Tongue hamartomas in pediatric patients: an international case series and literature review

Running title: Tongue hamartomas in pediatric patients

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Compliance with Ethical Standards

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Abstract

This study reports 9 additional tongue hamartomas in children paired with a literature review. A retrospective analysis was performed from 3 Oral Pathology laboratories. Additionally, a literature review was conducted through 5 electronic databases and gray literature. A total of 9 cases were identified in the retrospective analysis. Females outnumbered males with a ratio of 1.25:1. The age of presentation ranged from 2 weeks to 7 years. The posterior dorsum tongue was the most affected subsite (n = 4). One case was seen in a patient with oro-facial-digital syndrome, 2 cases in patients with cleft palates, and one case with an encephalocele. The most common predominant component was salivary gland tissue (n = 4). A literature search included 79 pediatric patients presenting with 95 tongue hamartomas. A slight female (n = 47) predilection was observed, with ages varying from 15 hours to 19 years. The posterior tongue

dorsum (n = 31) was the most affected site. Seven cases were seen in association with syndromes. The most common predominant component was smooth muscle (n = 35). Although hamartomas are rare in the oral cavity, they should be considered in the differential diagnosis of masses involving the posterior tongue dorsum in children.

Keywords: hamartoma, pediatric patients, oral cavity, posterior tongue

Introduction

Hamartomas consist of a proliferation of mature normal tissues that are considered endogenous to the site of occurrence, being considered a tumor-like malformation [1]. The characteristic properties of hamartomas were first described by Albrecht [2] in 1904 who coined the term *hamartia defect*. Stamm and Tauber [3] later reported the first case of lingual hamartoma in 1945. In the oral cavity, hamartomas occur almost exclusively on the tongue dorsum, frequently affecting newborns and infants, and presenting as polyps or nodules. Microscopically, they present as an ill-defined mass, with hamartomatous tissue components intermingled with the normal tissue of the tongue [2].

Tröbs *et al.* [4], performed a retrospective review of oral tumors and tumor-like lesions in pediatric patients over a 30-year period, reporting a total of 95 lesions, of which 17 were considered hamartomatous. In the oral cavity, hemangiomas and lymphangiomas are relatively common compared to hamartomatous lesions composed of other tissues subtypes. Horn *et al.* [5], described 17 tongue lesions in children over a 10-year period, with only a single documented hamartoma. The current literature is scarce on the incidence and histopathological spectrum of tongue hamartomas in pediatric patients, excluding vascular malformations. Therefore, the aim of this study is to elaborate on the epidemiology, clinical features, and histopathological spectrum of

tongue hamartomas in pediatric patients based on an international series of 9 additional cases paired with a literature review.

Materials and Methods

Study design

A retrospective analysis of all hamartoma cases until August 2021 was performed from the pathological files of the Oral Pathology Laboratory of Piracicaba Dental School, University of Campinas, Piracicaba, Brazil; Oral Pathology Laboratory of the Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; and the Oral Pathology Laboratory of the University of Pretoria, Pretoria, South Africa. Inclusion criteria were cases of hamartomatous lesions located in the tongue arising in pediatric patients aged 0 to 19 years old. Hamartomas located in sites other than the tongue, vascular malformations, and cases arising in patients greater than 19 years of age were excluded. Clinical data, including age, sex, site and size of the lesion, clinical appearance, clinical diagnostic hypotheses, and treatment were recorded from the available clinical charts. All archived hematoxylin and eosin (H&E)-stained slides were reviewed for diagnostic confirmation and to record the hamartomatous tissue components in each of the cases. Immunohistochemical reactions were carried out in selected cases using 3-μm tissue sections on silanized slides for the following antibodies: smooth muscle actin (SMA), S100, and CD34.

Literature review

Search strategies were performed in May 2021 without time restriction and adapted for each of the following electronic databases: PubMed, Scopus, EMBASE,

Web of Science, and LILACS. A gray literature search was carried out on Google Scholar, OpenGrey, and ProQuest Dissertations & Theses Global **(Supplementary Table S1)**. Rayyan QCRI [6] was used as the reference manager to screen the articles and remove duplicates. Additionally, the reference lists of selected articles were hand-screened to identify potential manuscripts that could have been missed during the search strategy.

The articles describing the clinicopathological profile of tongue hamartomas in pediatric patients with an age range of 0–19 years diagnosed by histopathological examination were included. Exclusion criteria included (1) studies in which data regarding tongue hamartomas were not available due to grouping with other diseases or sites other than tongue; (2) reviews, protocols, personal opinions, conference abstracts, and laboratory research; (3) studies published in languages other than English, Portuguese or Spanish; and (4) studies whose full texts were not available.

The study selection was conducted in two phases. The first phase consisted of reading the titles and abstracts of all articles. The studies that met the eligibility criteria proceeded to the second phase, where full texts were assessed and the final selection of included articles was undertaken.

The data extracted from each included study were publication data, sample, clinical features, and histopathological characteristics.

Results

Clinical findings

A total of nine cases of tongue hamartomas in pediatric patients were identified. All cases were located in the submucosal connective tissue of the tongue dorsum, with four cases (44.4%) located in the posterior region. A slight female predilection was observed with a male-to-female ratio of 1:1.25. The age of patients ranged from 2 weeks to 7 years, with a mean age of 2.1 years. The majority of the patients presented clinically with an asymptomatic, smooth-surfaced, and normochromic tongue mass. One infant (case 6) presented with an erythematous lesion. Three cases were associated with syndromes or developmental anomalies, including oro-facial-digital syndrome (case 3), cleft palate (case 4), and cleft palate with an associated encephalocele (case 8). The size of the lesion at presentation was available in 3 cases, being 1.0 cm in case 1, 1.0 cm in case 2, and 0.5 cm in case 9 in maximum diameter. The time of evolution was only known in two cases, with case 2 being reported as congenital mass, and case 8 with a history of 12 months. Clinical diagnoses were reported in three cases, including ectomensenchymal chondromyxoid tumor or lingual thyroid (case 1), traumatic fibroma (case 6), and hyperplastic papilla (case 7). All cases were treated via surgical excision and no recurrences have since been reported.

