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Oral Glomus Tumor: A Systematic Review Highlighting Clinical and Histopathological Characteristics of a Time-Reclassified Entity

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Abstract

Background: Oral glomus tumors are exceptionally rare perivascular neoplasms that are frequently misdiagnosed due to their nonspecific clinical presentation. Their rarity has historically resulted in inconsistent terminology and a limited understanding of their biological behavior. **Methods:** This systematic review was conducted according to PRISMA 2020 guidelines and requested to be recorded in PROSPERO (ID 1175198). A comprehensive literature search of PubMed, Scopus, and Web of Science (1954-2024) was performed to identify English-language case reports and case series describing histologically confirmed oral glomus tumors. Extracted data included demographics, tumor location and size, histopathological features, treatment modalities, recurrence, and follow-up. **Results:** A total of 740 records were identified, of which 31 studies met the inclusion criteria, yielding 34 confirmed oral glomus tumor cases. Patients ranged from 8 to 85 years, with a slight male predominance. The most frequently affected site was the lip, followed by the tongue, palatal mucosa, and other intraoral soft tissues. Tumor size varied from 0.3 to 4.5 cm. Classic glomus tumor was the most common subtype, with occasional reports of glomangiomyoma and one case of glomangiosarcoma. Surgical excision was curative in most patients. Recurrence occurred in a minority of cases, but metastasis was not reported in the only one case of glomangiosarcoma. **Conclusion:** Oral glomus tumors are predominantly benign, well-circumscribed lesions with excellent prognosis following complete surgical excision. Accurate diagnosis relies on thorough histopathological and immunohistochemical evaluation due to potential overlap with other mesenchymal tumors. This review provides the most updated synthesis of clinical, pathological, and outcome features of oral glomus tumors.

Keywords: Oral glomus tumour; Oral glomangioma; Oral glomangiomyoma; Oral glomangiosarcoma; Oral cavity; Oral mesenchymal tumours.

Abbreviations: CT: Computed Tomography; MRI: Magnetic Resonance Imaging; WHO: World Health Organization; AWD: Alive with Disease; GT: Glomus Tumor; HIF: Hypoxia-Inducible Factor; NED: No Evidence of Disease.

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Introduction

Oral cavity encompass a broad range of benign and malignant neoplasm, as well as inflammatory conditions resulting from autoimmune diseases or exogenous pathogens.

Glomus Tumors (GT) are considered a rare entity, as they constitute less than 2% of mesenchymal tumours. They arise from the modified smooth muscle cells of the glomus body [1], a vascular anatomical structure mostly located in the subungual regions of the hands and feet, which are in fact the most common sites of tumor onset [2-5]. The physiological role of these vascular structure is to contribute to the regulation of body temperature through the modulation of cutaneous blood flow [6-8]. Traditionally considered benign skin neoplasms, GTs can present possible occurrence in extracutaneous locations, although rarely [4,9]. Indeed, in addition to the subungual and acral regions, cases have been described in the gastrointestinal tract (particularly the stomach), head and neck region and genitourinary system [10-13]. Also today, when located in atypical site, these entities represented a clinical and diagnostic challenge, primarily due to the limited number of cases reported in the literature and the histological variability they may present, which has indeed led to continuous refinements in their nomenclature [14-19]. In the last WHO classification of skin tumors, 5th Edition it's not recommended to use the definition "glomangioma" or "glomangiosarcoma", while it's recognized the presence of different subtypes such as glomuvenous malformation (also called glomangiomyoma), glomus tumour of uncertain malignant potential and malignant glomus tumour [14].

From a molecular point of view, recent studies have demonstrated certain familial predispositions associated with germline loss of function mutations in the *GLMN* gene (1p22.1), which encodes glomulin, a cytoplasmic–nuclear protein involved in the regulation of angiogenesis and the stabilization of blood vessels. Furthermore, emerging evidence suggests that glomulin may contribute to tumorigenesis through mechanisms involving mTOR signaling and Hypoxia-Inducible Factor (HIF)–mediated oxidative stress. Notably, these pathways are also implicated in development of glomus tumors [20-22]. Rarely, GTs are associated with Neurofibromatosis type 1 (NF1), while sporadic GTs can harbor rearrangements involving MIR143 and NOTCH genes [14,23].

In addition, activating *BRAF* mutations (p.V600E) have been reported in rare instances of malignant glomus tumors [23,24]. These findings suggest potential therapeutic and prognostic implications.

