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RESEARCH

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A systematic review of the clinicopathological characteristics of oral leiomyomatous hamartoma

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Abstract

Background Oral leiomyomatous hamartoma (OLH) corresponds to an abnormal, benign and disorganized overgrowth of mature smooth muscle tissue, which can develop in any site where this tissue is found in healthy conditions. The present systematic review aimed to analyze the clinicopathological characteristics of OLH.

Materials and methods The protocol of this study was constructed following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and was registered in the Open Science Framework (OSF): OSF.IO/BMPUX. Five electronic databases were used to identify studies for this systematic review: PubMed, Web of Science, Dentistry & Oral Science Source, Scopus and ScienceDirect, from January 15th, 1945 to January 10th, 2024. The Joanna Briggs Institute (JBI) tool was used to assess the risk of bias and the quality of the included reports and case series.

Results A comprehensive search yielded 5,562 articles, of which 55 met the inclusion criteria. The total number of subjects studied in the included investigations was sixty-six. The subjects' ages varied from newborns to 61 years, with a mean age ± standard deviation of 71.23 ± 123.01 months. 50.7% were males and 49.3% were females. Most lesions presented normochromic color (24.24%), pedunculated base (31.81%), firm consistency (22.72%), with an average size of 1.20 cm, present on the dorsum of the tongue (31.81%) or anterior part of the alveolar border of the maxilla (30.30%). Treatment was carried out by surgical excision (78.46%) and half of the studies report that there were no recurrences.

Conclusions The cases described in the medical-dental literature provide valuable information to date on the clinicopathologic and immunohistochemical profile of OLH. Although it is a rare lesion, it should be considered as part of the differential diagnosis in newborns, infants, children and young adults with lingual and/or maxillary masses present in the midline.

Keywords Hamartoma, Leiomyoma, Immunohistochemistry, Tongue, Gingiva, Maxillary

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Introduction

Oral leiomyomatous hamartoma (OLH) corresponds to a disorganized, abnormal mass with a predominance of smooth muscle tissue, that can grow and develop at any site where this tissue is found in healthy conditions. In fact, most commonly, lesions occur at sites of fusion of processes and prominences during embryonic development [1]. The first cases were reported by Stamm and Tauber in 1945 [2], later Semba et al., in 1993 [3] considered it as a clinicopathological entity, with an immunohistochemical profile independent of other hamartomatous lesions. This lesion is most frequently observed in the midline of the dorsum of the tongue and in the anterior part of the alveolar border of the maxilla (region of the incisive papilla), mainly in children; however, if not diagnosed early, the lesion grows and can also affect adolescents and older adults [4–29]. Clinically, it presents as mass of polypoid appearance, similar in color to the adjacent mucosa, smooth surface, well-defined borders, pedunculated base, firm consistency and a size ranging from 0.2 to 4 cm in diameter [30–32]. It is usually an asymptomatic lesion, however, due to the extent of the lesion, it can create difficulty in chewing food [33]. Histologically, it is characterized by a stratified squamous epithelium overlying connective tissue with an irregular and disorganized proliferation of smooth muscle fibers arranged in fascicles and neurovascular elements [34–45]. Treatment is surgical and no recurrences have been observed, a characteristic aspect of benign lesions [46–55].

To the best of our knowledge, no systematic review summarizing the clinicopathological data (sociodemographic, clinical, histopathologic, immunohistochemical and therapeutic) of OLH has been previously performed in the literature, making it of utmost academic importance.

The purpose of this study is to explore the true biological profile of OLH. Therefore, the present systematic review of the literature aimed to describe the clinicopathological characteristics of OLH.

Materials and methods

Protocol and enrollment

This systematic review was performed according to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) recommendations [56]. The protocol was registered in the OSF database under (no. https://doi.org/10.17605/OSF.IO/BMPUX).

Eligibility criteria

Inclusion criteria were investigations of type: 1) Reports and case series, 2) written in english language. 3) The articles had to provide information such as age, sex, clinical appearance and histopathological characteristics of the lesion to confirm the definitive diagnosis of OLH, as well as those articles that evaluated its immunohistochemical profile. Exclusion criteria were: 1) review articles, 2) book chapters, 3) editorials, 4) letters to the editor, 5) protocols, 6) practice guidelines, 7) posters at congresses, as well as 8) reports or case series with lack of information for the confirmation of the diagnosis of OLH.

Sources of information and search

The electronic search was performed independently by two investigators (M.A.A.S and A.H) using five databases: PubMed, Web of Science, Dentistry & Oral Science Source, Scopus and ScienceDirect, from January 15th, 1945 to January 10th, 2024. Table 1 shows the search strategy used for PubMed. For the rest of the data bases, the keywords "Hamartoma", "Leiomyoma", "Diagnosis", "Surgery", "Mouth", "Tongue", "Gingiva", "Maxilla" and "Mandible" were used along with the use of Boolean operators "AND" and "OR". A manual search was also carried out in specific journals of pathology and oral medicine with the main purpose of enrich the search strategy. The journals were the following: "*Oral and Maxillofacial Surgery Clinics of North America*", "*British Journal of Oral & Maxillofacial Surgery*", "*Journal of Oral and Maxillofacial Surgery*", "*Medicina Oral Patologia Oral y Cirugia Bucal*", "*Oral Disease*" "*Oral Surgery, Oral Medicine, Oral Pathology*" and "*Journal of Oral Pathology & Medicine*".

Study selection

Two reviewers (M.A.A.S and M.N.V) independently evaluated the titles and abstracts of the articles. Publications that did not meet the inclusion criteria and were outside the scope of this study were eliminated. Whereas, articles that met the selection criteria were evaluated at full text. If any disagreement arose, it was resolved by discussion in consultation with a third investigator (A.H).

