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Glomus Tumor of the Oral Cavity: Report of a Rare Case and Literature Review

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Glomus tumor is a benign neoplasm composed of a perivascular proliferation of glomic cells that resembles the normal glomus body. Usually, it appears as a solitary, symptomatic small blue-red nodule, located in the deep dermis or subcutis of upper or lower extremities of young to middle-aged adults. Cases affecting the oral cavity are very rare, with only 23 well-documented cases reported in the English-language literature. Herein, we present a rare case of glomus tumor of the upper lip, and review the literature of cases involving the mouth.

Key Words: glomus tumor, immunohistochemistry, oral cavity, review, upper lip.

Introduction

Perivascular tumors are formed by cells derived from contractile perivascular myoid cells/myopericytes that support blood vessels, including glomus cells. According to the soft tissue tumors classification of the World Health Organization (WHO), these perivascular myoid tumors show more alignment with smooth muscle tumors rather than vascular tumors. They are generically denominated myopericytoma (MPC), with a spectrum including glomus tumor (GT), solitary myofibroma (SMF), and angioleiomyoma (ALM) (1,2).

The glomus apparatus is an arteriovenous anastomosis, with thermal regulation function, located at the stratum reticularis of the dermis, mainly in the subungual region, lateral areas of digit and palm of the hands, and on the feet ventral surface (3,4). Glomus cells are small, uniform, rounded cells, with a central nucleus, and amphophilic or pale eosinophilic cytoplasm (5).

GT resembles histologically the glomus body, being firstly described by Masson in 1924, possibly derived from modified smooth muscle cells of the glomus body. This tumor is commonly located in areas rich in glomus bodies, usually appearing as a small blue-red nodule, commonly associated with localized tenderness, paroxysmal pain, and sensitivity to cold or tactile stimulation. It occurs more commonly in young or middle-aged adults (6,7).

In head and neck region, including the oral cavity, solitary myofibroma and angioleiomyoma are relatively common. However, GT is extremely rare in the mouth. To the best of our knowledge, there are only 23 well-documented cases of GT involving the mouth reported in the English-language literature (2,3,8-27). The aim of this report is to describe the histopathological and immunohistochemical features of a rare case of GT involving the upper lip, and to review the pertinent literature.

Case Report

A 51-year-old female patient presented with a lightly painful nodule in the upper lip with approximately 6 months of duration. Intraoral examination revealed a submucosal, smooth-surfaced, well circumscribed, and normochromic nodule, which measured approximately 10 mm of diameter. The main clinical diagnoses was pleomorphic adenoma or canalicular adenoma, but mesenchymal benign tumors as neurofibroma, neuroma and angioleiomyoma were also considered. Under local anesthesia, the lesion was excised and the surgical specimen sent for histopathological analysis.

Microscopically, hematoxylin-eosin-stained sections showed an encapsulated proliferation of rounded pale eosinophilic epithelioid like cells, with prominent nuclei and inconspicuous nucleoli, which surrounded numerous convolutions of varying sized vessels in a myxoid stroma (Fig.1 A). The fibrous capsule contained numerous blood vessels and small nerve fibers. Within the tumor, some larger vessels presented prominent thickness of the wall forming a nodule of spindle cells that protruded into the lumen (Fig. 1 B). The tumors cells formed two patterns of arrangement, one loose surrounding the larger vessels, and one solid, with dense sheets of tumor cells permeated by many capillary-sized vessels (Fig. 1 C,D). The perivascular concentric layers of rounded clear-eosinophilic cells around larger vessels resembled the histological aspects of the glomus body. Cellular atypia or mitoses were not found.

Immunohistochemically, the tumor cells were positive for vimentin, CD34, α-SMA, muscle actin (HHF-35),

h-Caldesmon and negative for pan-cytokeratin (AE1/AE3), CD138, S-100 and desmin (Table 1). Basement membrane material around tumor cells was positive for type IV collagen in a chicken wire pattern (Figs. 2 and 3). Periodic-acid Schiff (PAS) was additionally performed, highlighting the network of basement membrane material (Fig. 3). According to the histopathological and immunohistochemical features, the final diagnosis was of GT. After 18 months of follow up, no recurrences were observed.

