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Clinico-pathologic correlations of myofibroblastic tumors of the oral cavity. II. Myofibroma and myofibromatosis of the oral soft tissues

Marilena Vered, Irit Allon, Amos Buchner, Dan Dayan

Department of Oral Pathology and Oral Medicine, School of Dental Medicine, Tel Aviv University, Tel Aviv, Israel

BACKGROUND: Myofibroma is a solitary benign tumor of myofibroblasts. Myofibromatosis describes multiple, simultaneous myofibromas at different sites in various organs. The clinico-pathologic correlations of myofibroma/myofibromatosis confined only to oral soft tissues were analyzed.

METHODS: In the English language literature, 41 myofibroma and 12 myofibromatosis cases involving the oral soft tissues were found. From our files, three new myofibroma cases were added.

RESULTS: Age at time of diagnosis of oral mucosa myofibroma ranged from birth to 70 years (mean 21.7 years), considerably higher than myofibroma in other parts of the body. Lesions occurred during the first decade (44%) and in the first year of life (17%). Male:female ratio was 1:1.6, contrary to the male predominance in other parts of the body. Common sites were the tongue (32%) and buccal mucosa (18%). Treatment was local excision, either complete ($n = 13$) or partial ($n = 3$), wide excision ($n = 4$), surgery, and chemotherapy ($n = 1$). Myofibromatosis involving oral soft tissues was diagnosed at birth in nine (75%) patients, within the first year in two, and as a young adult in one. Male:female ratio was 2:1. The tongue was the most common site (50%). Half the patients died of disseminated disease within a few days from birth, three were cured by partial or complete excision, and three experienced spontaneous regression. Histologically, oral mucosa myofibroma/myofibromatosis appearance agreed with findings in the literature.

CONCLUSIONS: Myofibroma should be included in the clinical differential diagnosis of masses of the oral soft tissues, especially in the tongue and buccal mucosa of children and adolescents. Histological differential diagnosis includes benign and malignant spindle-shaped lesions. Treatment of choice is local excision.

Correspondence: Prof. Dan Dayan, Department of Oral Pathology and Oral Medicine, School of Dental Medicine, Tel Aviv University, Tel Aviv 69978, Israel. Tel: +972 3 640 9305, Fax: +972 3 640 9250, E-mail: ddayan@post.tau.ac.il
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Introduction

Myofibroma/myofibromatosis are terms used to define benign neoplasms composed of contractile myoid cells and myofibroblasts (1). The literature dealing with myofibroma/myofibromatosis is confusing and lesions have been reported under different terms, such as congenital generalized fibromatosis, congenital mesenchymal hamartomas and infantile myofibromatosis (2). However, in the current WHO classification of soft tissue tumors, the accepted terminology is myofibroma for solitary lesions and myofibromatosis for multicentric lesions (1).

Generally, solitary and multicentric myofibromas can occur at any age, from newborns to old age, with an estimated frequency of 90% being discovered during the first 2 years of life (1, 3). The exact ratio between solitary and multicentric forms is difficult to evaluate, but it is estimated that the solitary lesions are more common than the multicentric (2). The most common sites are the cutaneous/subcutaneous tissues and the skeletal muscles, usually of the head and neck region. Patients with multicentric lesions may have a few nodules or more than 100 in several different sites (1–3).

The histopathologic features of the solitary or multicentric myofibroma are identical (2, 3). At low power, the lesions exhibit a multinodular proliferation with a zoned configuration. At the periphery of the nodules, there are light-stained areas composed of short fascicles or whorls of myofibroblasts that are spindle shaped, have pale pink cytoplasm and elongated, tapering nuclei. Considerable collagen deposition is seen among these cells. Hyalinization with a chondroid-like appearance can be found in these areas. Towards the center of the nodules there are dark-stained areas. The lesional cells become smaller, less differentiated, have less

cytoplasm and possess larger, basophilic nuclei. Thin-walled, irregularly branching hemagiopericytoma-like blood vessels may develop among these cells. In some myofibromas, this zonation phenomenon is not so apparent and the two cell types may be mixed throughout the lesion. Occasionally, the hemangiopericytoma-like pattern predominates and this has lead to the suggestion that cases of the so-called infantile hemangiopericytoma are, in fact, cases of myofibroma (3). Myofibromas do not exhibit significant atypia or pleomorphism and mitotic activity is usually minimal. Superficial lesions tend to be circumscribed, while deeper ones are more often diffuse and locally infiltrative.

Myofibromas of the oral soft tissues have been reported mostly as sporadic case reports, as small series or collectively with lesions of the jawbones (4). The aim of the present study is to report three new cases of myofibroma, to review the English language literature for cases of oral myofibroma and myofibromatosis associated with oral lesions, and to analyze them with regard to their clinico-pathologic correlations.

Material and methods

A MEDLINE search of the English language literature was performed from 1966 to 2005 with the following key words: congenital generalized fibromatosis, infantile myofibroma, infantile myofibromatosis, myofibroma, myofibromatosis, and infantile hemangiopericytoma. Tables and reference lists of the relevant articles were screened for articles published before 1966. Only well-documented cases of myofibroma and myofibromatosis involving the oral soft tissues were selected. Unfortunately, the large series of cases of myofibroma/myofibromatosis published by Foss and Ellis (4) provided a combined analysis of the oral soft tissue lesions, jawbones and salivary glands. As no individual data were given for these cases, it was excluded from the present analysis. The cases reported by Jordan and Regezi (5) and Chung and Enzinger (6) were also excluded due to lack of clinical data. From the files of the Department of Oral Pathology and Oral Medicine, School of Dental Medicine, Tel Aviv University, three additional cases of solitary myofibroma were retrieved.

A total of 44 well-documented cases of solitary myofibroma of the oral soft tissues (41 from the literature and three from our files) were available for analysis and 12 cases of myofibromatosis associated with oral lesions were found in the literature. Table 1 presents the cases of solitary myofibroma with regard to patients' demographic data, clinical presentation of the lesions, treatment modality and follow-up information (7–25) and Table 2 presents data of 12 cases of myofibromatosis associated with oral lesions (6, 8, 21, 26, 28–32).

