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Recurrent Epithelioid Hemangioendothelioma of the Oral Cavity: A Systematic Review

Hemangioendotelioma Epitelioide Recurrente de la Cavidad Oral: Una Revisión Sistemática

Yuri Lins Lobo[1]; Lucas Alves da Mota Santana[1]; Maryana Cruz Santos[2]; Gilmagno Amado Santos[3]; Lysandro Pinto Borges[4]; Rajiv Gandhi Gopalsamy[5]; Gina Delia Roque-Torres[6]; Bernardo Ferreira Brasileiro[1,7]; Carlos Eduardo Palanch Repeke[2]; Wilton Mitsunari Takeshita[8] & Cleverson Luciano Trento[1]

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ABSTRACT: This systematic review purposed to investigate the recurrent intraoral Epithelioid Hemangioendothelioma (EHE) cases into a comprehensive analysis of their demographic, clinical, and immunohistochemical findings. An electronic search was conducted in Embase, PubMed, Scopus, and Web of Science with no restrictions on language or year of publication. All papers included were case reports of recurrent intraoral EHE. The risk of bias was evaluated second to the criteria of the Joanna Briggs Institute (JBI) to systematic review of case reports. This systematic review identified 9 studies from 6 countries, totalizing 10 cases. It was observed a slight predilection for the male gender, with the most of cases reported in gingiva (n = 5/10; 50 %). The main immunohistochemical markers used for diagnostic confirmation of recurrent intraoral EHE were factor VIII and CD34, respectively (n = 2/7; 28.5 % each). No case evaluated resulted in metastasis or evolved into death. Despite the rare occurrence of intraoral Epithelioid Hemangioendothelioma, the rate of recurrence in the oral cavity is relatively high. The initial recognition of the lesion and a careful excision with a good safety margin are essential to minimize the risk of recurrence.

KEY WORDS: Hemangioendothelioma, oral cavity, recurrence.

INTRODUCTION

Epithelioid hemangioendothelioma (EHE) is an uncommon vascular neoplasm of low-to intermediate-grade malignancy, first described by Weiss and Enzinger (Ali *et al*., 2015; Rajendrakumar *et al*., 2019; Januzis *et al*., 2020; Weerakoon *et al*., 2022). Although the lesion is more commonly seen affecting the liver, lungs, and long bones, some cases have been described in the head and neck region, including areas of the oral cavity such as gingiva, tongue, and alveolar mucosa (Tasaki *et al*., 2020). Histopathologically, EHE is characterized by proliferation of neoplastic endothelial cells with fusiform aspect, immersed in a myxohyaline stroma, showing eosinophilic vacuolated cytoplasm (Rajendrakumar *et al*., 2019).

Although molecular techniques have advanced, the pathogenesis of this neoplasm remains unclear, with main studies suggesting possible genetic alterations, including fusion genes such as a t(1;3)(p36;q23–5) reciprocal translocation between WWTR1 and CAMTA1, or a t(11;X)(q13;p11) between YAP1 and TFE3 (Ali *et al*., 2015; Weerakoon *et al*., 2022). Despite the

[1] School of Dentistry, Federal University of Sergipe (UFS), Aracaju, SE, Brazil.
[2] School of Dentistry, Federal University of Sergipe (UFS), Lagarto, SE, Brazil.
[3] NOVA National School of Public Health, Public Health Research Centre, Universidade NOVA de Lisboa, Lisbon, Portugal.
[4] School of Pharmacy, Federal University of Sergipe (UFS), Aracaju, SE, Brazil.
[5] Division of Phytochemistry and Drug Design, Department of Biosciences, Rajagiri College of Social Sciences, Kochi, Kerala, India.
[6] Center for Dental Research, School of Dentistry, Loma Linda University, Loma Linda, California, USA.
[7] Oral and Maxillofacial Surgeon, Private Practice, Southwest Florida Oral and Facial Surgery, Fort Myers, Florida, USA.
[8] Department of Diagnosis and Surgery, School of Dentistry, São Paulo State University (UNESP), Araçatuba, SP, Brazil.