Table 1 The full search strategy used in the PubMed database

Data base	Search Strategy
PubMed	((((((((((("Hamartoma/congenital"[Mesh] OR "Hamartoma/diagnosis"[Mesh] OR "Hamartoma/pathology"[Mesh] OR "Hamartoma/surgery"[Mesh] OR "Hamartoma/therapy"[Mesh])) AND "Diagnosis"[Mesh]) AND "Diagnosis, Differential"[Mesh])) AND ("Leiomyoma/congenital"[Mesh] OR "Leiomyoma/diagnosis"[Mesh] OR "Leiomyoma/immunology"[Mesh] OR "Leiomyoma/pathology"[Mesh] OR "Leiomyoma/surgery"[Mesh] OR "Leiomyoma/therapy"[Mesh])) AND "Humans"[Mesh]) AND "Mouth"[Mesh])) OR "Tongue"[Mesh]) OR "Gingiva"[Mesh]) OR "Alveolar Process"[Mesh]) OR "Mandible"[Mesh]) OR "Maxilla"[Mesh]

Data collection and summary measures

Data collection was carried out by two reviewers (M.A.A.S and L.S.E.V) independently. The variables extracted were year of publication, authors, country, study design, number of cases, age, gender, clinical appearance, size, location, treatment, case follow-up and immunohistochemical profile of OLH.

Descriptive statistics were used for data analysis. Thus, continuous data were represented with mean ± standard deviation (SD), while qualitative variables were represented with absolute and relative frequency.

Quality assessment of individual studies

Two reviewers (M.A.A.S and A.H) assessed the quality of the studies independently following the Joanna Briggs Institute (JBI) guidelines [57]. This tool is responsible for assessing the demographic characteristics, medical history, current status, diagnostic tests, treatment, postsurgical condition, adverse events, and expected learnings of the reported case. Questions were graded as "No," "Yes," "Not applicable," or "Unclear." Studies were classified according to their quality, and were placed in three levels; poor, fair, and good quality [58].

Results

Study selection and general features of included studies

Initially 5,555 articles were found in the five databases, including PubMed ($n=5,400$), Web of Science ($n=22$), Dentistry & Oral Sciences Source ($n=6$), ScienceDirect ($n=111$) and Scopus ($n=16$). In the manual search, 7 articles were found, giving a total of 5,562 articles. During the identification phase, duplicates were eliminated ($n=110$), ensuring that each study was considered only once, and articles irrelevant to the topic of interest were excluded based on the title of the reports. We then reviewed the remaining 3,952 studies. After analyzing the

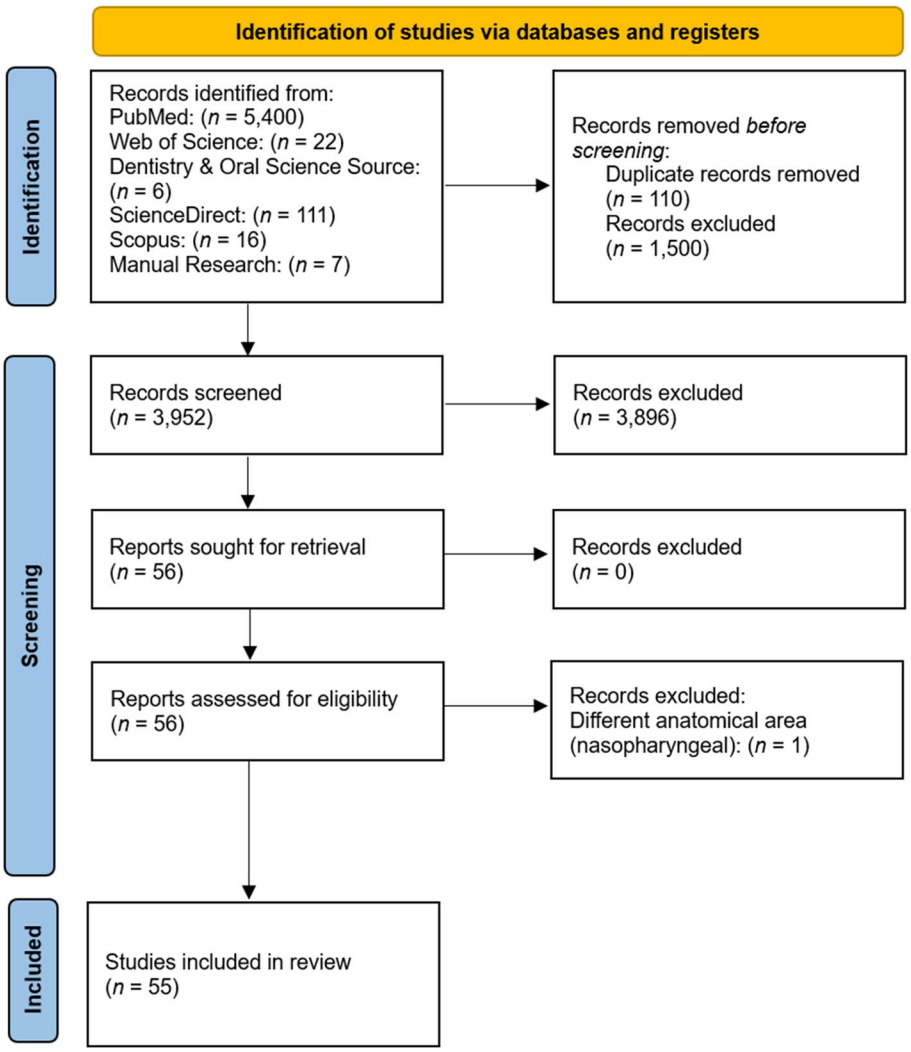

Fig. 1 PRISMA flow diagram. PRISMA: Preferred reporting items for systematic and meta-analyses

Table 2 Distribution of clinicopathological data for oral leiomyomatous hamartomas