Case 1

A 5-month-old female infant presented with a submucosal mass in the upper lip. About a month before, the parents became aware of the swelling which has continued to grow. The child was asymptomatic and experienced no breathing or feeding difficulties. Clinical examination revealed a fixed, rubbery mass, approximately 2 cm in diameter, occupying most of the upper lip (Fig. 1). The overlying oral mucosa and skin were intact. No additional lesions were found. A tentative clinical differential diagnosis of infantile fibromatosis, infantile fibrosarcoma, or unusual tumor of salivary gland origin was suggested. Under general anesthesia an incisional biopsy was performed via an intra-oral approach. Histopathologic examination revealed a mesenchymal lesion consisting of spindle-shaped cells that demonstrated a nodular biphasic pattern. At the periphery of the nodules, the spindle cells were arranged in short, interweaving fascicles, denoting a light-staining appearance (Fig. 2). Cells were uniform and had vesicular, cigar-shaped and tapering nuclei. Eosinophilic collageneous extracellular matrix was abundant in some areas and separated the spindle cells. Towards the center of the nodules, cells were more closely packed and possessed round basophilic nuclei. These densely crowded cellular areas appeared darker than the peripheral regions. Occasionally, a hemangiopericytoma-like stag horn vascular pattern was observed (Fig. 3). Mitotic activity in both light and dark areas was minimal. Immunohistochemical stains showed strong positive staining for vimentin, alpha smooth muscle actin (α-SMA) (Fig. 4) and muscle-specific actin (MSA, HHF-35) (Fig. 5), especially at the periphery of the nodules and to a lesser degree in their central regions. All lesional cells were negative for h-caldesmon (Fig. 6), CD-34 (Fig. 7), desmin, S-100, and cytokeratins. Based on the clinical setting, the morphologic configuration of the lesion and the positive immunohistochemical profile for myofibroblast cell markers, a diagnosis of myofibroma was established. The entire lesion was conservatively excised. The histopathologic features and immunohistochemical stains of the excised lesion were identical to those of the incisional biopsy. The lesion was well circumscribed but in several areas showed minimal infiltration into adjacent soft tissues, entrapping some salivary glands of the upper lip. Recovery was uneventful with no recurrence 4 years after treatment.

Case 2

A 41-year-old female presented with a painless mass in her left buccal mucosa of approximately 2 months duration. No significant change in size was reported. Clinically, a rubbery-to-firm nodule, approximately 3 cm in diameter, was found in the deep tissue of the buccal mucosa. Overlying skin and oral mucosa were intact. The lesion was suspected for a salivary gland tumor, a connective tissue lesion or muscle tissue tumor. Under local anesthesia the entire lesion was excised and submitted for histopathologic examination. At low power, the lesion was fairly well demarcated with its borders impinging into adjacent muscle tissue. The lesion featured a biphasic appearance: at the periphery it exhibited whorled nodules of myoid cells associated with pseudo-chondroid hyalinization (Fig. 8) and centrally more cellular areas associated with numerous small

Table 1 Demographic data, clinical presentation, treatment modality and follow-up information of 44 cases of solitary myofibroma of the oral soft tissues

	Clinical presentation					
Author	*Age*[a]*/gender*	*Location*	*Size*[b]	*Duration*	*Treatment*	*Follow-up/comments*
Kauffman and Stout (7)	6 y/M	Tongue	0.9	NI	Excision	6 mo, NED
Kauffman and Stout (7)	13 y/M	Tongue	1	NI	Excision	14 mo, recurrence
Briselli et al. (8)	5 w/F	Tongue	2.5	NI	Excision	5 y, NED
Alpers et al. (9)	Birth/F	Tongue	4	NI	Excision	2 mo, recurrence; partial excision and 15 cycles of chemotherapy; 1 y, NED
Van Baarlen and Bax (10)	Birth/F	Lip (lower)	8	NI	Partial excision	2 mo, regression
Daimaru et al. (11)	35 y/M	Buccal mucosa	2.2	6 mo	NI	3 y, NED
Speight et al. (12)	41 y/F	Tongue	2.5	3 mo	NI	NI
Speight et al. (12)	8 mo/M	Tongue	2	4 mo	NI	NI
Speight et al. (12)	5 y/M	Retromolar (mandible)	3	3 mo	NI	NI
Sleeman and Eveson (13)	10 y/F	Buccal mucosa	2.5	6 mo	Excision	1 y, NED
Baker et al. (14)	4 mo/M	Buccal mucosa	1	NI	Wide excision	26 mo, NED
Beham et al. (15)	60 y/M	Gingiva	0.5	NI	NI	No follow-up, recent case
Beham et al. (15)	41 y/F	Tongue	2.5	3 mo	Excision	18 mo, NED
Jones et al. (16)	8 y/F	Vestibule (mandible)	1.2	2 w	NI	NI
Jones et al. (16)	8 y/F	Gingiva (mandible)	1.5	2 w	NI	NI
Jones et al. (16)	11 y/M	Palate	1.5	NI	NI	NI
Jones et al. (16)	19 y/M	Vestibule (mandible)	2.5	NI	NI	NI
Jones et al. (16)	25 y/F	Buccal mucosa	0.8	NI	NI	NI
Jones et al. (16)	35 y/F	Vestibule (mandible)	0.7	NI	NI	NI
Jones et al. (16)	46 y/F	Lip (lower)	1	2 mo	NI	NI
Jones et al. (16)	53 y/M	Buccal mucosa	2	2 mo	NI	NI
Jones et al. (16)	55 y/F	Tongue	0.4	1 mo	NI	NI
Jones et al. (16)	70 y/F	Gingiva	0.8	4 mo	NI	NI
Lingen et al. (17)	11–56y/F	Tongue	1.5–2	1–6 mo	Excision in 2 tumors; wide excision in one tumor	1–6 mo, NED
Lingen et al. (17)	11–56 y/F	Buccal mucosa				
Lingen et al. (17)	11–56 y/F	Tongue				
Magid et al. (18)	5 mo/F	Tongue	2	NI	Hemiglossectomy	3 y, NED
Marciani et al. (19)	6 y/M	Palate (involvement of periosteum)	2.5	3 mo	Wide excision	Lesion suspected for recurrence 3 w after initial surgical procedure treated by wide excision; no further follow-up
De Souza et al. (20)	9 y/F	Gingiva and alveolar mucosa	2	3 mo	Excision	2 y, NED
Beck et al. (21)	6 y/F	Palate	2	NI	Excision	1.5 years, NED
Beck et al. (21)	8 y/M	Palate	2		Excision	9 y, NED
Ugar et al. (22)	21 y/M	Retromolar (mandible)	2	2 mo	Excision	6 mo, NED
Montgomery et al. (23)	42 y/F	Tongue	1	1–2 mo	NI	15 mo, NED
Montgomery et al. (23)	29 y/M	Retromolar (mandible)	1.8	1–2 mo	NI	16 mo, NED
Montgomery et al. (23)	46 y/F	Retromolar (mandible)	2.2	1–2 mo	NI	4 y, NED
Montgomery et al. (23)	50 y/M	Gingiva (mandible)	2.2	1–2 mo	NI	–
Montgomery et al. (23)	6 y/F	Palate	1	1–2 mo	NI	13 mo, NED
Montgomery et al. (23)	27 y/F	Palate	1	1–2 mo	NI	13 mo, NED
Montgomery et al. (23)	14 y/F	Tongue	0.8	1–2 mo	NI	2 y, NED
Liu and Chang (24)	5 y/M	Vestibule (mandible; (involvement of periosteum)	3	3 mo	NI	2 y, NED
Kassenoff et al. (25)	9 y/F	Buccal mucosa	1.8	1.5 mo	Partial excision	2y, stable residual tumor
Case 1	5 mo/F	Lip (upper)	2	1 mo	Excision	4 y, NED
Case 2	41 y/F	Buccal mucosa	2.5	NI	Excision	6 y, NED
Case 3	18 y[c]/M	Tongue	2	NI	Partial excision	9 y, NED