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intermediate malignant behavior with a propensity for recurrence, a low risk of metastasis has been observed (Ali *et al*., 2015). Thus, the purpose of this paper was to elucidate and summarize the available evidence on recurrent intraoral EHE in the literature, with emphasis on demographic, clinical, and immunohistochemical findings.

MATERIAL AND METHOD

Search strategy. This study adhered to the PRISMA guidelines and an electronic search was carried out on June 9th, 2024, using Embase, PubMed, Scopus, and Web of Science. The search terms "Epithelioid hemangioendothelioma", "Oral epithelioid hemangioendothelioma" and “recurrent” were used in the search strategies jointly with Boolean operators (“AND” and “OR”) to optimize retrieval of the studies. Additionally, a manual search was performed on July 29th, 2024.

Eligibility criteria. Eligibility criteria focused on studies providing sufficient clinical, histological, and immunohistochemical data to confirm a diagnosis of oral epithelioid hemangioendothelioma, irrespective of anatomical location within the maxillofacial complex. Only case series and reports published in English, Spanish, Portuguese, or French were included, with the exclusion of animal studies, in vitro studies, and other types of non-case series research.

Data extraction and Risk of bias assessment. Following initial screening and exclusion of duplicates using Rayyan QCRI software, two reviewers independently (L.A.M.S. and M.C.S.) assessed titles, abstracts, and full texts against inclusion and exclusion criteria. Discrepancies were resolved by a third reviewer (Y.L.L.). The extracted data from selected studies encompassed authorship details, publication year, study design, country, number of cases, participant demographics (age, sex), lesion characteristics, clinical course, histopathological and immunohistochemical findings, treatment modalities, and survival outcomes. The risk of bias was evaluated second to the criteria of the Joanna Briggs Institute (JBI) to systematic review (SR) of case reports (Supplementary File 1).

RESULTS

Data search. A total of 57 manuscripts were retrieved from the databases, of which 12 were duplicates. After reading of titles and abstracts, 8 manuscripts were considered potentially eligible. Of the 8 studies selected, 2 was excluded for not meeting the inclusion criteria. Additionally, an additional manual search found 3 articles. Therefore, a total of 9 studies were added to this systematic review (Figure 1). From the 9 eligible studies at the end of the screening, 10 individual cases were selected and included for data analysis. The cases recovered from the literature occurred in equal proportion in the American, Asian, and European continents. The demographic and clinicopathological data for cases of recurrence of intraoral EHE are summarized in Table I.

Supplementary File 1. Risk of bias assessed by the Joanna Briggs Institute Critical Appraisal Tools for use in JBI Systematic Reviews for Case Reports.

Authors	Q.1	Q.2	Q.3	Q.4	Q.5	Q.6	Q.7	Q.8	%yes/risk
Ellis *et al*. (1986)	No	No	Yes	No	Yes	No	No	Yes	37,5 %/high
Marrogi *et al*. (1991)	No	No	Yes	Yes	Yes	Yes	No	Yes	62,5 %/moderate
Orsini *et al*. (2001)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	87,5 %/low
Machálka *et al*. (2003)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	87,5 %/low
Cheng *et al*. (2007)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	87,5 %/low
Sun *et al*. (2007)	No	Yes	Yes	Yes	Yes	Yes	No	Yes	75 %/low
	No	Yes	Yes	Yes	Yes	Yes	No	Yes	75 %/low
Mohtasham *et al*. (2008)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	87,5 %/low
Kumar *et al*. (2013)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	87,5 %/low
Ali S *et al*. (2015)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	87,5 %/low

Q.1) Were patient’s demographic characteristics clearly described? Q.2) Was the patient’s history clearly described and presented as a timeline? Q.3) Was the current clinical condition of the patient on presentation clearly described? Q.4) Were diagnostic tests or assessment methods and the results clearly described? Q.5) Was the intervention(s) or treatment procedure(s) clearly described? Q.6) Was the post-intervention clinical condition clearly described? Q.7) Were adverse events (harms) or unanticipated events identified and described? Q.8) Does the case report provide takeaway lessons? U – Unclear.