Histopathological findings

All cases were covered by normal parakeratinized stratified squamous epithelium with focal areas of acanthosis. The lesions were ill-defined, intermixing with the normal tongue tissue. The most common histopathological spectrum was the presence of five concomitant components, including skeletal muscle, adipose tissue, salivary gland parenchyma, nerve bundles, and blood vessels (cases 4, 6, 7, and 8). In

these cases, salivary gland parenchyma represented the predominant component in three cases (cases 4, 7, and 8), and adipose tissue in a single case (case 6). Case 9 also presented with adipose tissue as the main component, however salivary gland parenchyma and blood vessels were also noted. Two cases presented with smooth muscle as a predominant component (cases 1 and 5), both showing blood vessels and adipose tissue, and one case (case 5) with the additional presence of nerve bundles. One case additionally contained focal hyaline cartilage (case 3), with another case presenting with a proliferation of fibrous connective tissue (case 8). Case 2 presented as a neurovascular hamartoma. Necrosis, cellular pleomorphism, and mitotic figures were not seen in any of the cases. The clinicopathological features and histopathological spectrum of all cases are summarized in **Table 1** and illustrated in **Fig. 1, Fig. 2.**

Immunohistochemistry was performed in two cases (**Figure 3**). Case 1 showed immunoreactivity for CD34 in the blood vessels, S100 in adipose tissue, and SMA in the smooth muscle component. Case 3 showed positivity for S100 in the adipose tissue and neural structures.

Literature review

The study selection process is summarized in **Figure 4** , and the demographical and clinical features of the 50 included studies detailed in **Table 2.** Fifty articles were included in the final selection, with 48 articles from databases, 1 [7] from gray literature, and 1 [3] from reference lists of included articles. The sample derived from these studies comprised a total of 79 cases and 95 lesions, derived from 41 case reports, 5 case series, 3 letters to the editor, and one correspondence **(Supplementary Table S2)**. The articles were published between 1945 [3] and 2021 [8]. The included studies originated from eighteen different countries: USA (16); Japan (11); UK (5); Italy (3); India (2); Mexico (2); Nigeria (2); Brazil and Peru (1); Chile (1); China (1); Israel (1);

Table 1. Clinicopathological features of the nine patients included in this case series

Case No.	*Origin*	*Sex*	*Age*	*Site*	*Clinical appearance*	*Predominant tissue component*	Component present in each hamartomatous lesion							*Syndromes/ abnormalities*
							Blood vessels	*Smooth muscle*	*Skeletal muscle*	*Adipose tissue*	*Salivary gland parenchyma*	*Nerve bundles*	*Cartilage*	
1	University of Campinas	F	4 y	Posterior dorsum tongue	Painless, smooth-surfaced, and normochromic nodule	Smooth muscle	X	X		X				
2	Federal University of Rio de Janciro	M	7 y	Anterior dorsum tongue	Painless, smooth-surfaced, and normochromic nodule	Nerve bundles	X					X		
3	University of Pretoria	F	1 y	Anterior dorsum tongue	Painless, smooth-surfaced, and normochromic nodule	Salivary gland	X		X	X	X	X	X	Oro-facial-digital syndrome
4	University of Pretoria	F	2 w	Anterior dorsum tongue	Painless, smooth-surfaced, and normochromic nodule	Salivary gland	X		X	X	X	X		Cleft palate
5	University of Pretoria	M	9 m	Middle dorsum tongue	Painless, smooth-surfaced, and normochromic nodule	Smooth muscle	X	X		X		X		
6	University of Pretoria	M	3 m	Middle dorsum tongue	Painless, smooth-surfaced, and erythematous nodule	Adipose tissue	X		X	X	X	X		
7	University of Pretoria	F	8 m	Posterior dorsum tongue	Painless, smooth-surfaced, and normochromic polyp	Salivary gland	X		X	X	X	X		
8	University of Pretoria	F	1 y	Posterior dorsum tongue	Painless, smooth-surfaced, and normochromic nodule	Salivary gland	X		X	X	X	X		Cleft palate; encephalocele
9	University of Pretoria	M	4 y	Posterior dorsum tongue	Painless, smooth-surfaced, and normochromic polyp	Adipose tissue	X			X	X			