NI, no information; NED, no evidence of disease.
[a]Age at time of diagnosis.
[b]Greatest diameter in cm.
[c]Lesion present from birth.

blood vessels (Fig. 9). No cellular atypia was observed. Lesional cells yielded a strong positive reaction for immunohistochemical staining of vimentin and α-SMA. HHF-35 was weak, focal and mainly located in the peripheral areas. Lesional cells were negative for desmin, h-caldesmon, CD-34 and S-100. A diagnosis

Table 2 Demographic data, treatment modality and follow-up information of 12 cases of myofibromatosis associated with lesions of the oral soft tissues

Author	*Age*[a]*/gender*	*Oral location*	*Size (diameter, cm)*	*Treatment*	*Follow-up*
Stout, case 12[b] (26)	Birth/M	Tongue	NI	Not relevant	DOD at 22 d
Stout, case 23 (26)	Birth/M	Tongue	NI	Not relevant	DOD at 1 d
Bartlett et al. (28)	Birth/F	Tongue	NI	Not relevant	DOD at 2 d
Ts'o and Teoh (29)	Birth/M	Tongue	NI	Not relevant	Died at 62 h
Benjamin et al. (30)	5 d/M	Vestibule (mandibular)	NI	No treatment	General spontaneous regression; NED at 15 mo
Briselli et al. (8)	Birth/F	Vestibule (mandibular) (multiple nodules)	NI	No treatment	General spontaneous regression; NED at 10 mo
Chung and Enzinger (6)	1 d/M	Tongue	NI	Not relevant	DOD
Chung and Enzinger (6)	2 d/M	Tongue	NI	Not relevant	DOD
Wiswell et al. (31)	Birth/F	Tongue	NI	No treatment	General spontaneous regression; NED at 9 mo
Beck et al. (21)	1 mo/F	Buccal mucosa	2	Excision (after initial regression of the central area)	6.5 y NED
Beck et al. (21)	4 mo/M	Floor of mouth (eroded bone)	3	Excision	4 y NED
Scheper et al. (32)	23 years[c]/M	Vestibule (mandible) (involvement of periosteum)	NI	Excision	1 y NED

DOD, died of disease; NED, no evidence of disease.
[a]Age at diagnosis.
[b]Originally published by Williams and Schrum (27) and termed 'congenital fibrosarcoma'.
[c]Patient was diagnosed with lesions of myofibroma on the scalp at 2 years of age, in the contra-lateral mandibular vestibule at 9 years of age, and on the temporal skin at 12 years of age.

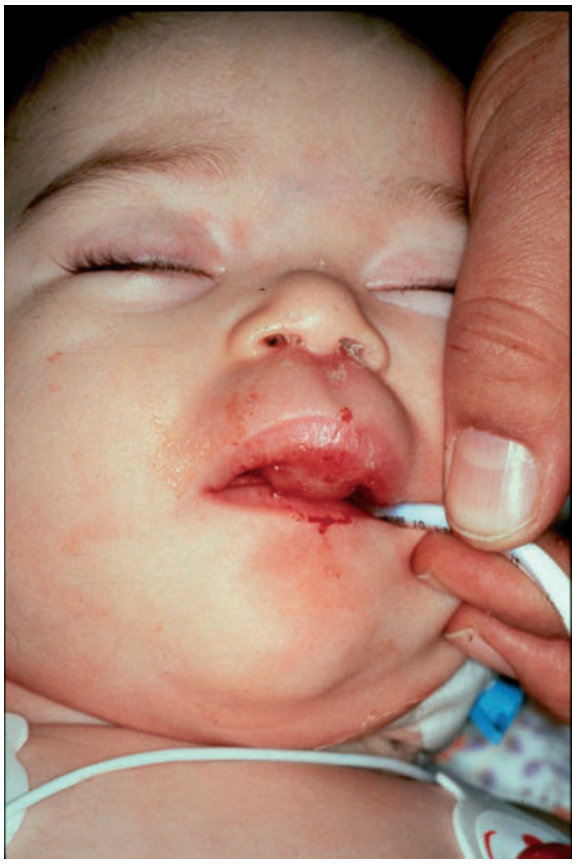

Figure 1 Patient in case 1 has a round-shaped swelling that occupies most of the upper lip and bulges into the oral cavity.

of myofibroma was established. There was no recurrence during 7 years of follow-up.