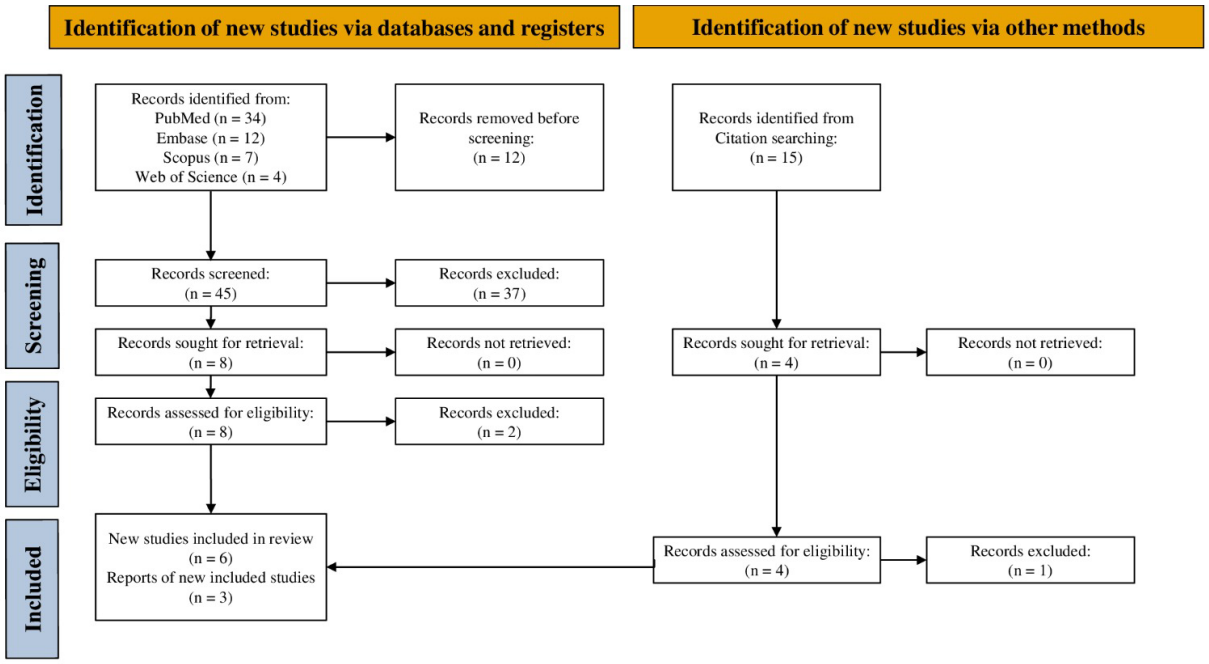

Fig. 1 Flow chart showing the search process.

Table I. Summary of the main cases of recurrent epithelioid hemangioendothelioma reported to the oral cavity.

