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REVIEW ARTICLE

Oral glomus tumor: A systematic review highlighting clinical and histopathological characteristics of a time-reclassified entity

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Abstract

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. This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines and registered in the International Prospective Register of Systematic Reviews (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. A total of 740 records were identified, of which 31 studies met the inclusion criteria, yielding 34 confirmed cases of oral glomus tumor. 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 case of glomangiosarcoma. 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, given the 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 tumor; Glomuvenous malformation; Glomangiomyoma; Malignant glomus tumor; Oral cavity; Oral mesenchymal tumor

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1. Introduction

The oral cavity encompasses a broad range of benign and malignant neoplasms, as well as inflammatory conditions resulting from 45 autoimmune diseases or exogenous pathogens. Glomus tumors (GT) are rare, accounting for less than 2% of mesenchymal tumors. 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 structures is to regulate body temperature by modulating cutaneous blood flow.[6-8] Traditionally considered benign skin neoplasms, GTs can occur in extracutaneous locations, although rarely.[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] Even today, when located at atypical sites, these entities pose a clinical and diagnostic challenge, primarily due to the limited number of reported cases and the histological variability described in the literature.[14-19] In the 5th edition of the World Health Organization (WHO) Classification of Skin Tumors, the historical terms "glomangioma" and "glomangiosarcoma" are discouraged. Lesions previously described as glomangiomas are now interpreted within the spectrum of glomuvenous malformation, whereas malignant lesions are designated as malignant GTs. This updated terminology is particularly relevant when reviewing older intraoral case reports. From a molecular point of view, recent studies have demonstrated familial predispositions associated with germline loss-of-function mutations in the *GLMN* gene (1p22.1), which encodes glomulin, a cytoplasmic–nuclear protein involved in angiogenesis and blood vessel stabilization. Furthermore, emerging evidence suggests that glomulin may contribute to tumorigenesis through mechanisms involving mTOR signaling and hypoxia-inducible factor-mediated oxidative stress. Notably, these pathways are also implicated in the development of GTs.[20-22] Rarely, GTs are associated with neurofibromatosis type 1, while sporadic GTs can harbor rearrangements involving *MIR143* and *NOTCH* genes.[23] In addition, activating *BRAF* mutations (p.V600E) have been reported in rare instances of malignant GTs.[24] These findings suggest potential therapeutic and prognostic implications. A correct diagnosis requires a thorough histopathological evaluation, supported by a specific immunohistochemical panel to differentiate from 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 GTs.

2. Materials and methods

2.1. Protocol and registration

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement and was submitted for registration in the International Prospective Register of Systematic Reviews (ID 1175198).

2.2. Search strategy

A systematic electronic search was performed in PubMed, Scopus, and Web of Science from database inception to December 31, 2024. Searches were limited to English-language studies involving human subjects, and the reference lists of all included articles were manually screened to identify additional eligible reports (Table 1).

Table 1. Full electronic search strategy used for each database

Database	Full search syntax
PubMed	("glomus tumor" OR "glomus tumour" OR glomangioma OR glomangiomyoma OR glomangiosarcoma OR "malignant glomus tumor" OR "glomuvenous malformation") AND ("oral cavity" OR mouth OR oral OR lip OR tongue OR palate OR buccal OR gingiva OR mandible OR mandibular OR "floor of mouth")
Scopus	("glomus tumor" OR "glomus tumour" OR glomangioma OR glomangiomyoma OR glomangiosarcoma OR "malignant glomus tumor" OR "glomuvenous malformation") AND TITLE-ABS-KEY ("oral cavity" OR mouth OR oral OR lip OR tongue OR palate OR buccal OR gingiva OR mandible OR mandibular OR "floor of mouth")
Web of Science	("glomus tumor" OR "glomus tumour" OR glomangioma OR glomangiomyoma OR glomangiosarcoma OR "malignant glomus tumor" OR "glomuvenous malformation") AND ("oral cavity" OR mouth OR oral OR lip OR tongue OR palate OR buccal OR gingiva OR mandible OR mandibular OR "floor of mouth")

2.3. 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 GT and case reports or case series with extractable clinical data.

2.4. Article identification procedure

The screening process was performed independently by two reviewers (G.C., pathologist; F.I., odontologist). Titles, abstracts, and full texts of all potentially eligible articles were assessed independently, and disagreements were resolved through discussion and consensus.

2.5. Data extraction

Data were extracted into a standardized matrix including study identification, sex, age, lesion site, pain, tumor size, diagnosis, treatment, recurrence/metastasis, and follow-up. When information such as lesion size or follow-up duration was not reported in the original article, it was recorded as unavailable, and no assumptions were made about missing values.