A correct diagnosis requires a thorough histopathological evaluation, supported by a specific immunohistochemical panel to make differential diagnosis with histological mimickers such as angioleiomyoma, leiomyoma, paraganglioma and myoepithelial tumors [25]. Given the scarcity of reported intraoral cases, the present systematic review aims to consolidate all available evidence regarding clinical presentation, histopathology, treatment modalities, and outcomes of oral glomus tumors.

Materials and methods

Protocol and registration

This systematic review was performed in accordance to PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and requested for the registration in PROSPERO under the number ID 1175198 (The International Prospective Register of Systematic Reviews).

Search processing

A structured search of PubMed, Scopus and Web of Science was performed using the following keywords: <"Glomus tumor" OR "Glomangioma" OR "Glomangiomyoma" OR "Glomangiosarcoma" AND ("oral cavity" OR "mouth" OR "lips" OR "tongue" OR "palate"). These terms were chosen because they most accurately reflect the objective of this review, which was to investigate, through an analysis of the existing literature, the rarity of glomus tumors occurring in the oral cavity (Table 1). Searches included publications from 1954 to 2024.

Table 1: Indicators for database searches.

Articles screening strategy	Keywords: "A": Glomus tumour; Glomangioma; Glomangiomyoma; Glomangiosarcoma "B": oral cavity; mouth; lips; tongue; palate
	Boolean Indicators: "A" AND "B"
	Electronic databases: Pubmed; Scopus; Web of Science.

Inclusion criteria

Two independent reviewers assessed all relevant papers according to the following inclusion criteria: (i) studies involving only human subjects; (ii) English-language full-text articles; and (iii) histologically confirmed oral glomus tumor and case reports or case series with extractable clinical data.

Article identification procedure

The evaluation was performed independently by two reviewers, G.C. (pathologist) and F.I. (odontologist). English-language articles meeting the predefined inclusion criteria were selected for full-text review. During the selection process, studies were excluded based on title, abstract, or full-text assessment according to predefined exclusion criteria. Two reviewers independently screened all titles, abstracts, and full texts. Discrepancies were resolved by consensus.

Data extraction

Data were extracted into a standardized matrix including: paper Identification (ID), sex, age, lesion site, size, diagnosis, treatment, recurrence/metastasis, follow-up.

Study evaluation

The article data were independently evaluated using a special electronic form designed according to the following categories: authors, year of study, aim of the study, materials and methods, and results.

Results

A comprehensive search across PubMed, Scopus, and Web of Science initially identified 740 records. After removing 32 duplicates, a total of 708 articles were screened by title and abstract. During this phase, 553 records were excluded because they were not relevant to the topic or did not meet the predefined inclusion criteria (Figure 1).

A total of 155 full-text articles were subsequently assessed for eligibility. Of these, 124 were excluded mainly due to the absence of confirmed oral glomus tumors, lack of histopathological diagnosis, non-English language, review-type format, or insufficient clinical data. Ultimately, 31 studies satisfied all criteria for inclusion in the present systematic review, yielding a total of 34 unique cases of histologically confirmed oral glomus tumors.

Table 2: Analysis of 31 studies describing 34 cases of oral glomus tumors.