Discussion

GT is uncommon, representing less than 2% of all benign soft tissue tumors (5). Most GTs are solitary, small, nodular painful lesions, usually affecting superficial soft tissues of distal extremities of adults on the third to fifth decades. Despite of this, it may occur at any age and location. Only subungual lesions show predilection for women (24). The present case showed similar characteristics, except for its location, in the upper lip¸ where it is very rare. A review of the English-language literature identified only 23 cases

Table 1. Immunohistochemical profile of the oral glomus tumor

Antibody	Clone	Result	Pattern
Pan Cytokeratin	AE1/AE3	Negative	NA
CD138	MI15	Negative	NA
CD34	QBEnd-10	Focally Positive	Membranous, 30% of tumor cells
Vimentin	Vim 3B4	Positive	Cytoplasmic, 100% of tumor cells
S-100	Polyclonal	Negative	NA
α-SMA	1A4	Positive	Cytoplasmic, 100% of tumor cells
Specific-Muscle Actin	HHF-35	Positive	Cytoplasmic, 100% of tumor cells
H-Caldesmon	h-CD	Positive	Cytoplasmic, most tumor cells
Desmin	D33	Negative	NA
Type IV collagen	CIV 22	Positive	Pericellular, most tumor cells

NA: not applicable

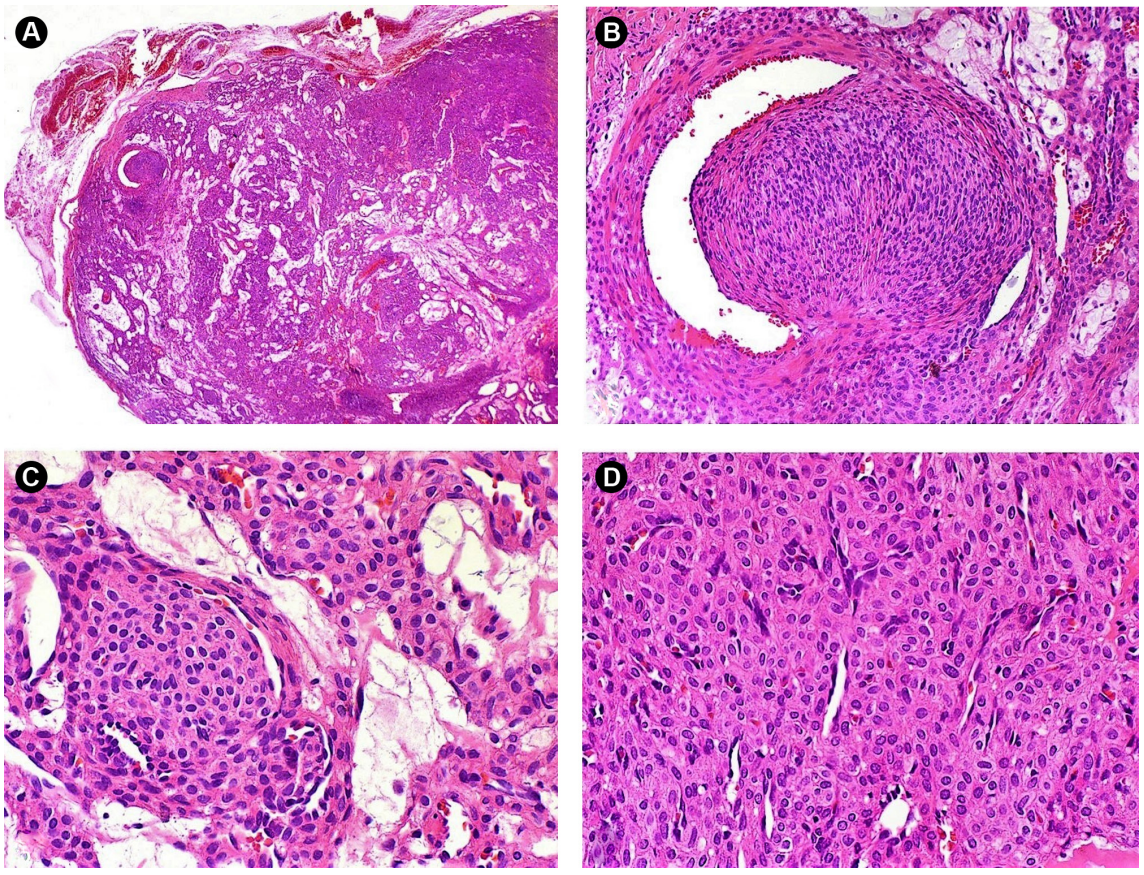

Figure 1. Histopathological features of glomus tumor. (A) At low power magnification, it is observed an encapsulated proliferation of round cells surrounding numerous convolutions of varying sized vessels in a myxoid stroma. The fibrous capsule contained numerous blood vessels and small nerve bundles (HE 25×). (B) Within the tumor, some larger vessels presented a prominent thickness of its wall in the form of a spindle cell nodule that protruded into the lumen (HE 200×). (C) Most of the tumor cells were rounded or ovoid, with epithelioid aspect and tenuous cellular membrane. The cytoplasm was eosinophilic and, in focal cells, it was clear. The nuclei was prominent with well-defined nuclear membrane and some showing inconspicuous nucleoli (HE 400×). (D) Within the solid areas, there were many capillary-sized vessels (HE 400×).