Author	Country	Sex	Age (Y)	Anatomical localization	IHC markers	Symptomatology	Recurrence time after first manifestation (Months)	Metastasis	Clinical Outcome (Death)
Ellis GL & Kratochvil (1986)	USA	M	67	Submandibular region	NI	NI	2 months	No	No
Marrogi *et al*. (1991)	USA	M	45	Gingiva	Factor VIII	NI	3 months	No	No
Orsini *et al*. (2001)	Italy	F	18	Buccal mucosa	Factor VIII	NI	9 months	No	No
Machálka *et al*. (2003)	Czech Republic	M	65	Mandible	Factor VIII, CD34, CD31, Actin and Vitemin	NI	48 months	No	No
Cheng *et al*. (2007)	USA	F	13	Gingiva	CD31 and Factor VIII	NI	3 months	No	No
Sun *et al*.	China	M	53	Buccal mucosa	CD34	NI	9 months	No	No
		M	46	Tongue	CD34	NI	4 months	No	No
Mohtasham *et al*. (2008)	Iran	M	9	Gingiva	CD31 and CD34	NI	12 months	No	No
Kumar *et al*. (2013)	India	F	30	Gingiva	CD31	NI	3 months	No	No
Ali *et al*. (2015)	United Kingdom	F	23	Gingiva	NI	NI	84 months	No	No

Note: M, male; F, female; Y, years; IHC, Immunohistochemical; NI, Not Informed.

Clinical and epidemiological aspects. The epidemiological data reported in the literature show a male predilection, with a ratio of 1.5:1 (male to female). The mean age of patients was 36.9 ± 20.1 years, ranging from 9 to 67 years (Ellis & Kratochvil,1986; Marrogi *et al*., 1991; Orsini *et al*., 2001; Machálka *et al*., 2003; Cheng *et al*., 2007; Sun *et al*., 2007; Mohtasham *et al*., 2008; Kumar *et al*., 2013).

Anatomically, the most affected site was the gingiva, with 50 % (5/10) of cases (Marrogi *et al*., 1991; Orsini *et al*., 2001; Cheng *et al*., 2007; Mohtasham *et al*., 2008; Kumar *et al*., 2013), followed by the buccal mucosa with 20 % (2/10), and the mandible, tongue, and submandibular region with 10 % (1/10) each (Ellis & Kratochvil,1986; Orsini *et al*., 2001; Machálka *et al*., 2003; Sun *et al*., 2007).

Regarding immunohistochemical tumor markers, analyses were performed in 8 of the 10 cases. Positivity was observed as follows: 28.5 % (2/7) of cases expressed only factor VIII, 28.5 % (2/7) expressed only CD34, 14.3 % (1/7) expressed only CD31, 14.3 % (1/7) expressed CD31 together with CD34, and 14.3 % (1/7) expressed factor VIII, CD34, CD31, actin, and vimentin (Marrogi *et al*., 1991; Orsini *et al*., 2001; Machálka *et al*., 2003; Cheng *et al*., 2007; Sun *et al*., 2007; Mohtasham *et al*., 2008; Kumar *et al*., 2013). No case reported metastasis or progression to death.

DISCUSSION

EHE is an exceedingly rare vascular neoplasm in the oral cavity, with approximately 31 cases reported in the literature, including both recurrent and non-recurrent cases (Bajpai & Pardhe, 2019). When considering only recurrent cases, the number of reports decreases substantially. The present systematic review identified only 10 cases of recurrent intraoral EHE.

The data obtained in this review indicate a male predilection, which contrasts with previous studies that reported a female predominance (Chi *et al*., 2005; Soni *et al*., 2023). It should be emphasized, however, that those earlier studies were based on observational analyses of clinical cases, without distinguishing between recurrent and non-recurrent presentations. To the best of our knowledge, this is the first study to systematically evaluate the recurrent cases of intraoral EHE.

Regarding the site of the lesion, a predilection for the gingiva was observed, affecting 50% of the cases, which corroborates the findings of Leader & Adair (2019). One possible explanation for the higher recurrence rate in gingival lesions is the absence of a sufficient safety margin during excision, as demonstrated by Bhattacharya *et al*. (2015). In their study, the authors highlighted the importance of wide excision due to the risk of local recurrence. Additionally, gingival tissue is highly vascularized, and residual neoplastic cells may occasionally exploit this vascular network to promote tumor reactivation, as also observed in other vascular lesions (Penmetsa *et al*., 2015; Belotti *et al*., 2021).