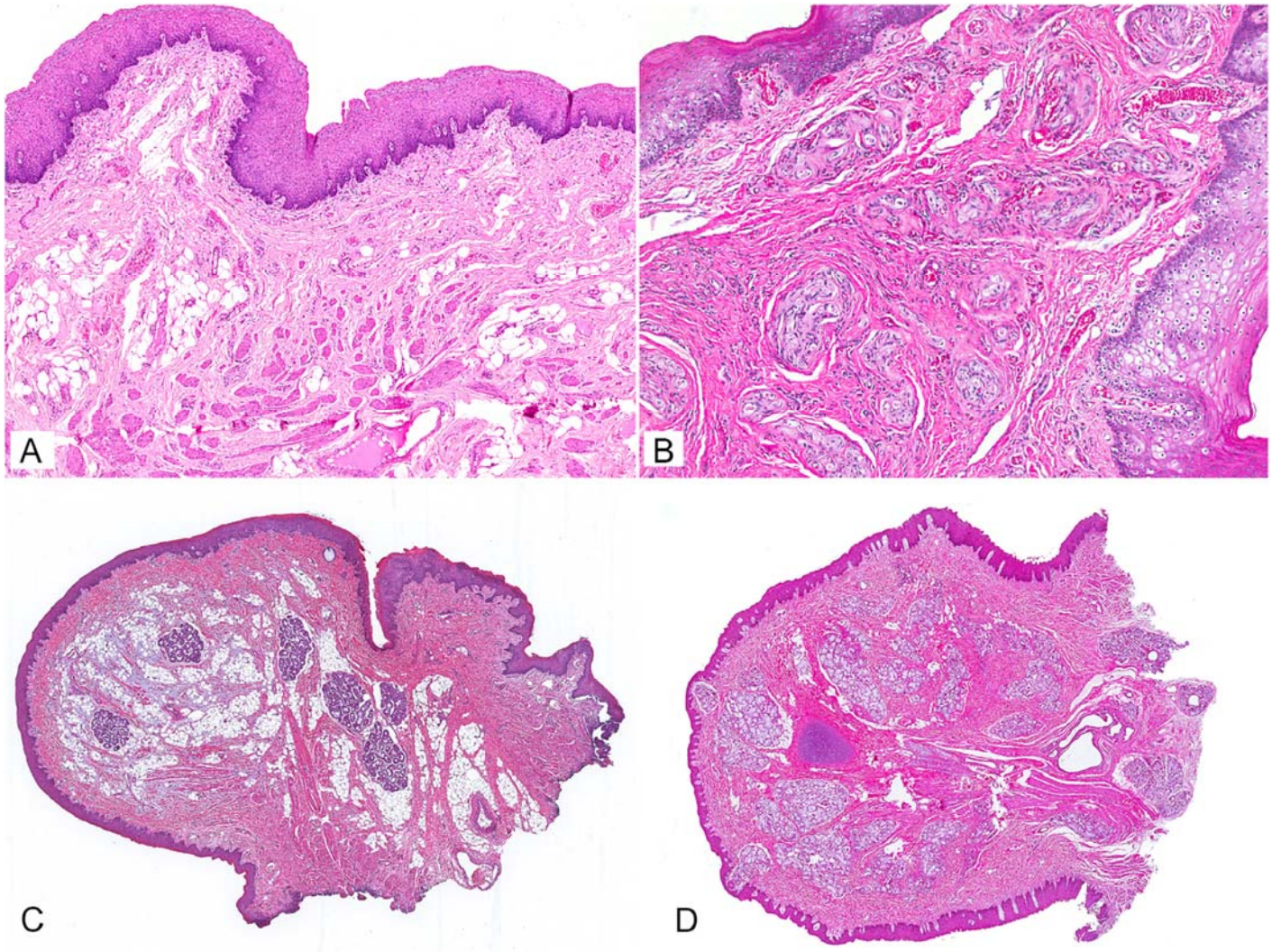
A
B
C
D

Figure 1 – Histopathological features of tongue hamartomas. A low-power magnification demonstrating an unencapsulated proliferation of disorganized hamartomatous tissue components merging with normal surrounding tissues. **(A)** Case 1 with smooth muscle as the predominant tissue component, in combination with adipose tissue and blood vessels (hematoxylin and eosin [H&E] stain, 2.5×). A high resolution of this slide is available as eSlide: VM06550. **(B)** Case 2 as neurovascular hamartoma, showing a proliferation of packed groups of nerve bundles and blood vessels (H&E stain, 5.0×). A high resolution of this slide is available as eSlide: VM06546. **(C)** Case 6 demonstrating adipose tissue as the predominant component, surrounded by salivary gland parenchyma, skeletal muscle, nerve bundles, and blood vessels (H&E stain, 2.0×). A high resolution of this slide is available as eSlide: VM06548. **(D)** Case 3 with salivary gland parenchyma as the predominant tissue component, in combination with adipose tissue, skeletal muscle, nerve bundles, blood vessels, and focal hyaline cartilage (H&E stain, 1.3×). A high resolution of this slide is available as eSlide: VM06547. Scale bar of A: 800 μm. Scale bar of B: 400 μm. Scale bar of C and D: 2 mm.

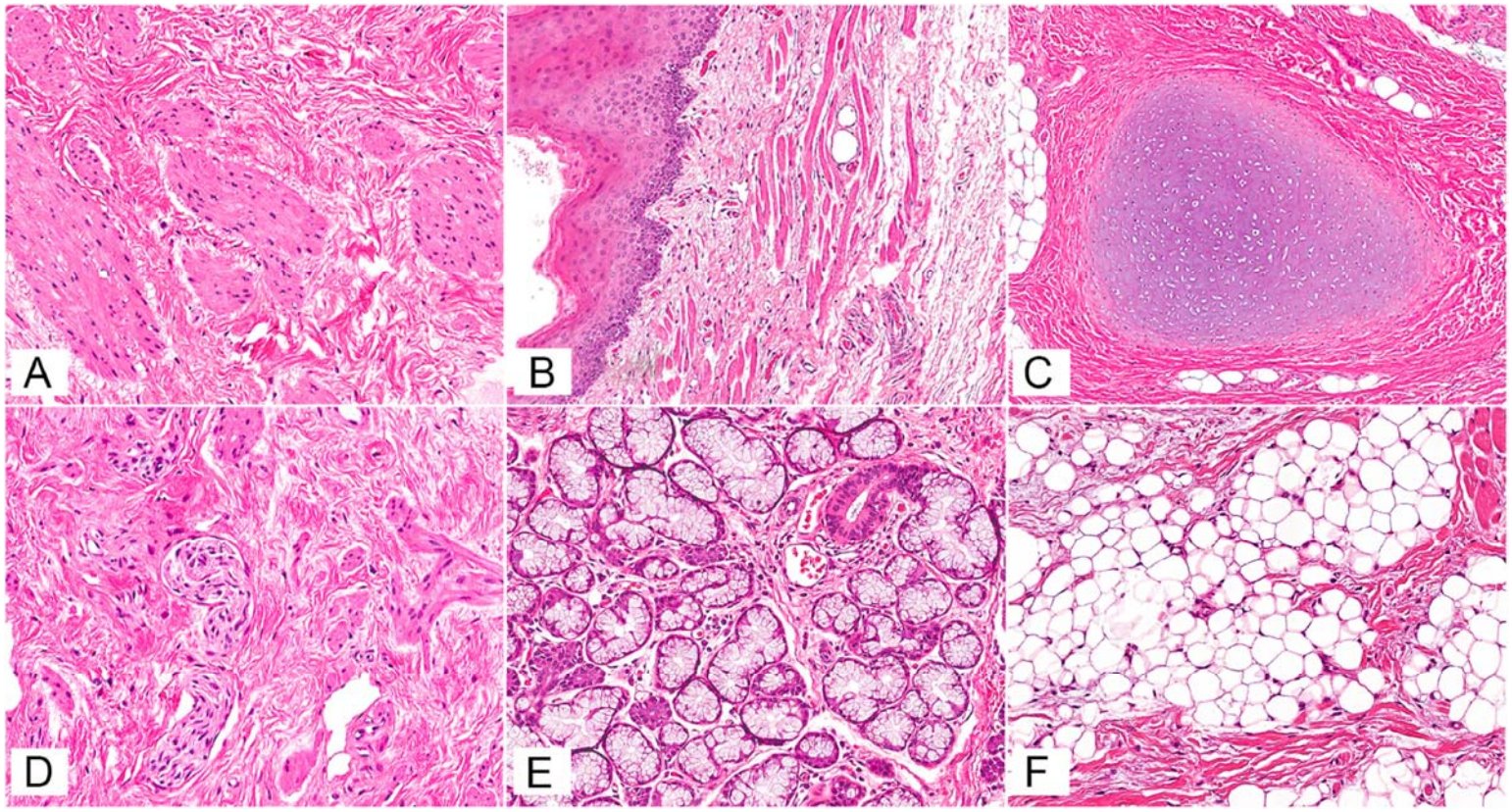

Fig. 2. A high-power magnification demonstrating individual hamartomatous tissue components. **(A)** Bundles of smooth muscle (Case 5: hematoxylin and eosin [H&E] stain, 20×). **(B)** Subepithelial proliferation of striated skeletal muscle fibers and blood vessels (Case 4: H&E stain, 20×). **(C)** Focal hyaline cartilage identified in a single case (Case 3: H&E stain, 10×). **(D)** Packed groups of nerve bundles (Case 5: H&E stain, 20×). **(E)** Salivary gland parenchymal tissue (Case 4: H&E stain, 20×). **(F)** Adipose tissue (Case 6: H&E stain, 20×). Scale bar of A, B, D, E and F: 200 μm. Scale bar of C: 300 μm.