Case 3

Hematoxylin- and eosin-stained slides and a paraffin-embedded block of an 18-year-old male were sent for consultation to the Department of Oral Pathology, Tel Aviv University. The initial diagnosis was leiomyoma. The patient had a mass on the dorsum of the tongue, which had been present from birth. The mass size has remained stable as long as he remembered, and measured 1.5 cm in diameter. The lesion was excised and submitted for histopathologic examination and further

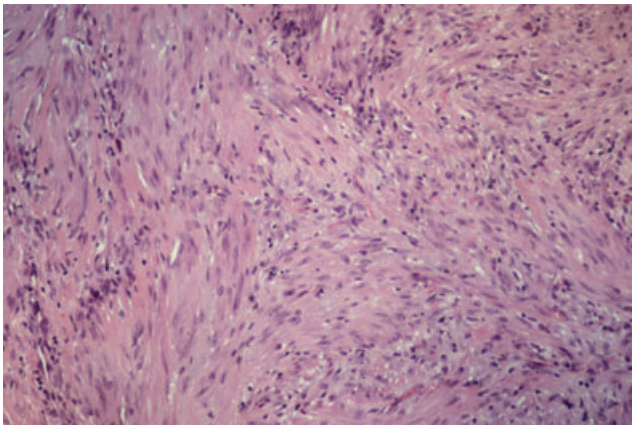

Figure 2 A representative light-stained area of the lesion in case 1 consisting of interwining bundles of spindle cells with abundant extracellular collageneous matrix (hematoxylin and eosin, original magnification ×200).

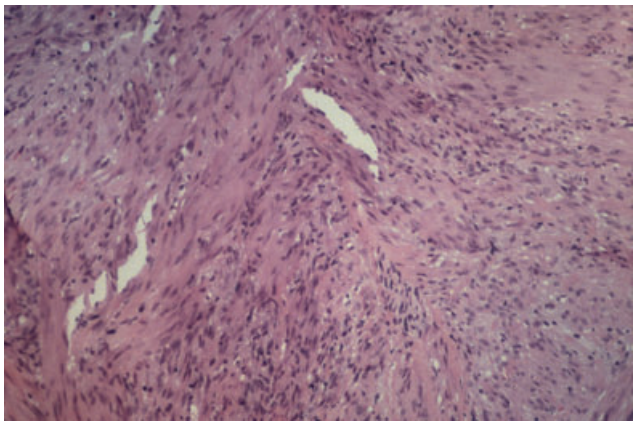

Figure 3 A dark-stained area comprising groups of densely packed cells adjacent to angular, hemangiopericytoma-like blood vessels (hematoxylin and eosin, original magnification ×200).

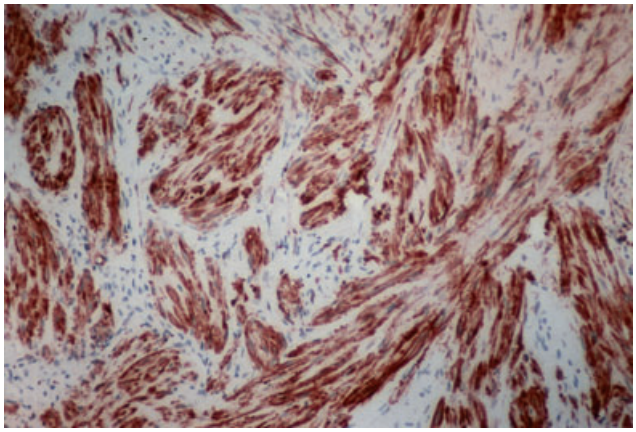

Figure 4 Bundles of lesional spindle cells intensely positive for alpha smooth muscle actin (ABC method, original magnification ×200).

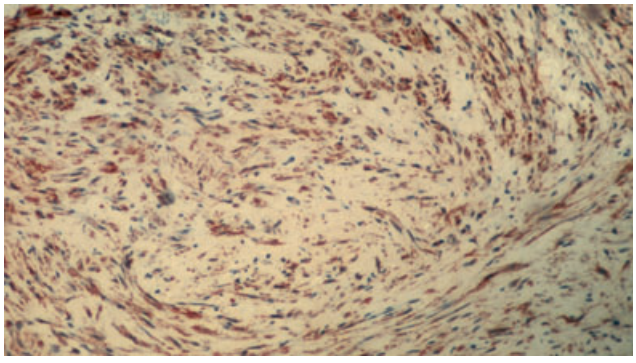

Figure 5 Most lesional cells show positivity for muscle-specific actin (HHF-35) (ABC method, original magnification ×200).

consultation. Histopathology revealed a poorly demarcated lesion composed of spindle-shaped cells arranged in short intersecting bundles and whorls (Fig. 10). In some areas, the abundant extracellular matrix denoted a 'light-stain' appearance. The spindle cells were uniform, had vesicular, tapering nuclei, eosinophilic cytoplasm

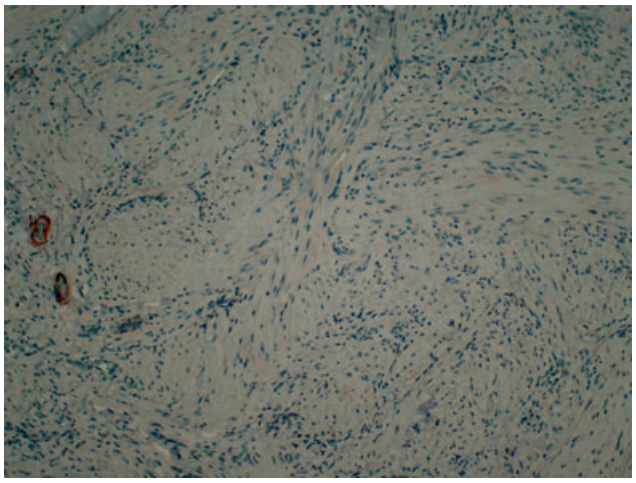

Figure 6 Lesional cells are negative for h-caldesmon. Positive stain is observed in two small blood vessels on the right border of the photomicrograph and serves as a positive control (ABC method, original magnification ×100).