ID	Sex	Age	Site	Tumor Size (cm)	Diagnosis	Treatment	Recurrence/Metastasis	Follow up reported
[25]	M	44	mandibular	4,5	glomus tumor	surgery	mandibular	AWD (96 months)
[26]	M	62	lower left lip	1	glomus tumor	surgery	absent	NED (12 months)
[27]	F	45	upper lip	1	glomangioma	surgery	absent	NED
[28]	M	46	upper lip	NA	glomus tumor	surgery	absent	NED (8 months)
[29]	M	54	upper lip	NA	glomus tumor	surgery	absent	NED
[30]	M	37	left oral mucosa	2	glomus tumor	surgery	absent	NED (24 months)
[31]	F	85	upper lip	NA	glomus tumor	surgery	NA	NED
[32]	F	46	palate mucosa	1,8	glomus tumor	surgery	absent	NED (120 months)
[33]	F	54	left mandibular	NA	glomus tumor (multifocal)	surgery	absent	NED
[33]	F	54	lower lip	NA	glomus tumor (multifocal)	surgery	absent	NED
[33]	F	54	anterior oral mucosa	NA	glomus tumor (multifocal)	surgery	absent	NED
[34]	M	51	tongue	2,5	glomangiosarcoma	surgery	lymph node	AWD (14 months)
[35]	F	24	left floor of the mouth	2,8	glomus tumor	surgery	absent	NED
[36]	F	51	upper lip	1	glomus tumor	surgery	absent	NED
[37]	F	17	lower lip	na	glomus tumor	surgery	absent	NED
[38]	M	80	upper lip	1,6	glomus tumor	surgery	absent	NED
[39]	F	58	tongue	2	glomus tumor	surgery	absent	NED
[39]	M	26	lip	1,5	glomus tumor	surgery	absent	NED
[40]	F	17	palate	2	glomus tumor	surgery	absent	NED
[41]	F	65	lip	1	glomus tumor	surgery	absent	NED
[42]	M	29	tongue	0,3	glomus tumor	surgery	absent	NED
[43]	F	63	ventral tongue	NA	glomangioma	surgery	absent	
[44]	F	51	lip	2	glomangioma	surgery	absent	NED (72 months)
[45]	M	32	mouth	0,6	glomus tumor	surgery	absent	NED (60 months)
[46]	M	71	palate	1,5	glomus tumor	surgery	absent	NED (12 months)
[47]	M	55	intraoral	0,5	glomus tumor	surgery	absent	NED (9 months)
[48]	M	34	lower lip	NA	glomus tumor	surgery	absent	NED
[49]	M	11	lower lip	0,3	glomangioma	surgery	absent	NED (84 months)
[50]	M	57	upper lip	0,8	glomus tumor	surgery	absent	NED
[51]	M	57	upper lip	NA	glomus tumor	surgery	absent	NED
[52]	M	65	lower lip	NA	glomus tumor	surgery	absent	AWD (4 months)
[53]	M	45	left oral mucosa	4,5	glomus tumor	surgery	absent	NED
[54]	F	67	upper lip	1	glomus tumor	surgery	absent	NED
[55]	M	8	mandible	3	glomus tumor	surgery	absent	NED

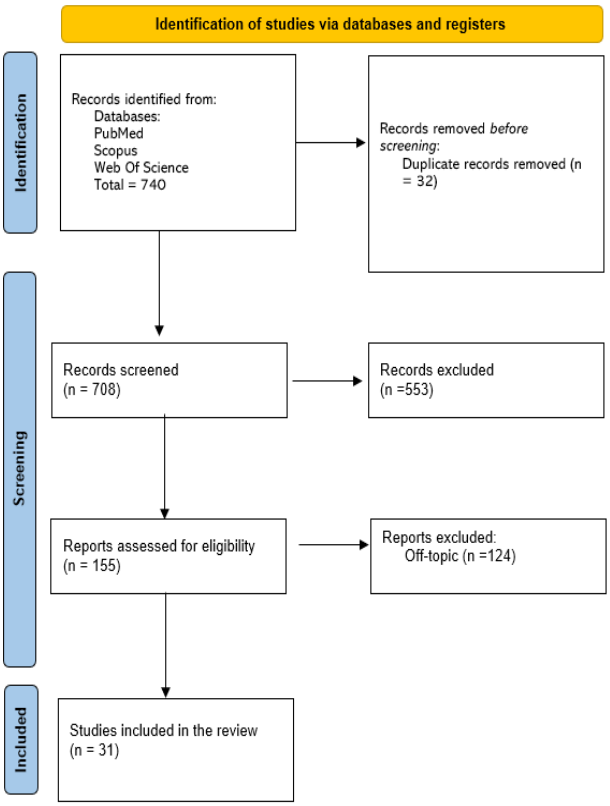

Figure 1: Identification of studies via databases and registers.

Overall, the table provides information on demographic distribution, clinical characteristics, prevalence by sex, age at diagnosis, presence of metastases to other sites, and follow-up. NED indicates: no evidence of disease, AWD indicates: alive with disease.

Patients ranged from 8 to 85 years old, and a slight male predominance was observed. The lip represented the most common tumor site, followed by the tongue, palatal mucosa, buccal mucosa, mandibular mucosa, and, less frequently, the floor of the mouth. Two cases were intraosseous, involving the mandible, representing the only confirmed central jaw presentations within the dataset. Tumor size ranged from 0.3 cm to 4.5 cm, with most lesions presenting as small, well-circumscribed nodules.

Histopathological examination revealed that classic glomus tumor was the most common subtype, with occasional reports such as glomangioma, and one case of glomangiosarcoma. Immunohistochemical staining typically demonstrated positivity for Smooth Muscle Actin (SMA) and vimentin, with variable expression of desmin and collagen IV.

Surgical excision was the treatment of choice in all cases. Recurrence occurred in a small minority of cases, generally associated with incomplete excision. The only one malignant case not demonstrated metastatic disease, although the authors suggest the potential occurrence. Follow-up periods ranged from several months to more than ten years, and the majority of patients remained free of disease throughout the observation period.