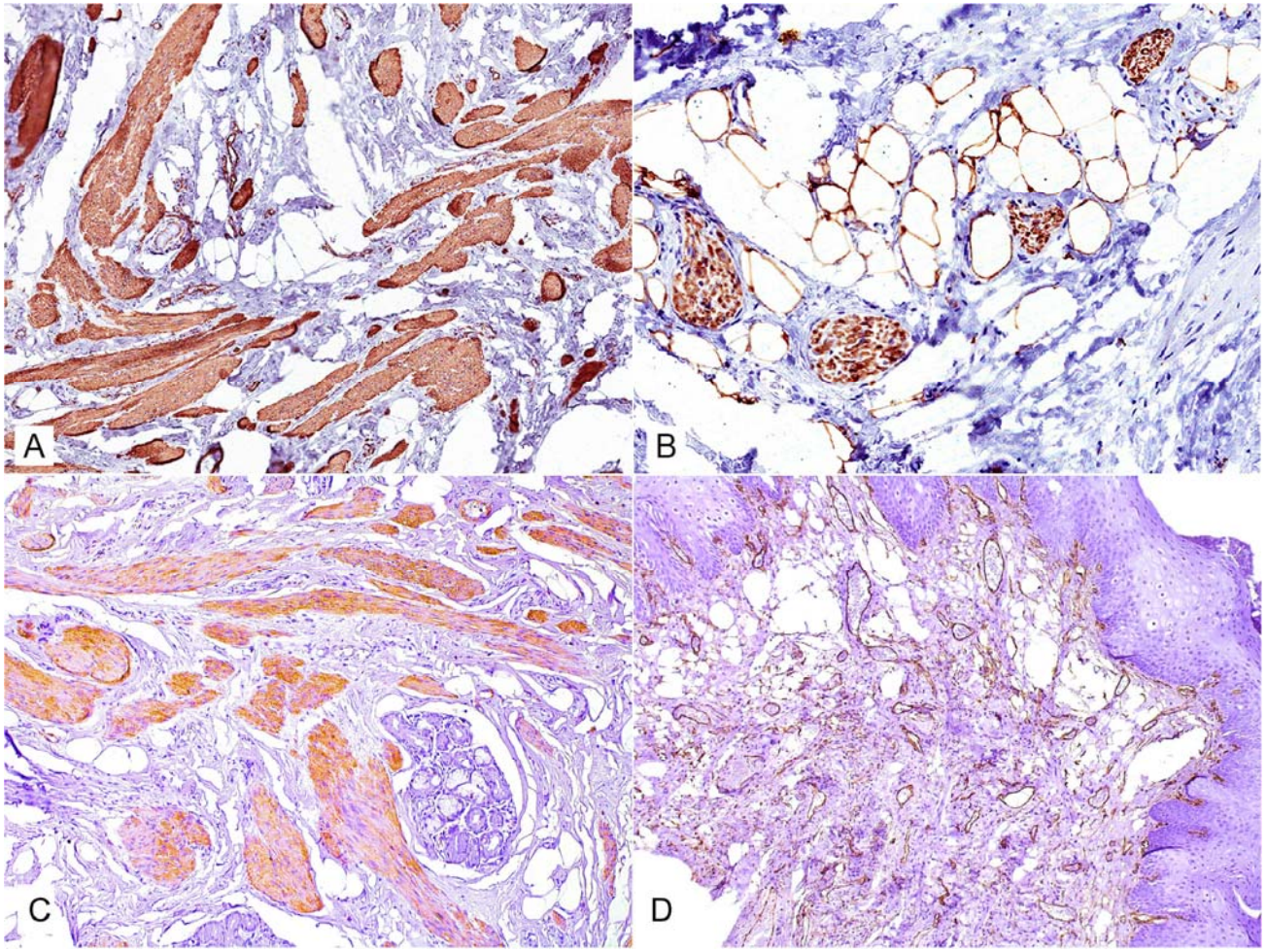

Fig. 3. Immunohistochemical features of tongue hamartomas (case 1). **(A)** Alpha-smooth muscle actin highlighting smooth muscle bundles (IHC, 10×). **(B)** S100 highlighting adipocytes (IHC, 20×). **(C)** h-Caldesmon highlighting smooth muscle bundles (IHC, 10×). **(D)** CD34 highlighting blood vessels (IHC, 10x).

Malaysia (1); Morocco (1); Norway (1); Taiwan (1); The Netherlands (1). The sample size of the included studies ranged from 1 to 18 patients. Ten patients had more than one lesion, in which 6 patients had 2 lesions [9-12], 3 patients had 3 lesions [13-15] and 1 patient had 4 lesions [16].

Females outnumbered males, with a ratio of 1.47:1. The patients' age ranged from 15 hours [17] to 19 years [18], with the majority occurring within the first 5 years of life (n=69; 87.3%). Regarding clinical characteristics, all lesions presented as an exophytic mass, varying from polypoid to nodular lesions. Most lesions appeared normochromic (n=35; 48.6%) with a smooth surface (n=56; 100%). The size of the lesions ranged from 0.1 cm [1] to 4.0 cm [9]. Most lesions were congenital (n=40 cases; 72.7%), however, those with a reported duration ranged from 3 months [16] to 83.75 months [19]. The posterior tongue dorsum (n=31; 32.6%) was the most frequently involved subsite. Eighteen patients (22.8%) reported symptoms, with dysphagia being described by 12 patients (57.2%). Fifteen patients (19.0%) presented an anomaly, including cleft palate (n=10; 41.7%) and bifid tongue (n=4; 16.6%). Seven cases (8.9%) [1, 10, 20, 21] presented with associated syndromes, with oro-facial-digital syndrome being described in 5 patients (71.4%). All cases were treated via surgical excision. The follow-up time ranged from 2 months 3, [8, 22, 23] to 144 months [8], with a mean period of 25.66 months and no reported recurrences.