2.6. Study evaluation

The methodological quality of the included case reports and case series was assessed independently by two reviewers using the Joanna Briggs Institute critical appraisal checklists for case reports and case series, as appropriate. Disagreements were resolved by discussion and consensus. Overall, the included literature showed moderate methodological quality, with the main limitations related to incomplete follow-up and inconsistent reporting in older reports.

3. 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 due to the absence of confirmed oral GTs, lack of histopathological diagnosis, non-English language, review-type format, or insufficient clinical data. Ultimately, 31 studies met all inclusion criteria for the present systematic review, yielding 34 unique cases of histologically confirmed oral GTs. Figure 1 in the manuscript is the PRISMA 2020 flow diagram illustrating the study selection process. It details the transition from the initial 740 identified records to the final 31 included studies (34 cases), documenting each stage of screening and exclusion. Table 2 summarizes the immunohistochemical markers reported across the included oral GT cases and highlights the markers most useful in the differential diagnosis. Overall, Table 3 provides information on demographic distribution, clinical characteristics, prevalence by sex, age at diagnosis, presence of metastases to other sites, and follow-up.

Markers reported in the literature included smooth muscle actin (SMA), vimentin, desmin, collagen IV, calponin, CD34, cytokeratins, and S100 when available. The most consistent pattern was positivity for SMA/vimentin with negative or limited staining for S100 and endothelial markers, supporting the distinction from neural and vascular mimics.

Patients' ages ranged from 8 to 85 years, with a slight male predominance. 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, and represented the only confirmed central jaw presentations in 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 GT was the most common subtype, with occasional cases corresponding to glomuvenous malformation (historically reported as "glomangioma") and one case corresponding to malignant GT (historically reported as "glomangiosarcoma"). Immunohistochemical staining typically demonstrated positivity for 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 and was generally associated with incomplete excision. The only malignant case did not demonstrate metastatic disease, although the authors suggest it may have occurred. Follow-up periods ranged from several months to more than 10 years, and the majority of patients remained free of disease throughout the observation period. Overall, oral GTs demonstrated a benign clinical course with excellent long-term outcomes when treated with complete surgical excision.

4. Discussion

4.1. Main clinical aspects of glomus tumors of the oral cavity

Oral GTs are rare entities and, in the 5th edition of the WHO Classification of Head and Neck Tumors, are not recognized as a distinct nosographic category due to their exceptional