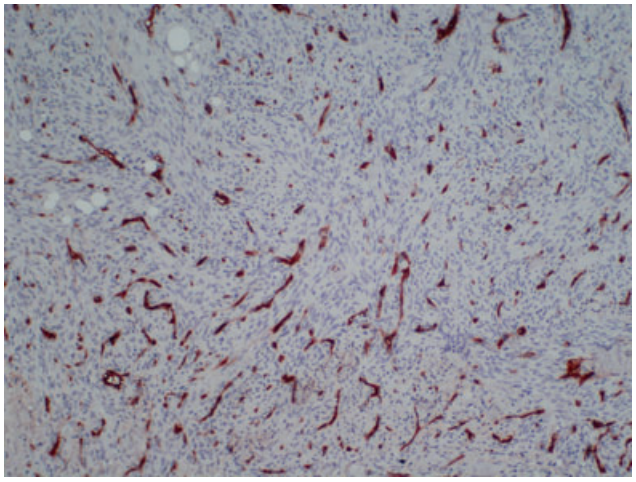

Figure 7 Lesional cells are negative for CD-34. Positive stain highlights the extensive vascular network of the lesion (ABC method, original magnification ×100).

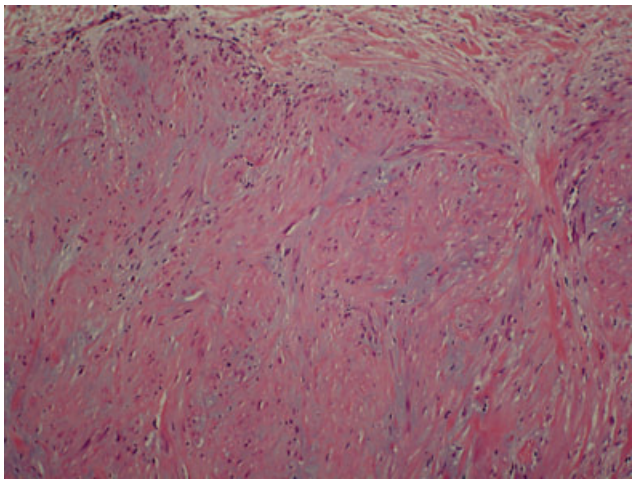

Figure 8 Peripheral area of the lesion in case 2 displays a chondroid-like appearance. The lesion is well demarcated from the surrounding tissue (upper border of the photomicrograph) (hematoxylin and eosin, original magnification ×100).

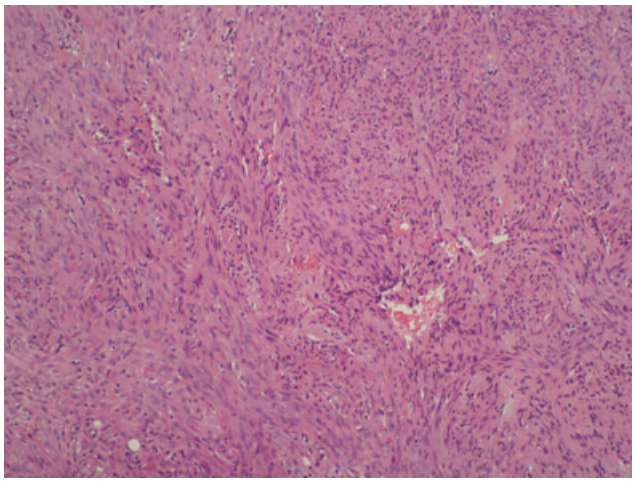

Figure 9 Centrally located area of the lesion in case 2 demonstrates densely packed cells with piknotic nuclei, among which an abundance of small, slit-like angular blood vessels are observed (hematoxylin and eosin, original magnification ×100).

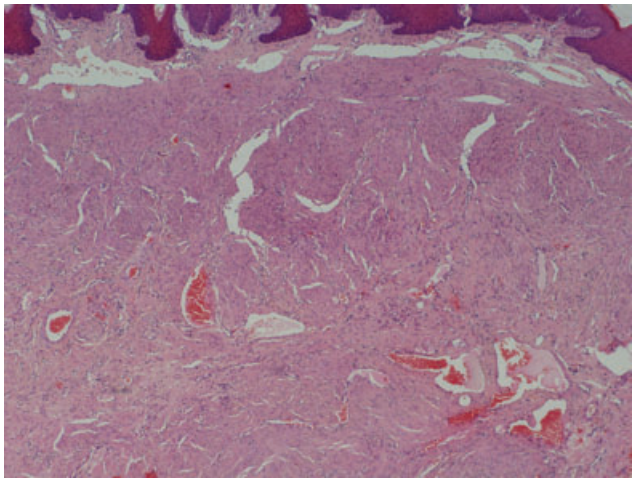

Figure 10 The lesion in case 3 shows a predominant hemangiopericytoma-like vascular pattern. The lesion's upper border is blending into the adjacent submucosa (hematoxylin and eosin, original magnification ×40).

and indistinct cell borders. In other areas, numerous irregular, angular-shaped (stag-horn) blood vessels surrounded by densely packed, round-shaped cells with more emphasized basophilic nuclei rendered a 'dark-stain' appearance. The light- and dark-stain areas were admixed throughout the lesion (Fig. 11). The lesion locally infiltrated into the adjacent muscle bundles of the tongue, but the surgical margins were free of tumor. Immunohistochemical stains yielded a positive reaction to vimentin, α-SMA and HHF-35. A negative reaction was obtained for desmin, h-caldesmon, and S-100, and a diagnosis of myofibroma was established. Picrosirius red stain highlighted the collageneous nature of the extracellular matrix in the light-stained areas, and under polarized light it demonstrated the predominance of the green-yellow colors of both the thin and thick collagen fibers (Fig. 12). This finding is characteristic of neoplastic lesions and not reactive conditions (33–35).