Overall, oral glomus tumors demonstrated a benign clinical course with excellent long-term outcomes when treated with complete surgical excision.

Discussion

Main clinical aspects of glomus tumors of the oral cavity

Oral glomus tumors are considered rare entity and in the latest World Health Organization (WHO) Classification of Head and Neck Tumours (5th edition), they are not recognized as a distinct nosographic entity, owing to their anecdotal occurrence and the difficulty in explaining their presence in an anatomical site where glomus bodies are not known to exist [56]. Our literature analysis confirms that the most frequent localization were lips and tongue, with a slight male predominance [57,58]; furthermore, the age at disease onset does not appear to have a significant impact, as reported cases span a wide age range, including pediatric patients.

Clinically, oral glomus tumors should be considered in the differential diagnosis of painful oral swellings, especially in middle-aged adults, regardless of gender, or in patients with a positive family history of this condition [56-58]. Exceptionally, they can present as multiple nodules, not necessarily localized exclusively to the oral cavity [59-61]. Overall, macroscopic aspects such as subcentimetric dimensions, popular shape, tense-elastic consistency, pink-purple color and mobility with respect to the deep layers represent recurrent clinical features, suffesting the benign nature of this entity, as well as it happens in other entities of the oral cavity (Figure 2) [62-65].

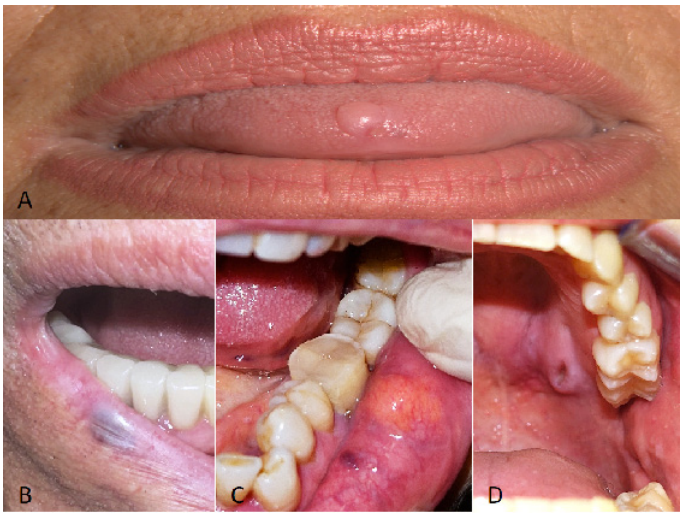

Figure 2: Main clinical features suggesting a differential diagnosis of glomus tumor.

The (Figure 2) shows some morphological aspects of oral lesions that could suggest a glomus tumor. As highlighted in the figure, these lesions can involve the tongue (Figure 2A), the lip (Figure 2B), the palate, and the oral mucosa in general (Figure 2C and D). This lesion can be small (Figure 2A) or larger and ulcerated (Figure 2D) and, above all, have a color ranging from purple (Figure 2B) to pink.

Imaging studies, including ultrasound, MRI, and CT, have been used only in selected cases, mainly when the extent of the lesion is unclear or when multifocal involvement is suspected, and have proven useful in assisting diagnostic and therapeutic planning [66]. Conversely, in the vast majority of cases, where a single, well-circumscribed lesion is easily accessible, imaging is generally

unnecessary [67]. Surgical excision not only provides optimal diagnostic material for the pathologist but, when performed with clear margins, is also considered the gold standard for curative treatment of glomus tumors. Local recurrences are rare [68]. Close patient monitoring is strongly recommended, particularly in cases where the final histopathological analysis reveals a higher histological grade or other cellular atypia, which could indicate a potential prognostic or predictive risk of malignancy [16]. Alternative therapeutic approaches reported in the literature, such as thermal ablation of the nodule for pain relief, are no longer used in clinical practice because they have proven not only ineffective but also incapable of providing tissue for histopathological analysis and accurate diagnosis. Therefore, it is strongly recommended that these patients be managed by a multidisciplinary team of experts in dentistry and maxillofacial surgery, particularly given the potential diagnostic pitfalls associated with similar lesions.