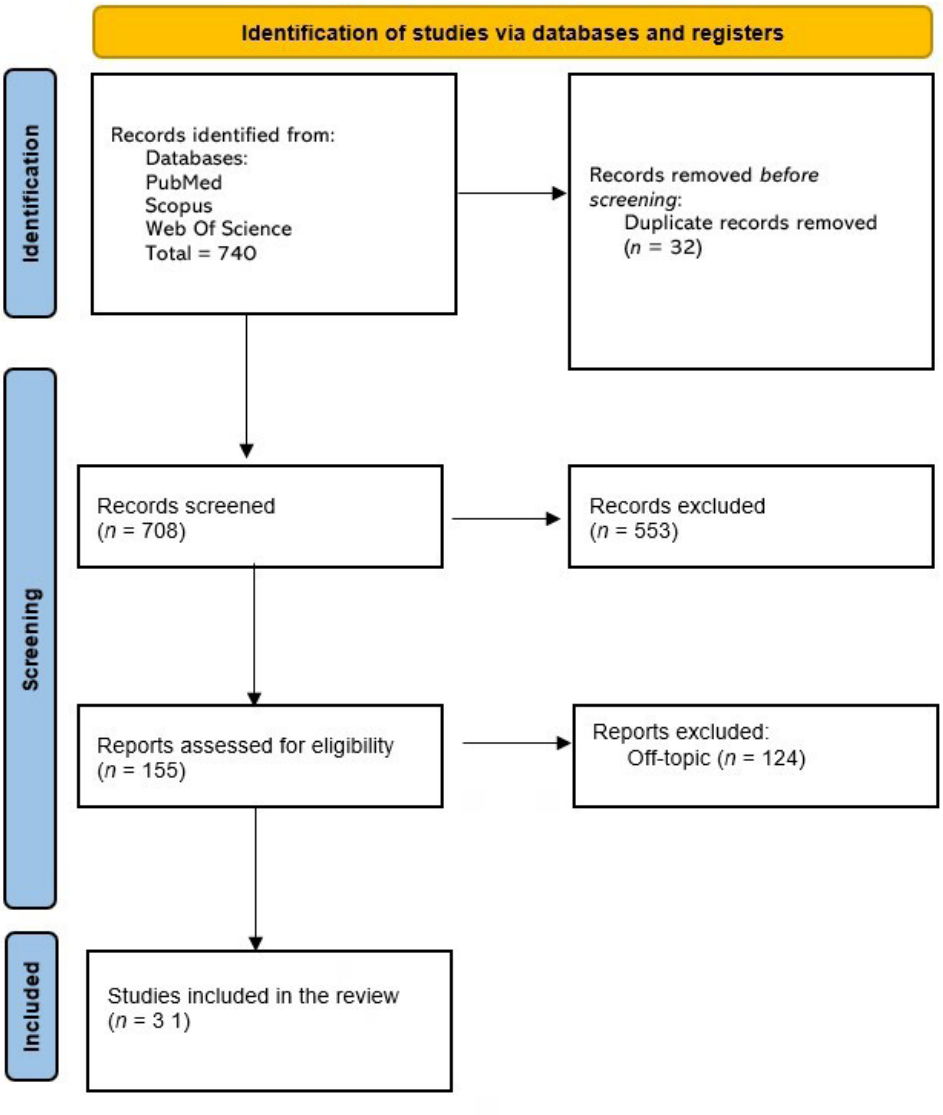

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of oral glomus tumors

Table 2. Summary of immunohistochemical markers reported in oral glomus tumors

Marker	Expression	Clinical significance
Smooth muscle actin	Strong and diffuse positive	Confirms the glomangiomatous/smooth muscle origin of the cells.
Vimentin	Positive	Indicates the mesenchymal origin of the tumor cells.
Type IV collagen	Positive (pericellular)	Highlights the characteristic external lamina around individual glomus cells.
CD34	Negative (usually)	Useful for differentiating from other vascular tumors (positive only in endothelial cells of vessels).
Desmin	Negative	Helps to distinguish from true smooth muscle tumors (leiomyomas).
S-100	Negative	Useful for ruling out neural tumors (such as schwannomas).

Table 3. Analysis of 31 studies describing 34 cases of oral glomus tumors

Reference	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	1.0	Glomus tumor	Surgery	Absent	NED (12 months)
27	F	45	Upper lip	1.0	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	2.0	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	1.0	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	2.0	Glomus tumor	Surgery	Absent	NED
39	M	26	Lip	1.5	Glomus tumor	Surgery	Absent	NED
40	F	17	Palate	2.0	Glomus tumor	Surgery	Absent	NED
41	F	65	Lip	1.0	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	NED
44	F	51	Lip	2.0	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	1.0	Glomus tumor	Surgery	Absent	NED
55	M	8	Mandible	3.0	Glomus tumor	Surgery	Absent	NED

Abbreviations: AWD: Alive with disease; NA: Not available; NED: No evidence of disease.

occurrence in the oral cavity.[56] Several hypotheses have been proposed to explain their occurrence in the oral cavity. The most widely discussed theory suggests origin from perivascular mesenchymal cells capable of glomus-like differentiation, whereas alternative explanations include ectopic glomus-like structures or migration of progenitor cells during development; however, these mechanisms remain speculative. Our literature analysis confirms that the most frequent localizations 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. According to the most recent WHO Classification of Skin Tumors (5th edition), GTs are classified based on biological behavior. Lesions previously described as glomangiomas are now included within the spectrum of glomuvenous malformation, whereas malignant lesions are classified as malignant GTs. This updated terminology is particularly useful when interpreting historical intraoral case reports. Compared to previously published case-based reviews and narrative summaries, the present systematic review provides an updated synthesis focused specifically on intraoral lesions and reinterprets older reports using current WHO terminology. This approach reduces diagnostic ambiguity and clarifies the clinicopathological spectrum of oral GTs exclusively to the oral cavity.[59-61] Overall, macroscopic aspects such as subcentimetric dimensions, papular shape, tense-elastic consistency, pink-purple color, and mobility with respect to the deep layers represent recurrent clinical features, suggesting the benign nature of this entity, as well as it happens in other entities of the oral cavity (Figure 2).[62-65]

Imaging studies, including ultrasound, magnetic resonance imaging, and computed tomography, 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 GTs. Local recurrences are rare.[68] Close