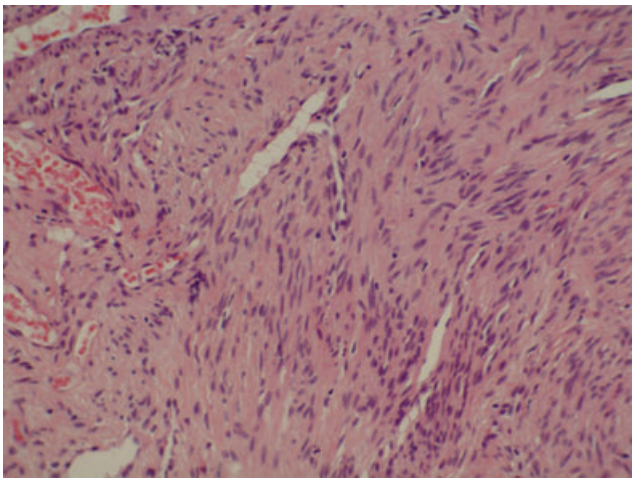

Figure 11 A mixture of light- and dark-stained areas of the lesion in Fig. 10 is highlighted (hematoxylin and eosin, original magnification ×200).

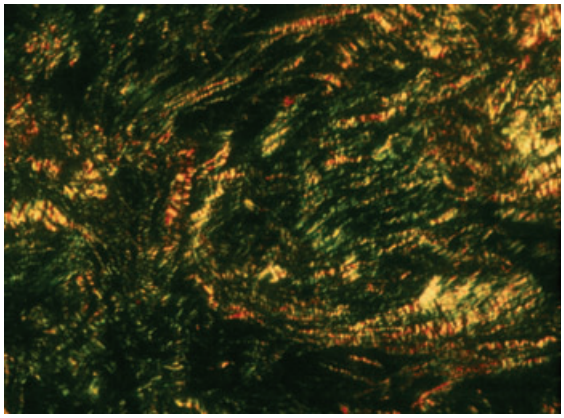

Figure 12 A section of the lesion in case 3 stained with picrosirius red and illuminated with polarized light showing that the fibrous stroma contains collagen fibers, which are predominantly within the yellowish-green and greenish range (original magnifications, ×100).

No evidence of clinical recurrence was reported after 9 years of follow-up.

Results

Demographic data, clinical presentation, treatment modality, and follow-up information of the 44 cases of solitary myofibroma of the oral soft tissues are presented in Table 1.

Age and gender

Age of patients at diagnosis ranged between birth and 70 years (mean 21.7 years, median 13 years). Age and gender distribution are shown in Fig. 13. In the first decade of life, 18 (44%) lesions were diagnosed in which seven (17%) were in the first year of life. There were 27 (61%) female and 17 (39%) male patients, with a female-to-male ratio of 1.6:1 (Fig. 14). In the first two decades of life, the female-to-male ratio was 1.2:1 and in patients older than 20 years the ratio increased to 1.8:1. The tongue was the most common location ($n = 14$,

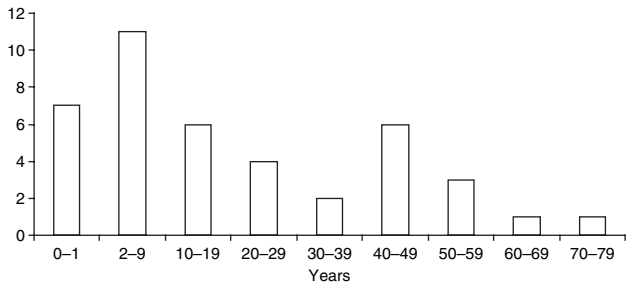

Figure 13 Age distribution of 41 patients with solitary myofibroma of the oral soft tissues.

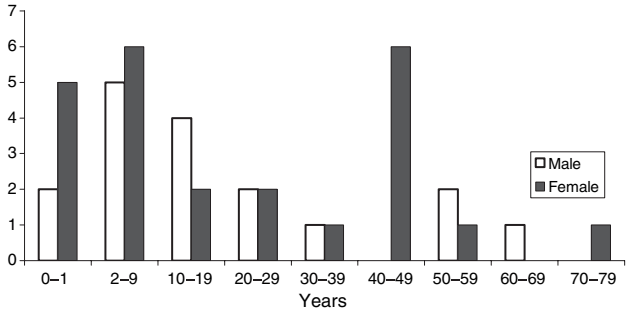

Figure 14 Gender distribution of 41 patients with solitary myofibroma of the oral soft tissues.

32%) followed by the buccal mucosa ($n = 8$, 18%), palate ($n = 6$, 13.6%), gingiva ($n = 5$, 11.4%), mandibular vestibule and retromolar region ($n = 4$, 9%, each), and lip ($n = 3$, 6.8%).

Clinical features
Patients usually presented with a rubbery-to-firm painless swelling of the affected area. Some lesions were superficial and bulged into the oral cavity and others located in the deeper submucosal tissues. One lesion at the base of tongue of a neonate caused breathing difficulties and required intubation (9). Seven lesions exhibited ulceration of the overlying oral mucosa. Three lesions, one in the palate (19), one in the mandibular vestibule (24), and one in the mandibular gingiva (20) involved the adjacent periosteum. Duration of lesion in infants and young children was difficult to assess, as they are painless and their discovery depends on the awareness of the parents. In general, myofibromas were reported to be present for as short as 2 weeks and as long as 6 months, mostly between 1 and 2 months. One lesion was exceptional as it was present for about 18 years (case 3). Three lesions demonstrated increased growth rate after initial surgical intervention (14, 18, 19). Size of lesions at time of diagnosis varied from 0.4 to 4 cm in the greatest diameter, with one exceptionally large lesion of about 8 cm (10).

Treatment
Data were available in 20 cases. Patients were cured by complete local excision in 13 cases and partial excision in three cases (10, 25, case 3). Wide excision was performed in four additional patients, either due to rapid growth after incisional biopsy (14, 18) or involvement of adjacent bony structure (19).

Follow-up data
Follow-up data were reported for 24 patients, ranging from 6 months to 13 years. Three (12.5%) lesions recurred probably due to incomplete initial excision (7 second case, 9, 19). No spontaneous regression was reported in any of the solitary myofibroma of the oral soft tissue cases.