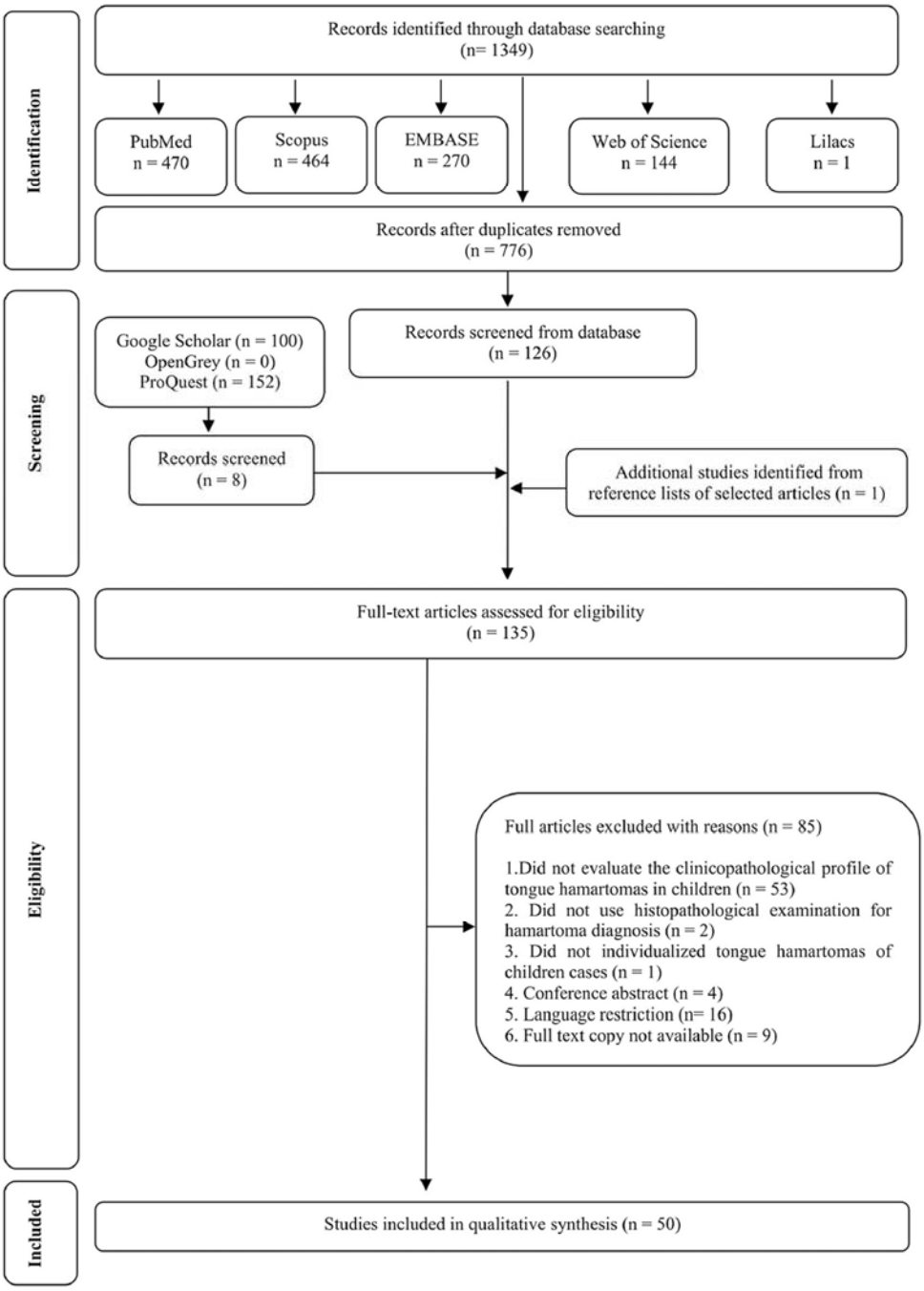

Fig. 4. Flow diagram of literature search and selection of studies.

Table 2. Demographical and clinical features of the 50 studies included in the literature review

Variable	*Number*	*Percentage**
Total number of lesions	95	-
Total number of patients	79	-
Continent ($n = 79$ patients)		
Africa	3	3.8%
Asia	21	26.6%
Europe	9	11.4%
North America	42	53.1%
South America	4	5.1%
Patients' sex ($n = 79$ patients)		
Female	47	59.5%
Male	32	40.5%
Patients' age ($n = 79$ patients)		
Range	15 h to 19 y	-
Site ($n = 95$ lesions)		
Anterior dorsum of tongue	14	14.7%
Middle dorsum of tongue	12	12.7%
Posterior dorsum of tongue	31	32.6%
Lateral tongue	19	20.0%
Ventral surface of tongue	5	5.3%
Others[†]	14	14.7%
Color ($n = 72$ lesions)		
Normochromic	35	48.6%
Pinkish	22	30.6%
Whitish	8	11.1%
Yellowish	7	9.7%
Surface ($n = 56$ lesions)		
Smooth	56	100%
Greater size, cm ($n = 78$ lesions)		
Range	0.1-4.0	-
Time of evolution, months ($n = 55$ lesions)		
Range (14 lesions)	3-83.75, mean of 27.8	25.5%
Congenital	40	72.7%
Unknown	1	1.8%
Presence of symptoms ($n = 21$ patients)		
Dysphagia	12	57.2%
Airway distress	2	9.5%
Sucking difficulties	2	9.5%
Snoring	2	9.5%
Others[‡]	3	14.3%
Syndromes ($n = 7$ patients)		
Apert syndrome	1	14.3%
Ectrodactyly-ectodermal dysplasia-clefting syndrome	1	14.3%
OFD syndrome	5	71.4%
Presence of abnormalities ($n = 24$ patients)		
Cleft palate	10	41.7%
Bifid tongue	4	16.6%
Others[§]	10	41.7%

Treatment (n = 92 lesions)		
Surgical excision	92	100%
Follow-up time, mo (n = 30 patients)		
Range	2-144, mean of 25.7	-
Recurrence (n = 38 patients)		
No	38	100%

*Reflects the percentage of lesions/patients where that parameter was reported.

†Dorsal, not otherwise specified (6); dorsal lateral (4); tongue, not otherwise specified (4).

‡Episodic vomiting (1); hearing loss (1); speech disorders (1).

§Ankyloglossia (1); encephalocele (1); cerebral palsy (1); heart defect (2); polysyndactyly (2); palatal fistula (1); labial-buccal frenulum deformity (1); absence of lingual frenulum (1).OFD, oro-facial-digital.