Due to its clinical and pathological similarities with other oral lesions (e.g., pyogenic granuloma, periodontal disease, and peripheral giant cell granuloma), the diagnosis of EHE is often challenging (Bhattacharya *et al*., 2015). For this reason, immunohistochemistry (IHC) analysis plays a critical role. In the present systematic review, CD31, CD34, and Factor VIII were the most frequentlyused IHC markers. According to Gordon-Nuñez *et al*. (2010), these markers not only confirm the endothelial origin of the lesion but also demonstrate its epithelioid nature, making them reliable indicators for EHE diagnosis. Importantly, IHC has significant clinical value in the differential diagnosis of mesenchymal tumors with overlapping features (Jebastin *et al*., 2021; Januzis *et al*., 2020), as exemplified in intraoral EHE.

Although intraoral EHE shows a tendency for local recurrence, no cases of metastasis have been reported in the literature. In contrast, extraoral EHE demonstrates a more aggressive clinical behavior, with an overall survival rate ranging from 1 to 5 years, as reported by several authors (Liu & He, 2022; Tomassen *et al*., 2023). These poorer outcomes are frequently associated with tumors located in soft tissues, the abdomen, and the lungs. Undoubtedly, the delayed diagnostic process in these anatomical sites may explain the increased severity, while in the oral cavity, neoplastic manifestations are usually more evident and clinically detectable.

When compared to other vascular tumors, Nagata *et al*. (2014) demonstrated that angiosarcomas show both a propensity for local recurrence and the ability to metastasize, which contributes to their aggressiveness and poor patient survival rates.

In conclusion, intraoral EHE is a rare neoplasm characterized by locally aggressive behavior and limited metastatic potential. Nevertheless, the recurrence rate in the oral cavity remains relatively high compared with the few cases of intraoral EHE described in the literature. For this reason, greater attention is required regarding therapeutic strategies, especially during surgical interventions. Careful excision with wide safety margins, combined with long-term clinical follow-up, is essential to reduce the risk of recurrence and to improve patient outcomes.

Data Availability Statement: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request

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RESUMEN: Esta revisión sistemática tuvo como propósito investigar los casos recurrentes de hemangioendotelioma epitelioide (HEE) intraoral mediante un análisis integral de sus hallazgos demográficos, clínicos e inmunohistoquímicos. Se realizó una búsqueda electrónica en Embase, PubMed, Scopus y Web of Science, sin restricciones de idioma ni de año de publicación. Todos los artículos incluidos correspondieron a reportes de casos de HEE intraoral recurrente. El riesgo de sesgo se evaluó de acuerdo con los criterios del Joanna Briggs Institute (JBI) para revisiones sistemáticas de reportes de casos. Esta revisión sistemática identificó 9 estudios provenientes de 6 países, totalizando 10 casos. Se observó una ligera predilección por el sexo masculino, con la mayoría de los casos reportados en encía (n = 5/10; 50 %). Los principales marcadores inmunohistoquímicos utilizados para la confirmación diagnóstica del HEE intraoral recurrente fueron el factor VIII y el CD34, respectivamente (n = 2/7; 28,5 % cada uno). Ninguno de los casos evaluados presentó metástasis ni evolucionó hacia el fallecimiento. A pesar de la rara ocurrencia del hemangioendotelioma epitelioide intraoral, la tasa de recurrencia en la cavidad oral es relativamente alta. El reconocimiento temprano de la lesión y una escisión cuidadosa con un buen margen de seguridad son esenciales para minimizar el riesgo de recurrencia.

PALABRAS CLAVE: hemangioendotelioma, cavidad oral, recurrencia.

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Corresponding author:
Yuri Lins Lobo, DDS.
School of Dentistry
Federal University of Sergipe (UFS)
Rua Cláudio Batista, s/n, Santo Antônio
Zip Code: 49060102
Aracaju, SE
BRAZIL

E-mail: yuriloboodonto@academico.ufs.br