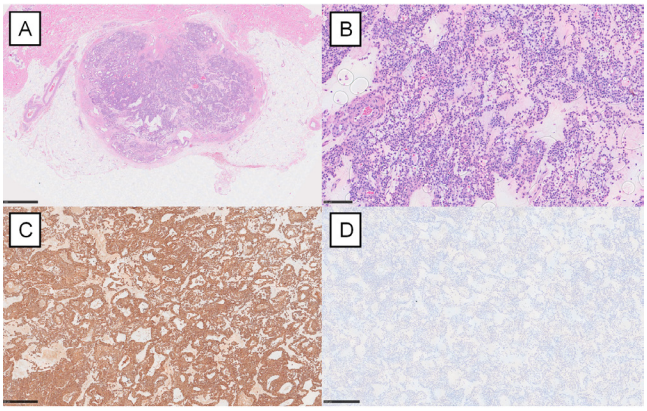

Figure 3: Histological overview of glomus tumor.

Oral glomus tumor: A histological overview

Most glomus tumors appear oval or rounded in shape on histological examination, usually lacking a true covering capsule but still presenting well-demarcated margins [16]. Therefore, even at low magnification, it is possible to determine whether the lesion has been incompletely excised or whether there are areas of infiltration into the surrounding connective tissue due to its irregular shape features that may indicate a risk of recurrence or a more aggressive behavior of the lesion [14,16]. High magnification shows a thin, delicate, and multi-branched vessels, composed of a single strand of cuboidal endothelial cells, that represent the anatomical scaffolding on which, externally, nests of glomus cells are located, each surrounded by very thin collagen fibres [14,16]. Individually distinct, glomus cells have a large, round, paracentral nucleus that may contain vacuoles, while the cytoplasm is sparse and slightly eosinophilic [69]. The stromal component is best appreciated at the periphery of the lesion, sometimes appearing edematous or mucoid (Figure 3) [70].

The (Figure 3A) shows at low magnification a well circumscribed nodular proliferation with pushing margins (EE scale bar 1 mm). The (Figure 3B) reveals it is made up of small, uniform glomus cell arranged in solid and cribriform nests, embedded in a fibrous stroma (EE scale bar 100 micron). In (Figure 3C), the lesion is diffusely positive for Smooth Muscle Actin (IHC scale bar 250 micron). In (Figure 3D), the lesion is totally negative for Desmin (IHC scale bar 250 micron).

The different percentage composition of the cellular elements that compose this tumor can determine a range of variants and morphological forms. The solid variant represents the vast majority of cases and is composed almost entirely of glomus cells arranged in 5-6 rows, small vessels with slightly dilated lumens, and rare smooth muscle cells. Approximately 20% of these tumors have a prominent vascular component with vessels that may be dilated, while only 5% show a greater increase in smooth muscle than the other two. Very rare cases may be multinodular and histologically characterized by infiltrative or diffuse growth features, also better known as glomangiomatosis.

The use of immunohistochemistry (positive staining for vimentin, SMA, muscle-specific actin, and calponin; negative staining for neuroendocrine markers, cytokeratin, CD31, S100, HMB45, and desmin can support the diagnosis against other entities such as angioleiomyoma, paragangliomas, neuroendocrine tumors, melanocytic lesions, pericytic and adnexal tumors (Figure 3).

The prognosis is generally favorable. Rarely, neoplasms with marked nuclear atypia, atypical mitoses and large size may present a variable malignant potential [70,71]. Recurrence is uncommon, generally associated with incomplete excision. Malignant transformation is extremely rare.

Conclusion

This systematic review confirms that oral glomus tumors are exceedingly rare perivascular neoplasms with a predominantly benign clinical course. Analysis of 34 histologically confirmed cases revealed that these lesions most commonly affect the lips and tongue, typically present as well-defined nodules, and are often indistinguishable from other mesenchymal tumors based solely on clinical and radiographic evaluation. Accurate diagnosis relies on meticulous histopathological and immunohistochemical assessment. Complete surgical excision remains the treatment of choice and yields excellent long-term outcomes, with low recurrence rates and extremely rare malignant behavior. This review provides the most updated and methodologically rigorous synthesis of the clinical, radiological, and pathological characteristics of oral glomus tumors to date.

Declarations

Author contributions: Conceptualization: E.C., F.I. and C.C.; methodology: S.C., F.C and S.D.S.; formal analysis: M.D.M., A.M.I. and G.D.; data curation: S.D.S., G.C., A.M and A.P.; writing—original draft preparation: E.C., F.M and F.C.; writing—review and editing: G.D., M.D.M., A.D.I., S.C., A.M., A.P., A.M.I. and G.C.; supervision G.D., C.C., F.I. and E.C. All authors have read and agreed to the published version of the manuscript.

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