involving the mouth, most of them in lips (Table 2).

GTs commonly are associated with a long history of pain, triggered by variations in temperature or tactile stimulation (1). The mechanisms of pain in GT are still unclear. Several mechanisms have been proposed, as the identification of substance P in nerve fibers of GT, and presence of numerous nerve fibers in the capsule of the lesion, as observed in the present case. Moreover, it was also hypothesized that contraction of myofilaments in the glomus cells in response to temperature changes increases the intracapsular pressure, stimulating unmyelinated nerve fibers (28,29).

A review of the literature on oral GTs, including the present case, revealed a mean size of 12 mm, slightly larger than most extraoral GTs, which commonly are equal or smaller than 10 mm (5). Half of oral cases presented pain or tenderness, and most involved the lips (54.2%), followed by hard palate, with few cases also described in the gingiva, tongue and buccal mucosa. In addition, the upper to lower lip ratio is 2.3:1. The mean age was 48.7 years (ranging from 10 to 85 years), without gender predilection, similar to extraoral GTs, except for subungual lesions that are more common in females. Since most cases of oral GTs occur in the lips, with an upper to lower lip ratio of 2.3:1 (37.5% and 16.6% respectively), the tumor cells may be considered of dermal or submucosal origin, depending on the specific localization (skin or mucosa). From the 13 cases of GT in lips, only seven had clinical image or described specifically if the GT was submucosal, in the vermilion or in the cutaneous portion of the lip. From these 7 cases, 6 were submucosal (5 in upper lip and one in lower lip) and one was located in the vermilion of the lower lip. Particularly in this case, the tumor occurred in the upper lip mucosa. The eventual occurrence of GT