Year	Author's	Country	Study type	No. Cases	Age (Mo)	Gender	Clinical aspect	Size (cm)	Location	Treatment	Follow-up/ Relapse
1945	Stamm and Tauber [1]	USA	Case report	1	Newborn	Female	Normochromic, smooth, sessile, firm tumor/ASX	NR	Tongue base	Surgical excision	2 No
1956	Perri et al., [3]	USA	Case report	1	408	Female	Yellowish, smooth, firm tumor/ASX	2.0	Tongue base	Surgical excision	NR
1962	Takahashi et al., [4]	Japan	Case report	1	2	Female	Congenital epulis	0.4	Median maxillary	NR	NR
1963	Hinshaw et al., [5]	USA	Case report	1	48	Female	Pinkish, smooth, pedunculated, firm mass/ASX	3.0	Tongue base	Surgical excision	NR
1968	Ishii et al., [6]	Japan	Case report	1	4	Female	4 lesions Grayish, smooth, firm tumor/ASX	3.0	Base, tip and dorsal tongue	Surgical excision	NR
1973	Yamashita et al., [7]	China	Case report	1	60	Female	NR	NR	NR	NR	NR
1981	Demuth and Johns [8]	USA	Case report	1	18	Male	Pedunculated tumor	NR	Tongue base	Surgical excision	6 No
1982	Mushimoto et al., [9]	Japan	Case report	1	11	Female	Congenital epulis	0.5	Median maxillary	NR	NR
1983	Kajiyama et al., [10]	Japan	Case report	1	53	Female	Congenital epulis	1.5	Median maxillary	NR	NR
1984	Becker et al., [11]	USA	Case report	1	Newborn	Male	Grayish, firm, mass/ASX	2.0	Tongue base	Surgical excision	NR
1986	Herzog et al., [12]	USA	Case report	1	15	Male	Normochromic, pedunculated lesion/ASX	1.0	Tongue dorsum	Surgical excision	NR
1987	Tohge et al., [13]	China	Case report	1	180	Male	NR	NR	NR	NR	NR
1990	Tamaki et al., [14]	China	Case report	1	15	Male	NR	NR	NR	NR	NR
1990	Kanekawa et al., [15]	Japan	Case report	1	36	Male	Congenital epulis	0.5	Tongue dorsum	NR	NR
1991	Seki et al., [16]	Japan	Case report	1	27	Female	Congenital epulis	0.8	Median maxillary	NR	NR
1991	Nishihara et al., [17]	Japan	Case report	1	Newborn	Male	NR	NR	NR	NR	NR
1992	Ng et al., [18]	Malasya	Case report	1	3	Female	Sessile mass/ASX	0.9	Anterior maxillary alveolar ridge	Surgical excision	NR
1993	Semba et al., [2]	Japan	Case report	1	26	Male	Normochromic, polypoid mass/ASX	0.5	Anterior maxillary alveolar ridge	Surgical excision	60 No
1994	Misawa et al., [19]	Japan	Case report	1	19	Female	Congenital epulis	0.3	Median maxillary	NR	NR
1995	Goldsmith et al., [20]	United Kingdom	Case report	1	16	Male	Pinkish, polypoid mass/ASX	NR	Tongue dorsum	Surgical excision	18 No
1996	Napier et al., [21]	United Kingdom	Case report	1	60	Female	Pinkish, sessile, firm mass/ ASX	1.0	Hard palate, left side	Surgical excision	12 No
1999	de la Rosa-García and Mosqueda-Taylor et al., [22]	Mexico	Case report	1	72	Male	Smooth, pedunculated, tubular tumor/ASX	1.3	Tip of the tongue	Surgical excision	12 No
2000	Takeda et al., [23]	Japan	Case report	1	10	Male	Pedunculated lesion/ASX	0.6	Anterior maxillary alveolar ridge	Surgical excision	NR
2001	Kobayashi et al., [24]	Japan	Case report	1	3	Male	Normochromic, pedunculated lesion/ASX	1.4	Tongue dorsum	Surgical excision	24 No

Table 2 (continued)

Year	Author's	Country	Study type	No. Cases	Age (Mo)	Gender	Clinical aspect	Size (cm)	Location	Treatment	Follow-up/ Relapse
2001	Corrêa et al., [25]	Brazil	Case report	1	72	Female	Normochromic, pedunculated, firm nodule/ASX	0.5	Anterior maxillary alveolar ridge	Surgical excision	NR
2005	Kujan et al., [26]	United Kingdom	Case report	1	11	Male	Normochromic, sessile, firm, nodule/ASX	1.0	Anterior maxillary alveolar ridge	Surgical excision	NR
2007	Kreiger et al., [27]	USA	Case series	5	8 days 4 5 12 60	Male Female Female Male Male	Pinkish, pedunculated, nodules/ASX	0.1–2	Tongue dorsum	Surgical excision	NR
2007	Zaitoun and Triantfyllou [28]	United Kingdom	Case report	1	96	Male	Pinkish, pedunculated, smooth, polypoid lesion/ ASX	0.6	Anterior maxillary alveolar ridge	Surgical excision	6 No
2007	Goold et al., [29]	USA	Case report	1	5	Male	Yellowish, smooth, mass/ ASX	2.3	Tongue base	Surgical excision	NR
2007	Iida et al., [30]	Japan	Case report	1	31	Male	3 lesions Smooth, firm, polypoid masses/ASX	0.5; 0.4; 0.2	1 = Anterior maxillary alveolar ridge 2 = Tongue dorsum	Surgical excision	NR
2007	Scarpelli et al., [31]	Brazil	Case report	1	6	Female	Normochromic, smooth, fibrous polyp/ASX	0.3	Maxillary alveolar ridge	Surgical excision	7 No
2008	Nava-Villalba et al., [32]	Mexico	Case series	2	228 5	Female Male	Normochromic, pedunculated, smooth, firm, polypoid lesion/ASX	0.5 0.7	Anterior maxillary alveolar ridge and Tongue dorsum	Surgical excision	6 60 No
2008	De Faria et al., [33]	Brazil	Case report	1	732	Female	Pinkish, pedunculated lesion/ASX	4	Tongue dorsum	Surgical excision	12 No
2009	McGuff et al., [34]	USA	Case report	1	240	Male	NR	1.0	Anterior maxillary alveolar ridge	Surgical excision	NR
2010	Hahn et al., [35]	Denmark	Case report	1	24	Female	Pedunculated tubular tumor/ASX	1.6	Tongue base	Surgical excision	NR
2011	Zhang et al., [36]	Japan	Case report	1	18	Female	Normochromic, firm, polypoid mass/ASX	0.7	Anterior maxillary alveolar ridge	Surgical excision	24 No
2011	Vaidyanathan et al., [37]	United Kingdom	Case report	1	14	Female	White color, well circumscribed, mobile mass/ASX	1.5	Left lateral border of tongue	Surgical excision	24 No
2012	Kuperan et al., [38]	USA	Case report	1	5	Male	Pedunculated mass/ASX	0.5	Tongue dorsum	Surgical excision	24 No
2012	Nakanishi et al., [39]	Japan	Case report	1	36	Male	Normochromic, pedunculated, smooth mass/ASX	1.3	Tongue dorsum	Surgical excision	10 No
2012	Hsu and Hsu [40]	Taiwan	Case report	1	17	Female	Pedunculated, granular mass/ASX	1.5	Tongue base	Surgical excision	12 No
2013	AlQahtani and Qannam [41]	Saudi Arabia	Case report	1	18	Male	Pinkish, pedunculated, smooth, polypoid mass	1.3	Anterior maxillary alveolar ridge	Surgical excision	NR