The most frequent predominant tissue component was smooth muscle (n=35; 44.3%), followed by smooth muscle and adipose tissue (n=10 lesions; 12.6%), and skeletal muscle (n=10; 12.6%). The three most frequently described hamartomatous components included smooth muscle (n=74), followed by salivary gland parenchyma (n=66), and blood vessels (n=52). The histopathological spectrum described in the included studies is summarized in **Table 3.**

Table 3. Hamartomatous components and predominant tissue components as described in the 50 studies (95 lesions) included in the literature review

Hamartomatous components	*No. of lesions*	*Predominant tissue component**	*No. of lesions (%)*
Smooth muscle	74	Smooth muscle	35 (44.3)
Salivary gland parenchyma	66	Smooth muscle and adipose tissue	10 (12.6)
Blood vessels	52	Skeletal muscle	10 (12.6)
Adipose tissue	52	Adipose tissue	9 (11.4)
Skeletal muscle	29	Neurovascular	4 (5.1)
Nerve bundles	16	Salivary gland parenchyma and adipose tissue	4 (5.1)
Fibrous connective tissue	18	Salivary gland parenchyma	3 (3.7)
Lymphatic vessels	4	Fibrovascular tissue	1 (1.3)
Lymphoid tissue	3	Meningoepithelial	1 (1.3)
Ganglia	2	Smooth muscle, salivary gland parenchyma and adipose tissue	1 (1.3)
Focal cartilage	2	Blood vessels, adipose tissue, smooth muscle	1 (1.3)
Sebaceous glands	1		
Hair follicle	1		
Meningoepithelial	1		

*In 16 lesions, the predominant tissue was not described.

Discussion

Hamartomas of the oral cavity are rare, with an extensive literature review mostly revealing single case reports only [9, 23-44]. Retrospective studies with a large sample size only included few cases of oral hamartomas in children, with most representing vascular lesions, such as hemangiomas and lymphangiomas [4,5]. Kreiger *et al*. [1] performed a retrospective review over an 18-year period of all tongue lesions in children, whereby 18 out of 135 tongue lesions were considered true hamartomas, representing the third most common lesion found at this subsite. In contrast, another study found only one hamartoma out of 17 pediatric tongue lesions [5]. This discrepancy may be due to the lack of standardization of the definition of 'hamartoma', resulting in the real incidence of this lesion in the oral cavity being underestimated. The current study reported nine additional tongue hamartoma cases along with an extensive review of the current literature. To the best of our knowledge the present study represents the second largest series of tongue hamartomas reported in pediatric patients.

Hamartomas are characterized by a proliferation of normal tissues that are considered endogenous to the site of occurrence [1]. Conversely, choristomas consist of tissue components that are exogenous to the site of occurrence [45]. The main diagnostic dilemma is the histopathological distinction between a benign mesenchymoma and a hamartoma. Mesenchymoma is defined by the presence of two or more benign mesenchymal tissues not normally found together, excluding fibrous connective tissue, without a dominant mesenchymal component [46]. Additionally, Bure and Barnes [47] propose reserving the diagnosis of hamartoma instead of mesenchymoma for cases that occur in individuals younger than 25 years of age, or, cases seen in association with other congenital anomalies or lesions such as hemangiomas or lymphangiomas. The nine cases in the current study all occurred in

children. Although only three cases (37.5%) were associated with syndromes or developmental anomalies, the lesions clearly exhibited a microscopically predominant tissue component in all cases. Additionally, 7/9 cases showed nerve bundles, and neural tissue has not been reported in mesenchymomas to date [46, 47]. Indeed, the true distinction between some cases of benign mesenchymoma and hamartoma may only represent a difference in terminology.

A review of the literature indicated that tongue hamartomas exhibit a slight female predilection (59.5%), although smooth muscle predominant hamartomas were reported more commonly in males. Most cases occur at birth or younger children up to the age of 5 years. Hamartomas can present anywhere in the tongue, with the dorsum being the most common subsite [1, 48]. This predilection can be explained by the midline tongue, especially the tongue base or foramen cecum region, being considered the fusion region in embryogenesis [49, 50]. In the current series, a slight female predilection (5 cases - 55.6%) was observed. Interestingly, all salivary gland predominant hamartomas affected female patients, supporting current literature whereby two-thirds of salivary gland predominant hamartomas occurred in females [51, 52]. The age of patients in the current series ranged from 2 weeks to 7 years, with 6 cases (66.7%) presenting in patients up to the first year of life. All cases affected the tongue dorsum.

Tongue hamartomas usually present as nodular or polypoid lesions with a smooth, normochromic surface [1, 48]. The clinical differential diagnosis of masses located in the tongue base in younger infants, especially congenital lesions, includes lingual thyroid and thyroglossal duct cyst. In older children, traumatic fibromas and choristomas may be considered [49, 53]. In the current series, most cases presented as nodular or polypoid lesions with a smooth, normochromic surface. Only one case

exhibited an erythematous surface. Although most hamartomas are asymptomatic slow-growing lesions, some cases, particularly those arising in the posterior tongue dorsum, may be associated with dysphagia, airway distress, snoring, sucking difficulties, and even episodic vomiting [8, 17, 18, 54]. Moreover, hamartomas are frequently associated with syndromes or developmental anomalies. Oro-facial-digital (OFD) syndrome is a complex disorder in which hamartomas have been well described as part of the clinical manifestations [10]. In the current case series, only one case presented with OFD syndrome. Kreiger *et al.* [1] found that four out of 18 hamartomas occurred in a setting of this syndrome. Other syndromes that have been described in association with tongue hamartomas include Apert syndrome [20] and Ectrodactyly-ectodermal dysplasia-clefting syndrome [21]. Although an association between hamartomas and syndromes does exist, it seems to occur in a minority of cases, with most cases arising in nonsyndromic patients. Hamartomas may also be related to midline craniofacial clefts [7, 16, 20; 55] and bifid tongues [12, 56]. In the current case series, two patients had concomitant cleft palates with one encephalocele.