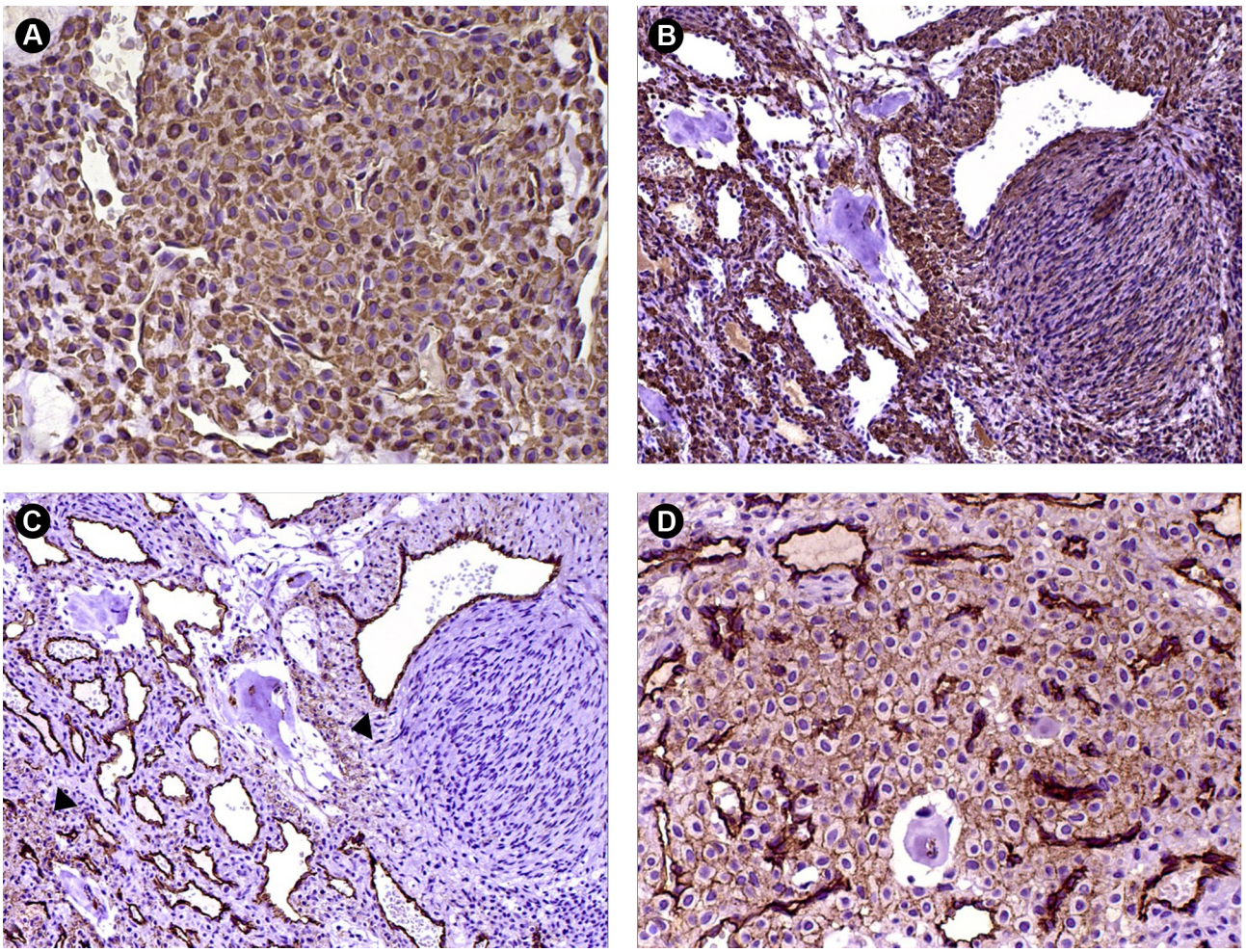

Figure 2. Immunohistochemical features of glomus tumor. (A) Vimentin showed a cytoplasmic positivity in all tumor cells (immunoperoxidase, 400×). (B) The totality of the tumor cells and blood vessels were intensely positive for α-SMA (immunoperoxidase, 200×). (C) CD34 highlighted the great vascularization of the lesion showing focal positivity in the tumor cells (arrowheads) (immunoperoxidase, 200×). (D) At high power magnification, strong membranous positivity of tumor cells for CD34, mainly in solid areas, representing approximately a third of the tumor (immunoperoxidase, 400×).

in head and neck is proportional to known distribution of glomus bodies in the face (15). However, the frequency and distribution of the glomus body in the oral mucosa must be better determined.

In the first description of GT, Masson described 3 different histological patterns that eventually occurs in the same case: angiomatous zone (most common), composed of large blood vessels; solid zone, with cellular areas of epithelioid and smooth muscle cells; and degenerating zone, presenting hyaline or myxoid changes (3,6). Currently, depending on the proportion of glomus cells, blood vessels and smooth muscle, GTs are subcategorized as solid (75%); glomangioma, with vascular predominance (20%), and glomangiomyoma, with smooth muscle cell predominance (5%) (4,5). In the present case, the solid variant predominated, with sheets of glomus cells and capillary vessels. Nevertheless, areas of the glomangioma variant were also observed. The stroma eventually showed myxoid changes as originally described by Masson (6). In oral GTs, the solid pattern is the most common, as occur in the skin.

GT express a smooth muscle-like phenotype, with consistent positivity for specific-muscle actin (HHF-35), α-SMA and h-Caldesmon. Ultrastructural features of pericytic/smooth muscle differentiation have been also observed by transmission electron microscopy (7). These characteristics indicate that GT can arise from modified smooth muscle cells of the glomus body. Additionally, GT shows strong pericellular positivity for type IV collagen in a "chicken-wire" pattern, which is also highlighted by PAS, confirming the presence of basement membrane around of glomus cells. Other immunomarkers, as desmin, cytokeratin and S-100 are usually negative (1,4). In cutaneous cases of solid GT, negativity for cytokeratin is