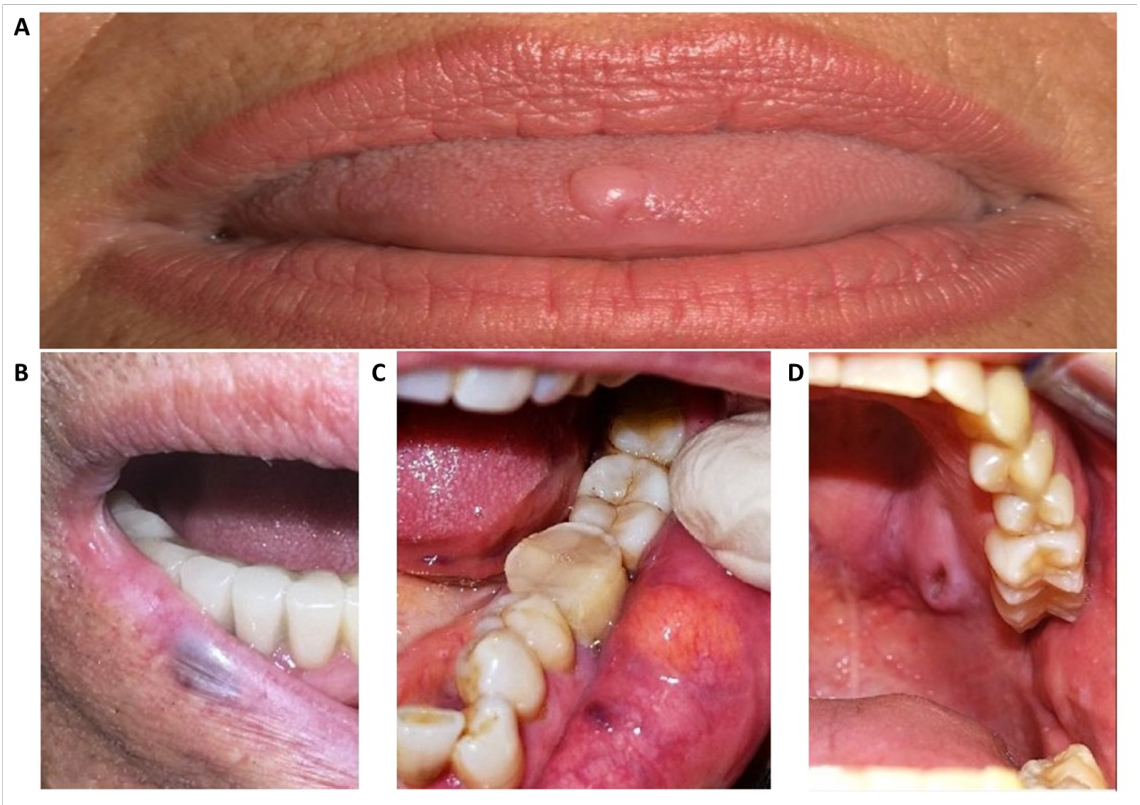

Figure 2. Main clinical features suggesting a differential diagnosis of glomus tumor. Representative clinical appearances of oral GTs and lesions included in the differential diagnosis. The images illustrate lesions involving the tongue (A), lip (B), palate (C), and oral mucosa (D), showing variable size, surface change, and coloration from pink to violaceous.

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 recommended that these patients be managed by a multidisciplinary team of dentists and maxillofacial surgeons, particularly given the potential diagnostic pitfalls associated with similar lesions. From a diagnostic standpoint, oral GTs may mimic several more common oral lesions, including mucocele, hemangioma or venous malformation, angioleiomyoma, myopericytoma, schwannoma, paraganglioma, and minor salivary gland tumors. Because the clinical presentation is often nonspecific, definitive diagnosis relies on careful histopathological examination supported by an appropriate immunohistochemical panel. Most GTs 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. High magnification shows 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 fibers.[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, which may appear edematous or mucoid (Figure 3).[70]

According to the 5th edition of the WHO Classification of Skin Tumors, lesions previously reported as glomangiomas are now interpreted as part of the spectrum of glomuvenous malformation, reflecting updated clinicopathological and molecular insights. Immunohistochemistry can assist the differential diagnosis: oral GTs typically show positivity for vimentin, SMA, muscle-specific actin, and calponin,