Microscopically, the proliferative tissue components in tongue hamartomas may include smooth or skeletal muscle bundles, salivary gland parenchyma, adipose tissue, blood vessels, nerve bundles, adnexal structures, cartilage, glial elements, fibrous connective tissue, and lymphoid tissue [1]. The most common hamartoma described in the literature comprises of smooth muscle (35 lesions; 44.3%), followed by smooth muscle and adipose tissue (10 lesions; 12.6%), and skeletal muscle (10 lesions; 12.6%). In the current study, hamartomatous tissue types included smooth or skeletal muscle bundles, salivary gland parenchyma, adipose tissue, blood vessels, nerve bundles, fibrous connective tissue, and cartilage. The most common hamartomas were salivary gland predominant, followed by adipose tissue and smooth muscle. Most authors

consider cartilage as an exogenous element of the tongue, and therefore strictly speaking a choristomatous structure. In the current case series a single case contained cartilaginous elements, however, this element was minor relative to the other hamartomatous components. Other exogenous elements found as minor components in the literature included sebaceous glands and hair follicles [1]. Differential histopathological diagnoses for hamartomatous lesions may include reactive lesions and benign neoplasms. Regarding reactive lesions, a traumatic neuroma may be difficult to distinguish from a neurovascular hamartoma. The vascular proliferation in a neurovascular hamartoma appears more related to the neural component, whereas in a traumatic neuroma these two components are separate and the neural component is much more prevalent [57]. Additionally, the presence of inflammation and reactive fibrosis are more suggestive of a traumatic lesion. To differentiate benign neoplasms, such as leiomyomas or lipomas, it is important to note the circumscription of the tumoral tissues, which in hamartomas appear intermingled with the normal surrounding tissues, showing an overall lack of circumscription [1].

The treatment of tongue hamartomas is via conservative surgical excision. The prognosis is excellent, with no recurrences reported in the literature [26, 48]. In the current case series, no recurrences were reported following simple surgical excision.

Although rare lesions in the oral cavity, it is important to consider a hamartomatous lesion in the differential diagnosis when encountering a mass in the tongue of a pediatric patient, particularly the dorsal region, even in the absence of known syndromes or developmental anomalies. Further case series are required to investigate the histopathological spectrum and better estimate the true incidence of tongue hamartomas in pediatric patients.

References

1. Kreiger PA, Ernst LM, Elden LM, Kazahaya K, Alawi F, Russo PA. Hamartomatous tongue lesions in children. Am J Surg Pathol. 2007;31:1186-1190.
2. Albrecht, H. Ueber Hamartome. Verh. Dtsch. Pathol. Ges. 1904;7:153-157.
3. Stamm C, Tauber R. Hamartoma of tongue. Laryngoscope. 1945;55:140-146.
4. Tröbs RB, Mader E, Friedrich T, Bennek J. Oral tumors and tumor-like lesions in infants and children. Pediatr Surg Int. 2003;19:639-645.
5. Horn C, Thaker HM, Tampakopoulou DA, et al. Tongue lesions in the pediatric population. Otolaryngol Head Neck Surg. 2001;124:164-169.
6. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Systematic Reviews. 2016;5:1-10.
7. Mba UC, Onah II. Tongue harmatoma in association with cleft palate: Case Report. Cleft Lip Palate Craniofac Anomal 2017;4:168-169.
8. Liu YC, Shih M, Hicks MJ, Sitton MS. Lingual Hamartomas: Clinical Characteristics, Diagnostic Evaluation, Treatment, and Outcomes. Laryngoscope. 2021;131:2080-2088.
9. Iida S, Kishino M, Senoo H, Okura M, Morisaki I, Kogo M. Multiple leiomyomatous hamartoma in the oral cavity. J Oral Pathol Med. 2007;36:241-244.
10. Matheny M, Hall B, Manaligod JM. Otolaryngologic aspects of oral-facial-digital syndrome. Int J Pediatr Otorhinolaryngol. 2000;53:39-44.
11. Saari J, Lovell MA, Yu HC, Bellus GA. Compound heterozygosity for a frame shift mutation and a likely pathogenic sequence variant in the planar cell polarity—ciliogenesis gene WDPCP in a girl with polysyndactyly,

coarctation of the aorta, and tongue hamartomas. Am J Med Genet A. 2015;167A:421-427.

12. Takagi Y, Machidaa J, Satoa H, Sakumaa H, Noda H, Oh-iwaa I. Congenital bifid tongue with lingual hamartoma: A case report and review of the literature. J Oral Maxillofaci Surg, Med Pathol. 2016;28:133-137.
13. Orstavik KH, Lindemann R, Solberg LA, Foerster A, Sørland SJ. Congenital heart defects, hamartomas of the tongue and polysyndactyly in a sister and brother. Clin Genet. 1992;42:19-21.
14. De la Sotta P, Salomone C, González S. Rhabdomyomatous (mesenchymal) hamartoma of the tongue: report of a case. J Oral Pathol Med. 2007;36:58-59.
15. Steele JC, Triantafyllou A, Field EA. Lingual striated muscle hamartoma or herniation? J Oral Pathol Med. 2004;33:454-455.
16. Ishii T, Takemori S, Suzuki JI. Hamartoma of the tongue. Report of a case. Arch Otolaryngol. 1968;88:171-173.
17. Carta F, Caria RA, Gerosa C, Sionis S, Puddu M, Ottonello G, Puxeddu R. Congenital remnants as a cause of neonatal respiratory impairment. J Pediatric Neonatal Individ Med. 2017;6:1-6.
18. Bhattacharya V, Khanna S, Bashir SA, Kumar U, Garbyal RS. Cleft palate associated with hamartomatous bifid tongue. Report of two cases. J Plast Reconstr Aesthet Surg. 2009;62:1442-1445.
19. Takato T, Fukuda O, Ohhara Y, Yanai A, Hirabayashi S, Nakatsuka T. Hamartoma of the tongue: two case reports. Plast Reconstr Surg. 1985;75:258-262.