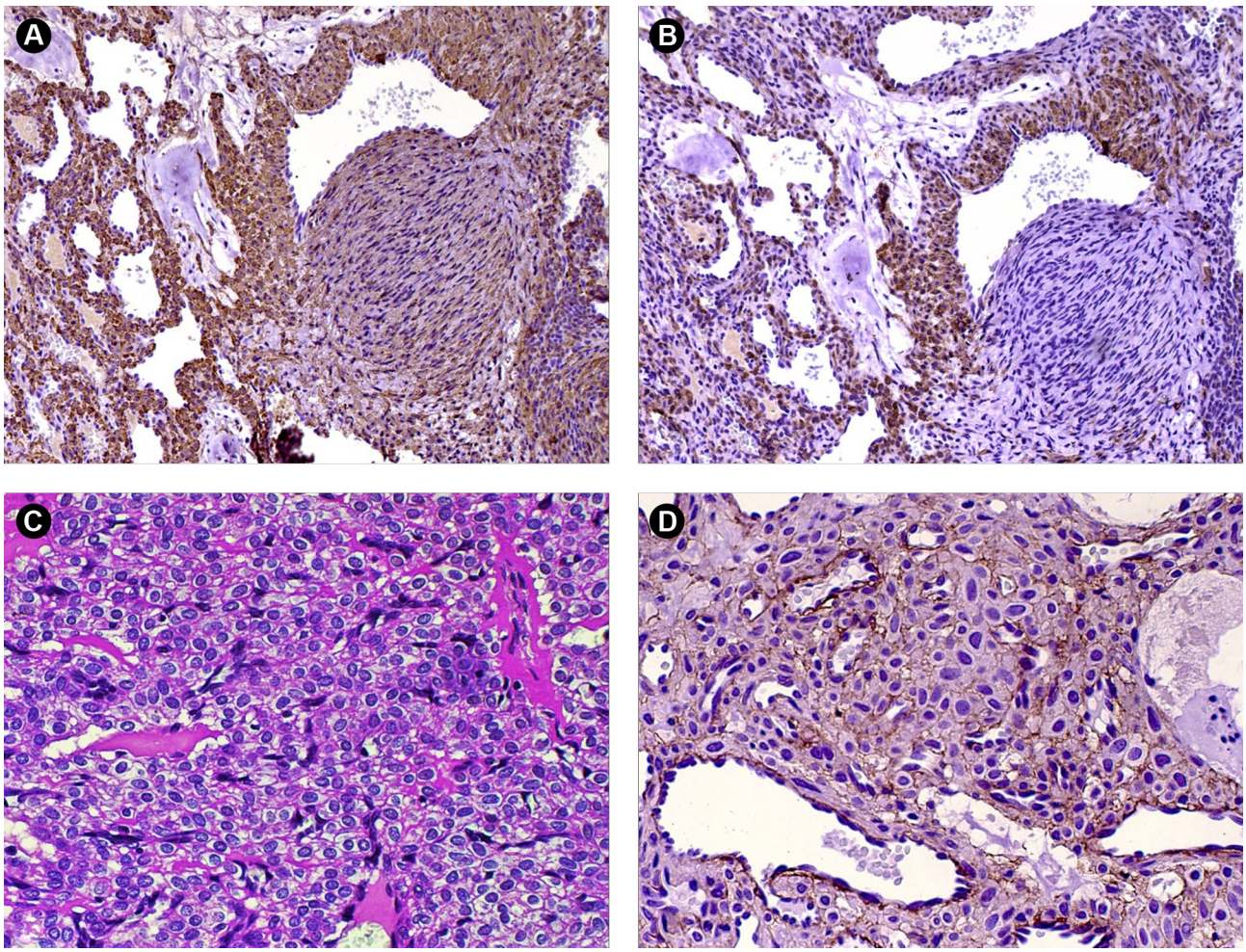

Figure 3. Immunohistochemical and histochemical features of glomus tumor. (A) Muscle actin (HHF-35) presenting strong positivity in all tumor cells and blood vessels (immunoperoxidase, 200×). (B) Most of the tumor was strongly positive for H-caldesmon, however also presented focal negative areas, principally in the focal nodules of spindle cell proliferations (immunoperoxidase, 200×). (C) Positive reactions for PAS highlighting the basement membrane material. (D) immunohistochemistry for type IV collagen highlighting a network of basement membrane material around cells, showing positivity in a "chicken wire" pattern (C: PAS, 400×; D: immunoperoxidase, 400×).

important to rule out an epithelial skin adnexal tumor as hidroadenoma, which can present epithelioid-like cells. The negativity for S-100 is helpful to distinguish a solid GT from intradermal nevi (4,30).