Table 2 (continued)

Year	Author's	Country	Study type	No. Cases	Age (Mo)	Gender	Clinical aspect	Size (cm)	Location	Treatment	Follow-up/ Relapse
2013	Wang et al., [42]	Taiwan	Case report	1	348	Male	Reddish, exophytic, firm mass/ASX	2.0	Tongue dorsum	Surgical excision	48 No
2013	Falci et al., [43]	Brazil	Case report	1	3	Male	Reddish, pedunculated, smooth, firm multilobated nodule/ASX	2.0	Anterior maxillary alveolar ridge	Surgical excision	24 No
2014	Damm et al., [44]	USA	Case report	1	NR	NR	Nodule	NR	Anterior maxillary alveolar ridge	Surgical excision	NR
2014	Majumder et al., [45]	USA	Case report	1	Infant	Male	Normochromic, pedunculated, smooth, firm, mass/ASX	0.7	Tongue dorsum	Surgical excision	NR
2016	Raghunath et al., [46]	India	Case report	1	195	Female	Reddish, sessile, smooth, ovoid, mass	2.0	Anterior maxillary alveolar ridge	Surgical excision	NR No
2016	Fadzilah et al., [47]	Malaysia	Case report	1	2	Male	Pinkish, pedunculated mass	1.5	Tongue base	Surgical excision	NR No
2016	da Silva et al., [48]	USA	Case report	1	48	Female	Pinkish, smooth nodule	0.5	Anterior maxillary alveolar ridge	Surgical excision	NR
2017	Loomba et al., [49]	India	Case report	1	24	Female	Pedunculated, firm mass	2.5	Anterior maxillary alveolar ridge	Surgical excision	NR No
2017	Dhua et al., [50]	India	Case report	1	5	Male	Smooth, ovoid mass	1.5	Tongue dorsum	Surgical excision	12 No
2018	Nguyen et al., [51]	Australia	Case report	1	240	Male	Yellowish, exophytic, polypoid lesion	1.5	Tongue dorsum	Surgical excision	NR
2019	Sánchez-Romero et al., [52]	Brazil Peru Brazil Brazil	Case series	4	120 180 36 48	Female Female Male Female	Normochromic, sessile nodule Yellowish, sessile nodule Normochromic, pedunculated nodule Sessile, nodule/ASX	1.0 1.2 0.5 0.6	Tongue dorsum Anterior maxillary alveolar ridge Tongue dorsum Tongue dorsum	Surgical excision	NR No
2022	Montero et al., [53]	Spain	Case report	1	2	Female	Tumor of hard consistency	1.0	Tongue dorsum	Surgical excision	NR No
2022	Pérez-de-Oliveira et al., [54]	Brazil	Case series	2	48 9	Female Male	Normochromic, smooth, nodule	1.0 NR	2 = Tongue dorsum	Surgical excision	NR No
2024	Yaconskie et al., [55]	USA	Case series	3	1 180 48	Female Male Female	Pinkish, cylindrical nodule Normochromic, smooth sessile mass Normochromic, smooth, bilobed nodule	1.2 1.5 1.0	3 = Anterior maxillary alveolar ridge	Surgical excision	4 11 NR No

Abbreviations: NR Not reported, *Mo* Months, *ASX* Asymptomatic, Follow-up (months) and Relapse (Yes or No)

abstracts of the remaining articles, 3,896 records were excluded for not meeting the selection criteria. Fifty-six articles were assessed for eligibility by reading the full text, and one article was eliminated due to the report of a case of OLH present in an anatomic site other than those comprising the oral cavity (nasopharynx) [58]. Therefore, a total of 55 articles were included for the qualitative analysis of the present review. Details of the study selection are shown in Fig. 1.

Fifty case reports [1–26, 28–31, 33–51, 53, 55] and 5 case series [27, 32, 52, 54, 55] in the medical literature were reviewed in this study. All included papers were published in the english literature [1–55]. The total number of subjects studied in the included investigations was sixty-six. The ages of the subjects ranged from 1 month of birth to 61 years, with a mean age ± (SD) of 71.23 ± 123.01 months (6 years). The 50.7% were males and the remainder (49.3%) were females. The 55 articles were published in 13 different countries [1–55]. Fourteen (25.45%) studies were conducted in USA [1, 3, 4, 8, 11, 12, 27, 29, 34, 38, 44, 45, 48, 55] and Japan [2, 4, 6, 9, 10, 14–16, 19, 23, 24, 30, 36, 39], six (10.90%) studies in Brazil [25, 31, 33, 43, 43, 52, 54], five (9,09%) studies in UK [20, 21, 26, 28, 37], three (5.45%) studies in China [7, 13, 14] and India [46, 49, 50], two (3.63%) studies in Malaysia [18, 47], Mexico [22, 32] and Taiwan [40, 42], and other studies (1.81%) in Denmark [35], Saudi Arabia [41], Australia [51] and Spain [53] (Table 2).

Clinicopathologic features

Of the OLH studied, 24.24% have a normochromic appearance, 30.30% are smooth surface, 31.81% have a pedicled base, 22.72% are of firm consistency, with an average size of 1.20 ± 0.77 cm. Most (31.81%) of the OLH were located in the midline of the lingual dorsum, followed by the maxillary anterior alveolar ridge (30.30%). Treatment consisted of surgical excision (78.46%) and in half of the reported studies (50%), there were no recurrences of the lesion (Table 3).

