of epithelioid hemangioma with lymphadenopathy, peripheral eosinophilia and increased IgE are factors that help in the differential diagnosis (13).

In relation to the pyogenic granuloma, the diagnosis can be assisted by the clinical appearance of the lobular lesion. Furthermore, the squamous cell carcinoma, unlike the EH, the factor VIII-RAg, Eulex and mucin are negative. The absence of epithelioid cells with intracytoplasmic vacuoles, presence of fibrosarcoma-like spindle cells assist to differentiate Kaposi sarcoma of the EH (1).

Based on the analysis of the literature and in the case reported here, we conclude that the EHs are angiosarcomas whose etiology remains unknown, exhibiting particular histopathological and immunohistochemical features, being required a careful evaluation and with various diagnostic techniques to recognize and treat properly this entity, mainly taking into account their relatively malignant biological behavior.

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