Myofibromatosis

Histopathologic findings
Microscopic description was provided for 41 cases. Under low-power examination, lesions were well circumscribed with alternating fascicular and cellular areas, which imparted a nodular zonal pattern and biphasic (light- and dark-stained areas) appearance in 32 (78%) lesions. The pattern of light-stained area predominated in three (7.5%) lesions and the pattern of dark-stained area (hemangiopericytoma-like) in six (15%) lesions. Necrosis with/without calcifications was noted in only four cases. Normal mitotic figures were observed, as well as a mild degree of pleomorphism. At high power, most lesions exhibited focal infiltration into the adjacent tissues, usually seen in lesions of the tongue.

Misdiagnoses were rendered in nine (20.5%) cases and included the following entities: neurofibroma, leiomyoma, vascular leiomyoma, atypical cellular smooth muscle tumor, benign mesenchymal tumor, intravascular fasciitis, nodular fasciitis, and fibrous histiocytoma.

Immunohistochemical findings
Immunohistochemical analysis was performed in 35 lesions, yielding a consistent positive strong reaction of the lesional cells to vimentin and α-SMA, and a negative reaction to desmin, S-100, and cytokeratins, with the exception of two lesions, where positive reaction to desmin (18) and focal S-100 (16) was reported.

Demographic data, treatment modality, and follow-up information of the 12 cases of myofibromatosis associated with oral soft tissue lesions are presented in Table 2.

Nine (75%) lesions were diagnosed at birth or shortly after and two (16.7%) additional lesions at 1- and 4-months of age. One oral lesion was identified at the age of 23 years; however, the patient was diagnosed with a previous oral lesion at the age of 9 years. There were eight males and four females, with a male-to-female ratio of 2:1. The tongue was involved in seven (58.3%) cases, the mandibular vestibule in three (25%), and the buccal mucosa and the floor of the mouth in one (8.3%) case each. Three patients were treated by surgical excision. Three additional patients were followed up between 9 months and 6.5 years, during which time gradual regression of the oral lesions was observed. All six patients are well and alive. The remaining six patients died of a generalized disease several days after birth.

Detailed description of the histologic findings of the oral lesions of myofibromatosis was provided in only one case (32) and consisted of a lobular architecture with a bi-phasic pattern. An immunohistochemical study revealed positivity of the lesional cell to smooth muscle actin.

Discussion

Myofibroma/myofibromatosis is the most common fibrous proliferation in childhood with a predisposition for the soft tissues of the head and neck region (2, 31). Nevertheless, the literature lacks a comprehensive review on the clinical features of myofibroma and myofibromatosis associated with the oral soft tissues. The uniqueness of the present study lies in its selective analysis of the lesions of the oral soft tissues independently of those affecting the jawbones, salivary glands, and subcutaneous location.

Generally, myofibroma/myofibromatosis appears from newborns to old age (1), but it is estimated that about 90% of the lesions are diagnosed before 2 years of age, in which two-thirds are already present at birth or shortly after (3). Thus, there is an agreement that these tumors are typically diagnosed in infancy and early childhood. The findings of the present study showed that myofibroma of the oral soft tissues has a notable tendency to appear later in life. Only 17% were diagnosed during the first year of life. Given that most of the lesions were reported during the first two decades (55%), the entity of myofibroma of the oral soft tissues is a tumor of children and teenagers rather than infants.

Generally, myofibroma/myofibromatosis are more common in males than in females (1, 6) and the male-to-female ratio is 1.5:1 (6) and 2:1 (2). The results of the present study showed that myofibroma of the oral soft tissues had a female predominance with a female-to-male ratio of 1.6:1.

Location of myofibroma in the oral soft tissues is remarkable for its preponderance in the tongue, followed by the buccal mucosa, palate, gingiva, mandibular vestibule, and retromolar area, and least common in the lip. A similar location of the lesions was reported by Foss and Ellis (4), but the lip was the second most common location after the tongue.

Clinically, myofibroma of the tongue manifested as an exophytic mass, for which the most relevant clinical differential diagnoses should include irritation fibroma, granular cell tumor, neurofibroma, and schwannoma. Myofibroma of the buccal mucosa, the second most common location, should be clinically differentiated from lymphoid hyperplasia, lipoma (deep seated), and salivary gland tumors.

Detailed histopathologic description of myofibroma was provided in 41 cases, in which most lesions ($n = 32$) exhibited a typical bi-phasic pattern. A few lesions ($n = 6$) were composed predominantly of hemangiopericytoma-like areas and a few others ($n = 3$) exhibited mainly fasciculi of myoid-like cells.

Based on the information that oral soft tissue myofibroma is most commonly found in young patients with preponderance to the tongue and buccal mucosa, the following is the histopathologic differential diagnosis of the most feasible spindle cell lesions in relation to the parameters of age and location.

For the tongue, the main tumors to be considered are those of neurogenic and smooth muscle cell origin, as well as other myofibroblastic tumors. Tumors of neurogenic origin are quite common in the tongue. They may demonstrate spindle-shaped cells with various stromal degenerative changes (i.e. myxomatous, hyalinization) and can be excluded due to their immunoreactivity for S-100, which is consistently negative in myofibroma. Leiomyoma can pose one of the most difficult histopathologic differential diagnoses due to the similarity of individual cell morphology and general tumor architecture (36). However, differentiating between myofibroma and leiomyoma currently appears to be less problematic based on the immunoreactivity of the lesional cells in leiomyoma to markers, such as desmin and h-caldesmon (37, 38), which are negative in myofibroma. It can be assumed that prior to the time of immunohistochemistry, some oral lesions diagnosed as leiomyomas, are, in fact, myofibromas. Numerous studies in the past support the diagnosis of leiomyoma using histochemical stains, such as Masson's trichrome (39), van Gieson (40) and Mallory's phosphotungstic acid hematoxylin (PTAH) stain (41). These stains have been proven to be non-specific for distinguishing smooth muscle cells and myofibroblasts precise types of cells (41, 42). Low-grade myofibroblastic sarcoma, which shows a preference for the oral cavity, and especially for the tongue, also should be considered (43). In addition to the fact that it predominantly occurs in adult patients, microscopically, it is characterized by an infiltrative growth pattern with at least focally moderate nuclear atypia consisting of enlarged, hyperchromatic, and irregular nuclei. Although only a few cases have been reported, it seems that the bi-phasic pattern of myofibroma is not a feature of this low-grade myofibroblastic malignancy.