Immunohistochemical features

In relation to the immunohistochemical profile, spindle smooth muscle cells were positive for desmin, SMA, MSA, caldesmon, CD34, collagen IV and calpontin. The stromal fibroblastic cells were positive only for vimentin and CD117. Meanwhile, the peripheral nerve fibers were positive for S-100 protein and CD34 (Table 4).

Quality assessment

According to the criteria established by JBI, 35 (63.3%) articles were of good quality [1–3, 5, 6, 8, 11, 18, 20–24, 28, 31–33, 36, 38–43, 45–50, 54, 55]. The rest (20/36.7%) were of fair quality [4, 7, 9, 10, 12–17, 19, 25, 26, 29, 30, 34, 35, 37, 44, 51] (Tables 5 and 6).

Table 3 Summary of clinicopathological data for oral leiomyomatous hamartoma

Parameters	Values	%
Papers	55	
Total cases	66	
Age (*months*)		
Mean ± Standard deviation	71.23 ± 123.01	
Range	0–732 (61 years)	
Gender (*n* = 65)		
Male	33	50.7
Female	32	49.3
Clinical aspects		
Color		
Normochromic	16	24.24
Pinkish	10	15.15
Grayish	2	3.03
Yellowish	4	6.06
Reddish	3	4.54
White	1	1.51
NR	30	45.45
Surface		
Smooth	20	30.30
NR	46	69.69
Base		
Pedunculated	21	31.81
Sessile	9	13.63
NR	36	54.54
Consistency		
Firm	15	22.72
NR	51	77.27
Size (cm)	1.20 ± 0.77	
Location		
Tongue base	9	13.63
Tongue tip	2	3.03
Tongue dorsum (Midline)	21	31.81
Lateral border of tongue	1	1.51
Anterior maxillary alveolar ridge (incisive papilla)	20	30.30
Median maxillary	5	7.57
Hard palate	1	1.51
NR	7	10.60
Treatment		
Surgical excision	51	78.46
NR	9	21.54
Follow-up (months)	17.04 ± 14.35	
Relapse		
No	33	50
Yes	0	-
NR	33	50

Abbreviations: NR Not reported

Table 4 Immunohistochemical profile of oral leiomyomatous hamartoma

Immunomarker	Biological function	Main observations
Desmin [60]	Muscle-specific type III intermediate filament. Plays a crucial role in maintaining the structure of sarcomeres, interconnecting the Z-disks and forming the miofibrillas, linking them not only to the sarcolemmal cytoskeleton, but also to the nucleus and mitocondrias	+ Smooth muscle spindle cells [18, 22, 23, 25, 26, 28, 30, 32, 36, 37, 40, 41, 43, 46, 52, 55]
Vimentin [61]	Vimentins are class-III intermediate filaments found in various non-epithelial cells, especially mesenchymal cells. Vimentin is attached to the nucleus, endoplasmic reticulum, and mitochondria, either laterally or terminally	+ Stromal fibroblastic cells [18, 30, 39, 46]
S-100 protein [62]	Small zinc- and- and calcium-binding protein that is highly expressed in astrocytes and constitutes one of the most abundant soluble proteins in brain	+ Peripheral nerve fibers [18, 22, 23, 25, 26, 28, 30–33, 36, 42, 43, 46, 51, 52, 54, 55]
SMA [63]	The alpha actins are found in muscle tissues and are a major constituent of the contractile apparatus	+ Smooth muscle spindle cells [22–28, 30–33, 36, 38, 39, 41–43, 46, 48, 50–52, 54, 55]
MSA [64]	Specific for smooth muscle cells, myofibroblasts and myoepithelial cells. It is useful for the identification of smooth muscle tumors	+ Smooth muscle spindle cells [31, 32, 42, 52]
Glial fibrillary acidic protein [64]	A class-III intermediate filament, is a cell-specific marker that, during the development of the central nervous system, distinguishes astrocytes from other glial cells	- Smooth muscle spindle cells, stromal and nerves components [23, 33]
Neuron-specific enolase [65]	Has neurotrophic and neuroprotective properties on a broad spectrum of central nervous system neurons. Binds, in a calcium-dependent manner, to cultured neocortical neurons and promotes cell survival	- Smooth muscle spindle cells [23]
Caldesmon [66]	Actin- and myosin-binding protein implicated in the regulation of actomyosin interactions in smooth muscle and non-muscle cells (could act as a bridge between myosin and actin filaments). Stimulates actin binding of tropomyosin which increases the stabilization of actin filament structure	+ Smooth muscle spindle cells [28, 52, 54]
CD34 [52]	Adhesion molecule with a role in early hematopoiesis by mediating the attachment of stem cells to the bone marrow extracellular matrix or directly to stromal cells	+ Smooth muscle spindle cells [52] and Peripheral nerve fibers [28] + Endothelial cells [52, 54]
Human factor XIII [67]	Factor XIII is activated by thrombin and calcium ion to a transglutaminase that catalyzes the formation of gamma-glutamyl-epsilon-lysine cross-links between fibrin chains, thus stabilizing the fibrin clot	+ Stromal fibroblastic cells [43]
CD117 [68]	Tyrosine-protein kinase that acts as a cell-surface receptor for the cytokine KITLG/SCF and plays an essential role in the regulation of cell survival and proliferation, hematopoiesis, stem cell maintenance, gametogenesis, mast cell development, migration and function, and in melanogenesis	+ Stromal fibroblastic cells [28]
Laminin [69]	Mediate the attachment, migration and organization of cells into tissues during embryonic development by interacting with other extracellular matrix components	- Smooth muscle spindle cells [28]
Colagen IV [70]	It forms the scaffolding of the basement membranes on which the cells of the epithelia and endothelia sit and which even surround the muscle fibers	+ Smooth muscle spindle cells [28]
Ki67 [71]	Cell cycle regulation	+ Lower layers of the epithelium [28] < 1% in all components of the lesion and negative in the smooth muscle cells [52]
Melanosome [28]	Melanin synthesis, storage and transport	- Smooth muscle spindle cells, stromal and nerves components [28, 33]
Calpontin [72]	Thin filament-associated protein that is implicated in the regulation and modulation of smooth muscle contraction	+ Smooth muscle spindle cells [52]
CD31 [73]	Cell adhesion molecule which is required for leukocyte transendothelial migration under most inflammatory conditions	- Smooth muscle spindle cells, stromal and nerves components [33]