20. Fowler CB, D'Silva NJ. Clinical-pathological conference: case 5. Head Neck Pathol. 2010;4:234-237.
21. Hanna R, Argenyi ZB, Benda JA. Hamartoma of the tongue in an infant with a primary diagnosis of ectrodactyly-ectodermal dysplasia-cleft lip and palate syndrome. J Cutan Pathol. 1994;21:173-178.
22. Herzog S, Bressman J, Giglio JA. Case 61: Tongue mass in an infant. J Oral Maxillofac Surg. 1986;44:463-436.
23. Owen G, Berry J, Bicknell P. Hamartoma of the tongue. The Journal of Laryngology & Otology. 1993;107:363-367.
24. de la Rosa-García E, Mosqueda-Taylor A. Leiomyomatous hamartoma of the anterior tongue: report of a case and review of the literature. Int J Paediatr Dent. 1999;9:129-132.
25. Kobayashi A, Amagasa T, Okada N. Leiomyomatous hamartoma of the tongue: case report. J Oral Maxillofac Surg. 2001;59:337-340.
26. Hsu YC, Hsu WC. Tongue base hamartoma in a child. J Formos Med Assoc. 2012;111:406–407.
27. Hemmaoui B, Sahli M, Jahidi A, Benariba F. Hamartoma of the tongue. Eur Ann Otorhinolaryngol Head Neck Dis. 2017;134:295-296.
28. Ameh EA, Mshelbwala PM, Farindadi AH. Lingual hamartoma in an infant. Annals of Tropical Paediatrics. 2006;26:137-139.
29. Becker GD, Ridolfi R, Ingber C. Lingual Hamartoma in a Newborn. Otolaryngology–Head and Neck Surgery. 1984;92:357-359.
30. Ferlito S, Di Prima T, Viglianisi A, Gangemi P. Lingual hamartoma in a child: a case report. J Oral Maxillofac Surg. 2010;68:2643.

31. Goldsmith P, Soames JV, Meikle D. Leiomyomatous hamartoma of the posterior tongue: a case report. J Laryngol Otol. 1995;109:1190-1191.
32. Goold AL, Koch BL, Willging JP. Lingual hamartoma in an infant: CT and MR imaging. AJNR Am J Neuroradiol. 2007;28:30-31.
33. Heitink-Pollé KMJ, Ultee CA, van der Deure J, et al. A hypothyroid neonate with a lingual tumour. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2007;92:142.
34. Magro G, Di Benedetto A, Sanges G, Scalisi F, Alaggio R. Rhabdomyomatous mesenchymal hamartoma of oral cavity: an unusual location for such a rare lesion. Virchows Arch. 2005;446:346-347.
35. Majumder A, Ulualp SO, Timmons C. Tongue mass in an infant. JAMA Otolaryngol Head Neck Surg. 2014;140:773-774.
36. Murphy L, French P, Waters A, Clement WA, Kubba H. Dorsal midline tongue masses in children. Int J Pediatr Otorhinolaryngol Extra. 2016;13:40-43.
37. Nakanishi K, Nomura J, Matsumura Y, Yanase S, Kato H, Tagawa T. Leiomyomatous hamartoma of the tongue in an infant: a case report. J Dent Child (Chic). 2012;79:111-114.
38. Nava-Villalba M, Ocampo-Acosta F, Seamanduras-Pacheco A, Aldape-Barrios BC. Leiomyomatous hamartoma: report of two cases and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;105:39-45.
39. Seki N, Shintani T, Tsubota H, Watanabe K, Ogasawara N, Ueda Y, Himi T. Lingual hamartoma in a newborn with chromosome 2q terminal deletion. Int J Pediatr Otorhinolaryngol Extra. 2008;3:109-112.

40. Tekkeşin MS, Chiosea SI, Ozolek JA. Hamartoma of the Oral Cavity with Ectopic Meningothelial Elements in Infants: A Rare Entity with Report of Two Cases. Head Neck Pathol. 2020;14:268-271.
41. Vaidyanathan M, Williams CE, Morgan PR. Rhabdomyomatous mesenchymal hamartoma of the tongue. BMJ Case Rep. 2011;2011:1-2.
42. Yamashita Y, Kurokawa H, Zhang M, Fukuyama H. Sinmyouzu K, Takahashi T. Congenital Leiomyomatous Hamartoma of the Tongue. Asian J Oral Maxillofac Surg. 2007;19:62-65.
43. Yin S, Zhao Z. Incomplete Cleft Palate, Bifid Tongue, and Oral Hamartomas: A Rare Congenital Anomaly. J Craniofac Surg. 2020;31:184-185.
44. Zalzal GH, Patterson K, Cotton RT. Congenital tumors of the dorsum of the tongue. Int J Pediatr Otorhinolaryngol. 1994;28:219-227.
45. Chou LS, Hansen LS, Daniels TE. Choristomas of the oral cavity: A review. Oral Surg Oral Med Oral Pathol. 1991;72:584–593.
46. Jones AC, Trochesset D, Freedman PD. Intraoral benign mesenchymoma: a report of 10 cases and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;95:67-76.
47. Bures C, Barnes L. Benign mesenchymomas of the head and neck. Arch Pathol Lab Med 1978;102:237-241.
48. Sánchez-Romero C, Bonan PRF, Pires FR, Oliveira Silva-Junior G, Delgado Azañero W, Almeida OP, Perez DEDC. Leiomyomatous Hamartomas of the Oral Cavity: Clinicopathological and Immunohistochemical Features of 4 Cases and Literature Review. Int J Surg Pathol. 2019;27:624-630.

49. Zalzal GH, Patterson K, Cotton RT. Congenital tumors of the dorsum of the tongue. Int J Pediatr Otorhinolaryngol. 1994;28:219-227.

50. Napier SS, Devine JC, Rennie JS, Lamey PJ. Unusual leiomyomatous hamartoma of the hard palate: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1996;82:305-307.

51. Miyamoto Y, Nagayama M, Hayashi Y. A cleft palate child with lobulated tongue and lingual hamartoma: report of a case. J Oral Maxillofac Surg. 1991;49:644-646.

52. Noguchi T, Jinbu Y, Itoh H, Matsumoto K, Sakai O, Kusama M. Epignathus combined with cleft palate, lobulated tongue, and lingual hamartoma: report of a case. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;101:481-486.

53. Kuperan AB, Harirchian S, Mirani N, Quraishi HA. Case report of a congenital lingual leiomyomatous hamartoma: new epidemiologic findings and a review of the literature. Int J Pediatr Otorhinolaryngol. 2012;76:1528-1530.

54. Fadzilah N, Azman M, See GB. Congenital Midline Tongue Base Mass in An Infant: Lingual Hamartoma. J Clin Diagn Res. 2016;10:M01-MD03.

55. Daramola OO, Suchi M, Chun RH. Lingual Hamartoma Associated with a Cleft Palate in a Newborn. Ear, Nose & Throat Journal. 2014;93:E9-E37.

56. Dhua AK, Kumar K, Nagendla MK, Bhatnagar V, Mridha AR. Lingual leiomyomatous hamartoma with bifid tip of tongue and ankyloglossia in an infant. Oral Surgery. 2017;10:e30-e34.

57. Allon I, Allon DM, Hirshberg A, Shlomi B, Lifschitz-Mercer B, Kaplan I. Oral neurovascular hamartoma: a lesion searching for a name. J Oral Pathol Med. 2012;41:348-353.