In lesions of the buccal mucosa, spindle cell lesions to be considered in the histopathologic differential diagnosis include nodular fasciitis, desmoid-type fibromatosis, fibrous histiocytoma, solitary fibrous tumor, and infantile/congenital fibrosarcoma. Nodular fasciitis is characterized by a mucin-rich stroma rendering most lesions a 'tissue culture-like' or 'feathery' appearance (44). It may demonstrate extravasated red blood cells and varying degrees of lymphocytic inflammation, but it lacks the nodular architecture with a bi-phasic pattern seen in myofibroma. The desmoid-type fibromatosis has to be cautiously differentiated from myofibromas because of its significantly more aggressive and destructive behavior (45). Microscopically, it is characterized by gross infiltration into the adjacent tissues without the bi-phasic pattern of myofibroma. Furthermore, most lesions of desmoid-type fibromatosis are associated with strong immunoreactivity for beta-catenin (46), which is not a feature of myofibroma. Fibrous histiocytoma usually contains xanthoma cells, touton-type giant cells and usually associated with a lymphocytic infiltrate (47). The macrophage cells within this tumor yield a positive

immunoreactivity to CD68. These features are not characteristic of myofibroma.

Solitary fibrous tumor is another lesion to be included in the histopathologic differential diagnosis of myofibroma of the buccal mucosa, mainly due to the hemangiopericytoma-like pattern of the vascular network, which is similar to that seen in myofibroma (48). It can be differentiated from myofibroma because of its characteristic immunoreactivity for CD34 and CD99, which is negative in myofibroma.

The list of differential diagnosis should also include infantile/congenital fibrosarcoma, which is rare in the oral soft tissues, and has no preference for a certain oral location (49). Infantile/congenital fibrosarcoma may demonstrate overlapping features with myofibroma and hemangiopericytoma. Differentiation from myofibroma could rely on the fact that the intersecting fascicles usually exhibit a herring-bone pattern and, although the tumoral cells show minimal pleomorphism, mitotic activity is prominent. Immunohistochemical stains may be misleading, as several cases have shown reactivity to smooth muscle cell markers (i.e. α-SMA, HHF-35). However, most infantile fibrosarcomas possess a chromosomal translocation, which is not associated with myofibroma (49).

The difficulty in diagnosing myofibroma is reflected by the fact that misdiagnoses are not uncommon, with 20% of misinterpretations according to the present study. In the study of Foss and Ellis (4), in 66 cases submitted to the AFIP for consultation, a total of 77 histopathologic differential diagnoses other than myofibroma were registered, consisting of various benign conditions and locally aggressive or malignant tumors.

Generally, the histopathologic features of myofibroma of the oral soft tissues were in accordance with those described for myofibroma (solitary or multicentric) from other parts of the body (2, 3). However, one major difference was that while necrosis and calcifications were a common finding in tumors in the whole body, only four cases of myofibroma of the oral soft tissues demonstrated necrosis and/or calcifications (9, 10, 13, 14). Areas of necrosis are suggested to be associated with spontaneous regression of myofibroma (50). In oral myofibroma, only one lesion with necrosis and calcifications has been reported to regress spontaneously after partial excision (10). The occurrence of spontaneous regression of myofibromas may be mediated by apoptosis (50), which is used in many processes of normal embryonic and post-natal normal development (51). This may explain why myofibromas that are present at birth or appear shortly after, tend to regress spontaneously. It can be assumed that myofibroblasts that are influenced by various temporal and spatial factors become more resistant to apoptosis as they move away from birth. Therefore, lesions of myofibroma of the oral soft tissues that generally develop in children and older patients do not tend to regress spontaneously.

The clinical course in patients with myofibroma of the oral soft tissues was usually benign, when complete local excision was the treatment of choice. However, the biological behavior of the lesions was sometimes unexpected. On the one hand, there were a few lesions that were partially excised and then either remained stable (3, case 3) or regressed spontaneously (10). On the other hand, there were lesions that grew considerably after incisional biopsy or incomplete initial excision (9, 14, 18, 21 first case). All patients were cured after a second conservative surgical procedure. Only one case in which the tumor was at the base of the tongue responded to chemotherapy (9). The benefit of chemotherapy for oral myofibroma is difficult to assess. Use of low-dose chemotherapy has been reported in a few cases of life-threatening myofibromatosis with a fair degree of success (52–54), but further studies are needed to establish a suitable protocol for the solitary myofibroma of the oral soft tissues.

Myofibromatosis associated with lesions of the oral soft tissues is extremely rare, with only 12 cases reported in the English language literature. All patients, except one, were diagnosed before 2 years of age. There were twice as many males than females. These demographic data are in accordance with that reported in patients with multicentric myofibromas in different sites of the body. The most common intraoral location was the tongue. Usually lesions present as solitary swellings with the exception of one case where multiple nodules were present (8). Of the patients with oral lesions as part of generalized myofibromatosis, half died of their disease within a few days after birth, and the remaining half are well and alive, either after local excision or following spontaneous regression of the oral lesions.

In summary, myofibroma of the oral soft tissues may develop over a wide age range but it is frequently seen in children and adolescents and has a female preponderance. The tongue is the most common affected site. The histopathologic differential diagnosis consists of spindle cell tumors of neurogenic and smooth muscle cell origin, as well as other myofibroblastic lesions with variable biologic behavior ranging from reactive to benign-aggressive to malignant tumors. Conservative surgical excision is the treatment of choice. Watchful waiting may be appropriate in cases where the lesion was not completely excised, especially in young children. Spontaneous regression is not a feature of solitary myofibroma of the oral soft tissues.

Myofibromatosis associated with oral lesions is rare and usually appear in neonates and infants, with a male dominance. The most affected oral site is the tongue. The oral lesions were either locally excised or regressed spontaneously. Only 50% of the patients survived.

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