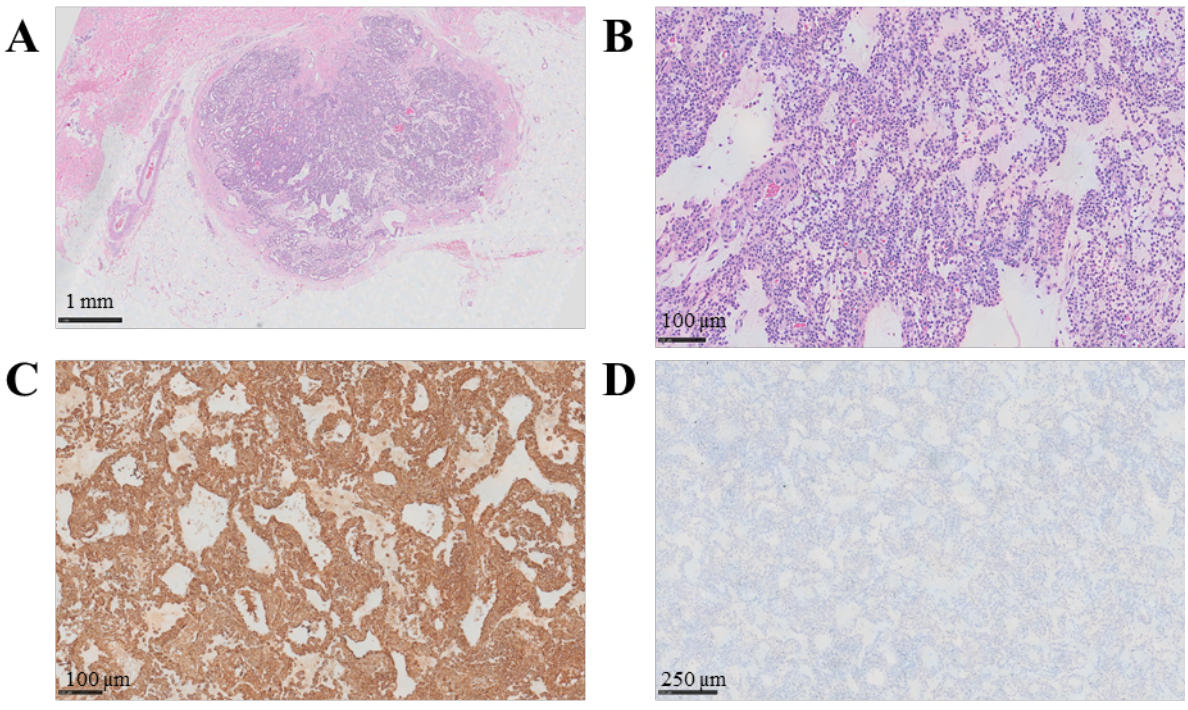

Figure 3. Histological overview of oral glomus tumor. (A) Low-power view showing a well-circumscribed nodular proliferation with pushing margins (hematoxylin and eosin [H&E] staining; scale bar: 1 mm, magnification: 2×). (B) Higher magnification showing uniform glomus cells arranged in solid and cribriform nests within a fibrous stroma (H&E staining; Scale bar: 100 µm, magnification: 20×). (C) Diffuse immunoreactivity for smooth muscle actin (immunohistochemistry [IHC] staining; scale bar: 100 µm, magnification: 20×). (D) Absence of desmin expression (IHC staining; scale bar: 250 µm, magnification: 10×).

whereas neuroendocrine markers, cytokeratins, CD31, S100, human melanoma black-45, and desmin are usually negative or only focally expressed. This profile helps distinguish GTs from angioleiomyoma, paraganglioma, neuroendocrine tumors, melanocytic lesions, pericytic tumors, and adnexal neoplasms. The prognosis is generally favorable. Rarely, neoplasms with marked nuclear atypia, atypical mitoses, and large size may present a variable malignant potential.[71] Recurrence is uncommon and is generally associated with incomplete excision. Malignant transformation is extremely rare.

5. Conclusion

This systematic review confirms that oral GTs are exceedingly rare perivascular neoplasms with a predominantly benign clinical course. Analysis of 34 histologically confirmed cases showed that these lesions most commonly involve the lips and tongue, usually present as well-circumscribed nodules, and remain difficult to distinguish clinically from other oral mesenchymal lesions. Accurate diagnosis relies on careful histopathological and immunohistochemical evaluation. Complete surgical excision remains the treatment of choice and is associated with excellent outcomes, low recurrence rates, and, to date, extremely rare malignant behavior in oral GTs.

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Conflict of interest

The authors declare no conflict of interest.

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Ethics approval and consent to participate

The study was reviewed and approved by the Institutional Review Board/Ethics Committee of Independent Ethics Committee of the Azienda Ospedaliero-Universitaria Policlinico Consorziale of Bari (Approval No. 4575). Written informed consent for participation and publication of clinical and histopathological images was obtained from the patient(s) prior to publication.

Consent for publication

Written informed consent for publication was obtained from the patient(s) for the publication of anonymized clinical and histopathological images and related clinical information. The authors confirm that all relevant consent forms have been obtained and are available upon reasonable request.

Availability of data

Not applicable.

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