The pattern of CD34 expression in GT is variable. Most authors report that CD34 is negative in tumor cells, highlighting only the endothelium of blood vessels (24). Nevertheless, some authors have described cases with tumor cells positive for CD34, in a membranous pattern (7,31,32). Our case also showed focal positive areas of intense membranous staining of CD34 in the glomus cells.

The treatment of GT is the surgical excision, including those located in the oral cavity. The recurrence is rare (27). Although rare, malignant glomus tumor (MGT) have been described. MGT may progress from a preexisting GT or the lesion may arise de novo, without a preexisting GT. The current criteria for MGT include tumors larger than 2 cm, presence of atypical mitoses, marked atypia nuclear and increasing mitotic activity. In contrast to GT, MGT usually appears as a deep lesion, characterizing as subfascial or visceral mass, and the symptoms include compression of the adjacent tissues (33). Recent review revealed that only one case of MGT have been described in oral cavity (33).

In summary, oral GT is very rare, occurring predominantly in the lips of adults, without gender predilection. It usually appears as a submucosal and well-circumscribed nodule, with varied symptomatology. Immunohistochemical positivity for muscular markers is helpful to confirm diagnosis. Most GT are benign and may be treated by simple surgical excision, providing immediate and permanent pain relief.

Table 2. Cases of oral glomus tumor reported in the English-language literature

Case	Year	Author	Age	Gender	Location	Symptoms	Size (mm)	Type
1	1954	King (8)	32	M	Gingiva	Tenderness	6	Solid
2	1965	Harris and Griffin (9)	35	F	Periodontium	Pain	5	Mixed
3	1967	Sidhu (10)	10	F	Hard palate	Unkn†	Unkn	Unkn
4	1976	Charles (11)*	17	F	Hard palate	No	Unkn	Glomangioma
5	1979	Sato et al. (12)	29	M	Tongue	No	3	Unkn
6	1981	Tajima et al. (13)	63	F	Tongue	No	Unkn	Unkn
7	1985	Saku et al. (14)	45	M	Buccal mucosa	No	45	Solid
8	1986	Ficarra et al. (15)	51	F	Upper lip (mucosa)	No	20	Glomangioma
9	1986	Moody et al. (16)	65	F	Upper lip	No	10	Solid
10	1987	Stajcic and Bojic (17)	55	M	Tongue	Unkn	Unkn	Unkn
11	1992	Geraghty et al. (18)	71	M	Hard palate	No	15	Solid
12	1995	Kusama et al. (19)	57	M	Upper lip	Tenderness	Unkn	Solid
13	1996	Savaci et al. (20)	55	F	Buccal mucosa	Pain	10	Glomangioma
14	1997	Sakashita et al. (21)	54	M	Upper lip (mucosa)	No	12	Solid
15	2000	Yu et al. (22)*	54	F	Face, lower lip, buccal mucosa	No	Unkn	Glomangioma
16	2001	Kessaris et al. (23)	46	F	Hard palate	No	18	Solid
17	2004	Rallis et al. (24)	85	F	Upper lip (mucosa)	Pain	13	Solid
18	2005	Lanza et al. (25)	65	M	Lower lip	Unkn	Unkn	Unkn
19	2008	Ide et al. (2)	57	M	Upper lip	Unkn	8	Solid
20	2008	Ide et al. (2)	54	M	Upper lip	Unkn	12	Solid
21	2010	Boros et al. (3)	34	M	Lower lip (mucosa)	No	15	Unkn
22	2010	Dérand et al. (26)	11	F	Lower lip (vermilion)	No	3	Glomangioma
23	2018	Vasconcelos et al. (27)	67	F	Upper lip (mucosa)	Pain	10	Solid
24	2018	Current case	51	F	Upper lip (mucosa)	Pain	10	Solid

* Multiple lesions. †Unkn: unknwon

Resumo

Tumor glômico é uma neoplasia benigna composta de uma proliferação perivascular de células glômicas que lembram o corpo glômico normal. Usualmente, ele se apresenta como um nódulo pequeno, solitário, sintomático e azul-avermelhado, localizado na derme profunda ou subcutânea de extremidades superiores ou inferiores de adultos jovens e de meia-idade. Casos afetando a cavidade oral são muito raros, com apenas 23 casos bem documentados relatados na literatura de língua Inglesa. A seguir, nós apresentamos um caso raro de tumor glômico do lábio superior, e revisão da literatura dos casos envolvendo a boca.

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