Abbreviations: + Positive,—Negative immunostaining, *SMA* Alpha-smooth muscle actina, *MSA*/*HHF35* Muscle specific actin, *CD34* Cluster of differentiation 34, *CD117* Cluster of differentiation 117, *CD31* Cluster of differentiation

Discussion

The study published by Kreiger et al., in which they evaluated a total of 135 lesions on the tongue showed that 18 cases were diagnosed as hamartomas and of these, only 5 cases were diagnosed as leiomyomatous hamartomas (incidence of 3.70%) [27]. On the other hand, a

Table 5 Results of the quality assessment for cases reports

No	Authors	Q.1	Q.2	Q.3	Q.4	Q.5	Q.6	Q.7	Q.8	Overall Score and Quality
1	Stamm and Tauber [1]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
2	Perri et al., [3]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
3	Takahashi et al., [4]	Y	Y	Y	U	U	N	N	Y	4 (Fair)
4	Hinshaw et al., [5]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
5	Ishii et al., [6]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
6	Yamashita et al., [7]	Y	Y	Y	U	U	N	N	Y	4 (Fair)
7	Demuth and Johns [8]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
8	Mushimoto et al., [9]	Y	Y	Y	U	U	N	N	Y	4 (Fair)
9	Kajiyama et al., [10]	Y	Y	Y	U	U	N	N	Y	4 (Fair)
10	Becker et al., [11]	Y	Y	Y	Y	Y	N	N	Y	6 (Good)
11	Herzog et al., [12]	Y	Y	Y	U	U	N	N	Y	4 (Fair)
12	Tohge et al., [13]	Y	Y	Y	U	U	N	N	Y	4 (Fair)
13	Tamaki et al., [14]	Y	Y	Y	U	U	N	N	Y	4 (Fair)
14	Kanekawa et al., [15]	Y	Y	Y	U	U	N	N	Y	4 (Fair)
15	Seki et al., [16]	Y	Y	Y	U	U	N	N	Y	4 (Fair)
16	Nishihara et al., [17]	Y	Y	Y	U	U	N	N	Y	4 (Fair)
17	Ng et al., [18]	Y	Y	Y	Y	Y	N	N	Y	6 (Good)
18	Semba et al., [2]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
19	Misawa et al., [19]	Y	Y	Y	U	U	N	N	Y	4 (Fair)
20	Goldsmith et al., [20]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
21	Napier et al., [21]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
22	de la Rosa-García and Mosqueda-Taylor et al., [22]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
23	Takeda et al., [23]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
24	Kobayashi et al., [24]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
25	Correa et al., [25]	Y	Y	Y	Y	U	N	N	Y	5 (Fair)
26	Kujan et al., [26]	Y	Y	Y	Y	U	N	N	Y	5 (Fair)
28	Zaitoun and Triantfyllou [28]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
29	Goold et al., [29]	Y	Y	Y	Y	U	N	N	Y	5 (Fair)
30	Iida et al., [30]	Y	Y	Y	Y	Y	U	N	Y	6 (Fair)
31	Scarpelli et al., [31]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
33	De Faria et al., [33]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
34	McGuff et al., [34]	Y	Y	Y	U	U	N	N	Y	4 (Fair)
35	Hahn et al., [35]	Y	Y	Y	U	U	N	N	Y	4 (Fair)
36	Zhang et al., [36]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
37	Vaidyanathan et al., [37]	Y	U	Y	Y	Y	U	N	Y	5 (Fair)
38	Kuperan et al., [38]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
39	Nakanishi et al., [39]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
40	Hsu and Hsu [40]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
41	AlQahtani and Qannam [41]	Y	Y	Y	Y	Y	U	N	Y	6 (Good)
42	Wang et al., [42]	Y	Y	Y	Y	Y	Y	Y	Y	8 (Good)
43	Falci et al., [43]	Y	Y	Y	Y	Y	Y	N	Y	8 (Good)
44	Damm et al., [44]	Y	Y	Y	U	U	N	N	Y	4 (Fair)
45	Majumder et al., [45]	Y	Y	Y	Y	Y	U	N	Y	6 (Good)
46	Raghunath et al., [46]	Y	Y	Y	Y	Y	U	N	Y	6 (Good)
47	Fadzilah et al., [47]	Y	Y	Y	Y	Y	Y	N	Y	7 (Good)
48	da Silva et al., [48]	Y	Y	Y	Y	Y	Y	Y	Y	8 (Good)
49	Loomba et al., [49]	Y	Y	Y	Y	Y	Y	Y	Y	8 (Good)

Table 5 (continued)

No	Authors	Q.1	Q.2	Q.3	Q.4	Q.5	Q.6	Q.7	Q.8	Overall Score and Quality
50	Dhua et al., [50]	Y	Y	Y	Y	Y	Y	Y	Y	8 (Good)
51	Nguyen et al., [51]	Y	Y	Y	Y	U	U	N	Y	5 (Fair)
53	Montero et al., [53]	Y	Y	Y	Y	Y	Y	Y	Y	8 (Good)

Question (Q); *N/A* Not aplicable, Y Yes, N No, U Unclear

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 unanticiped events identified and described?

Q.8: Does the case report provide takeway lessons?

Quality Rating: Poor: 0–2, Fair: 3–5 and Good: 6–8

more recent study, which evaluated 9 hamartomas in the tongue of pediatric patients, showed that only two cases (22.22%) were of the leiomyomatous type [54]. It is important to note that the incidence of this pathology is low, because it is a condition that occurs infrequently, which is why it is difficult to determine from the available literature. However, since most of the research was published after 2007, the incidence is probably increasing due to a higher level of knowledge and awareness on the part of clinicians and researchers in the area, which leads to a more accurate diagnosis [27–55].

In our study, the mean age of presentation was 71.23 ± 123.01 months (6 years), with no gender predilection (male-to-female ratio of 1:1), which is consistent with information reported in the literature [1–55]. In general, most OLH are diagnosed at birth [1, 11, 17]. Despite this, a case reported by de Faria et al., demonstrated the presence of an OLH in a 61-year-old systemically healthy woman, who reported having had the lesion since birth. The lesion presented slow growth until puberty and thereafter, no change in size. Later, the presence of dysphagia, dysphonia and dyspnea forced the patient to seek medical assistance [33]. This explains the

Table 6 Results of the quality assessment for cases series

No	Authors	Q.1	Q.2	Q.3	Q.4	Q.5	Q.6	Q.7	Q.8	Q.9	Q.10	Overall Score and Quality
27	Kreiger et al., [27]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10 (Good)
32	Nava-Villalba et al., [32]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10 (Good)
52	Sánchez-Romero et al., [52]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10 (Good)
54	Pérez-de-Oliveira et al., [54]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10 (Good)
55	Yaconskie et al. [55],	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10 (Good)

Question (Q); N/A, not aplicable; Y, yes; N, no; U, unclear

Q.1: Where there clear criteria for inclusion in the case series?

Q.2: Was the condition measured in a standard, reliable way for all participants included in the case series?

Q.3: Were valid methods used for identification of the condition for all participants included in the case series?

Q.4: Did the case series have consecutive inclusion of participants?

Q.5: Did the case series have complete inclusion of participants?

Q.6: Was there clear reporting of the demographics of the participants in the study?

Q.7: Was there reporting of clinical information of the participants?

Q.8: Were the outcomes or follow up results of cases clearly reported?

Q.9: Was there clear reporting of the presenting sites(s)/clinics(s) demographic information?

Q.10: Was statistical analysis appropriate?

Quality rating: Poor: 0–3, Fair: 4–7 and Good: 8–10

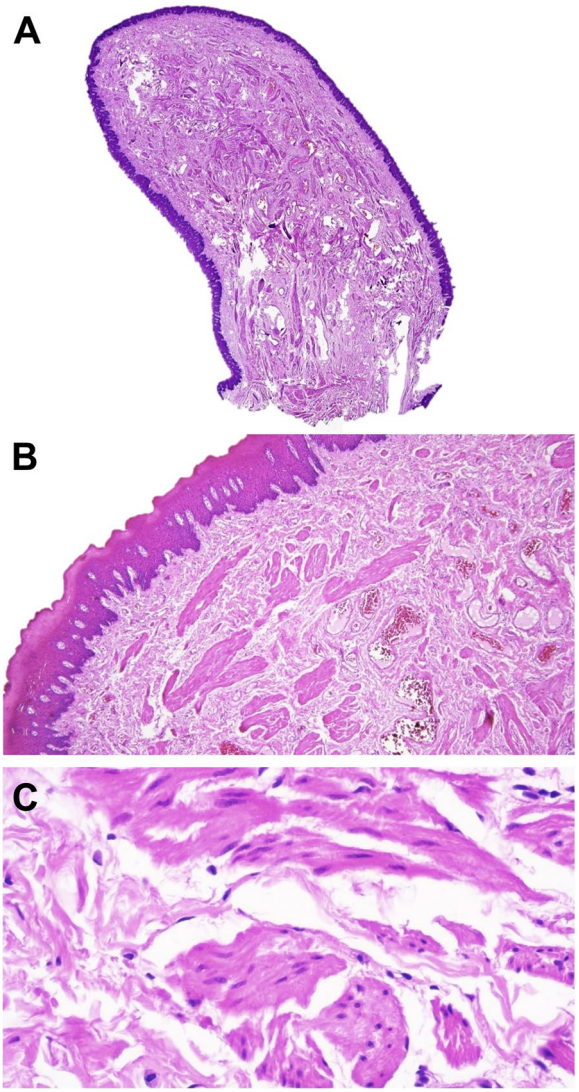

Fig. 2 Histopathological features of OLH. **A** Shows a polypoid lesion composed of multiple fascicles of smooth muscle tissue, of variable size and erratic direction, accompanied by blood vessels mainly arterial and towards its central part, as well as towards its base they become venous. venous type (H&E × 10). **B** Shows fascicles of smooth muscle tissue arranged in random directions and immersed in a fibrous stroma, covered by stratified squamous epithelium (H&E × 200). **C** Shows numerous short fascicles of smooth muscle tissue, immersed in a stroma of dense fibrous connective tissue, well vascularized (×400)

benign (asymptomatic) behavior of OLH. Therefore, the presence of these growths in the geriatric population happens when there is no early diagnosis (lack of training by the treating physician) and consequent treatment plan or simply when the individual ignores them [52].

This benign tumor-like malformation presents as a single, normochromic, smooth-surfaced, well-defined, pedunculated and/or sessile-based, asymptomatic, firm-consistency enlargement with an average size of 1.20 cm in diameter, present on the midline of the posterior third of the tongue and/or maxillary anterior alveolar ridge [1–55]. Two cases have been published in the literature on the presence of multiple OLH lesions. On the one hand, Ishii et al., reported the presence of four lesions in a four-month-old girl, with a tumor-like appearance, grayish color, smooth surface and firm consistency, located at the base of the tongue on the right side, on the tip and dorsum of the tongue on the left side [6]. Iida et al., reported the presence of three lesions in a three-month-old child, with a polypoid appearance, smooth surface, firm consistency and asymptomatic, located in the region of the incisal papilla and dorsum of the tongue [30]. Therefore, it is advisable to perform a detailed and very thorough intraoral examination for another location, due to the multiple occurrence of this disease. Generally, they are indolent lesions and may present as bilobulated nodules [55], with a pink, yellowish, reddish or grayish color [1, 3, 5, 6, 11, 20, 21, 24–29, 31–33, 36–48, 51, 52, 54, 55]. Some tumor masses have a sessile base [18, 21, 52] and in relation to their size, the smallest OLH reported in the literature was 0.2 cm [30], up to 4 cm lesions [33].

Microscopically, OLH is characterized as a tissue containing a diffuse proliferation of fascicles and bundles of eosinophilic spindle cells of variable size, oriented longitudinally and/or transversely, surrounded by a stratified squamous epithelium. Around the fascicles, connective tissue clefts can be observed. The fascicles and bundles are composed of spindle cells compatible with mature smooth muscle cells, with indefinite boundaries, elongated blunt ends and cigar-shaped nuclei. Fibroblast-like cells, blood vessels, adipose tissue, glandular tissue and nerve fibers can also be observed in the stroma [1–55] (Fig. 2).

The immunohistochemical profile of OLH includes the use of biomarkers such as desmin, smooth muscle alpha actin, muscle-specific actin, caldesmon, CD34, collagen IV and calpontin, positive for smooth muscle spindle cells [18, 22–28, 30–33, 36, 38, 39, 41–43, 46, 48, 50–52, 54, 55]. Neuron-specific enolase, laminin, melanosome and CD31 were negative for this cell type [23, 28, 33]. Vimentin, human factor VIII and CD117 were positive for stromal fibroblast cells. S-100 protein was positive for peripheral nerve fibers [18, 22, 23, 25, 26, 28, 30–33, 36, 42, 43, 46, 51, 52, 54, 55] and CD34 was positive for endothelial cells [52, 54]. These markers prove to be useful in differentiating OLH from other smooth muscle tumors. In addition, OLH shows a low proliferation index (Ki-67 = < 1%), which justifies the slow and noninvasive growth of the lesion [28, 52].

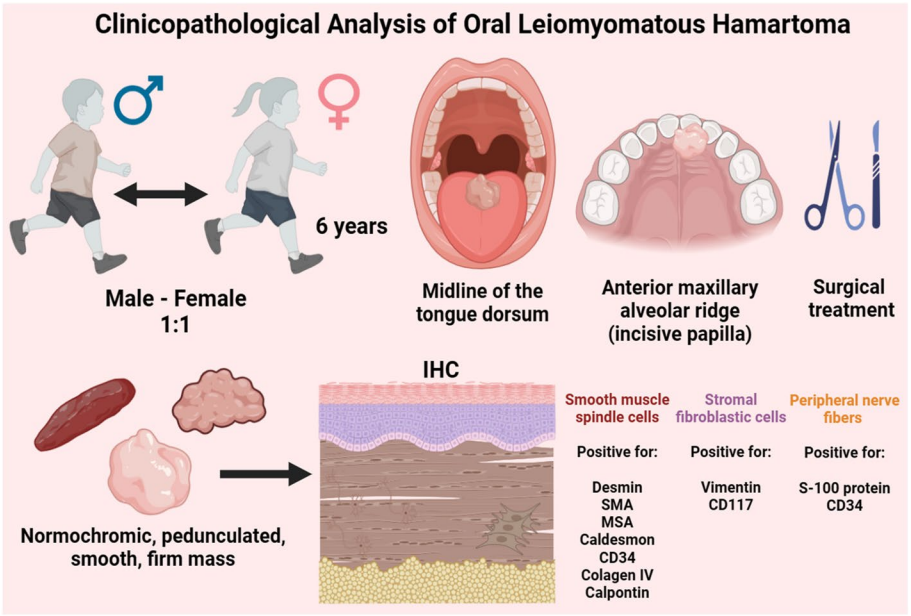

Fig. 3 Summary of the clinicopathological and immunohistochemical features of oral leiomyomatous hamartoma. Abbreviations: IHC immunohistochemistry; SMA Alpha-smooth muscle actina; MSA Muscle specific actin; CD34 Cluster of differentiation 34; CD117 Cluster of differentiation 117; CD34 Cluster of diferrentiation 34

Hamartomas correspond to benign overgrowths of mature, differentiated tissue specific to the anatomic area in which it develop. Most of them are located in the pancreas, spleen, liver, lungs, nasopharynx and oral cavity. They are classified as epithelial, mesenchymal and mixed (epithelial and mesenchymal). Mesenchymal hamartomas can be subdivided according to the tissue that predominates in their constitution, thus leiomyomatous hamartomas are the most common subtype in the oral cavity [59]. According to the clinical appearance, histopathologic features and immunohistochemical profile OLH should be differentiated from other soft tissue lesions such as lingual thyroid and thyroglossal duct cyst, fibroma, neurofibroma, fibromyxoma, fibromyoma, rhabdomyoma, angioma, lymphangioma, leiomyoma and leiomyosarcoma [1, 33, 44, 46–55].

The best treatment modality for OLH is surgical excision, as it results in complete resolution of the lesion [1–55]. In fact, in the hands of expert surgeons and unlike the incisional biopsy that only takes a part of the lesion for study, surgical excision is a safe, reliable technique, with good aesthetic and functional results, which allows the patient to improve his quality of life [74]. The prognosis is excellent, in half of the reported cases, no signs of recurrence were observed [1, 2, 8, 20–22, 24, 28, 31–33, 36–40, 42, 43, 46, 47, 49, 50, 52–55].

One of the main limitations of the present study was the lack of detailed information in the reports and case series, mainly in relation to the post-surgical condition of the individual, if he/she had presented any type of adverse event, as well as a short-term follow-up, which could have led to underestimate some of the results found. For this reason, the importance of publishing reports and case series of higher quality is emphasized.

This new information about the clinicopathological characteristics of OLH will be relevant for the clinician in understanding its pathobiology and for the clinical behaviour to be followed in this type of benign hamartomas.

Conclusion

In conclusion, the present systematic review showed that the 66 cases of OLH reported in the medical literature to date present a well-defined clinicopathologic and immunohistochemical profile. The lesions are asymptomatic, normochromic, pedunculated base and a firm consistency. It is important to mention that it frequently occur in the midline of the dorsum of the tongue and/or in the anterior parte of the alveolar ridge of the maxilla. Despite their benign behavior, it is important to identify their distinctive presentation to avoid misdiagnosis and thus provide adequate treatment (Fig. 3).

Abbreviations

OLH	Oral leiomyomatous hamartoma
SMA	Alpha-smooth muscle actina
MSA	Muscle specific actin
CD34	Cluster of differentiation 34
CD31	Cluster of differentiation 31
CD117	Cluster of differentiation 117

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Authors' contributions
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Data availability
The data supporting this study's findings are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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