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Clinico-pathologic correlations of myofibroblastic tumors of the oral cavity: 1. nodular fasciitis

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BACKGROUND: Nodular fasciitis (NF), a soft tissue lesion mainly composed of myofibroblastic cells, is well documented in various body locations however, in the oral cavity it is rare. The NF has non-specific histologic characteristics that might result in misdiagnosis and mistreatment. The aim of the study was to analyze clinico-pathologic correlations of NF occurring in the oral cavity.

METHODS: A total of 36 cases of oral NF were analyzed including review of the English language literature and five new cases from our files.

RESULTS: Oral mucosa NF was found to peak in the fourth and fifth decades, which is a decade later than NF occurring in other sites of the body. The most common locations were the buccal mucosa (52.8%) and the lips (16.7%). Duration of lesions ranged from 3 days to 2 years, with approximately 61% being present for more than a month, which is longer than the duration of NF from other body locations. Histologically, oral NF showed varying degrees of cellularity and frequently contained myxomatous areas, and often demonstrated local infiltration into adjacent tissues. However, the myofibroblastic, spindle-shaped lesional cells were uniform and lacked any major signs of atypia. Mitotic figures, characteristically abundant in NF lesions throughout the body, ranged from absent to moderately high in oral NF cases. Treatment modality of choice was complete surgical excision. Recurrence was reported for only one case. Extensive, mutilating surgical procedures for oral mucosa NF are unnecessary, since lesions resolve even when surgical margins are partly involved.

CONCLUSIONS: The NF should be included in the clinical differential diagnosis of superficial and deep soft tissue masses of the oral cavity, especially of the buccal mucosa. Histopathologically, NF should be differentiated from other spindle cell lesions, mainly myofibroma, neurofibroma, fibrosarcoma, solitary fibrous tumor, fibromatosis and fibrous histiocytoma.

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Introduction

Myofibroblasts were first described as key contractile cells in the granulation tissue in the wound healing process (1). Biologically, myofibroblasts are modified fibroblasts with smooth muscle cell-like properties and, in response to mechanical stress, alter their function, appearance and immunophenotype in relation to the stages of the wound healing process (2). Histologically, Myofibroblasts are regarded as cells of uncertain position in the morphologic spectrum between fibroblasts and smooth muscle cells (3, 4). Ultrastructurally, myofibroblasts differ from fibroblasts by presenting actin myofilaments with dense bodies, sub-plasmalemmal attachment plaques, and indented nuclei (2, 4–6), and from smooth muscle cells by possessing an abundance of rough endoplasmic reticulum (RER) and golgi cisternae. Actin myofilaments (stress fibers) are located at the periphery in the sub-plasmalemma region in myofibroblasts and not distributed throughout the cytoplasm as in smooth muscle cells. Myofibroblasts also contain fibronexus adhesion complexes, through which their cytoplasm is in continuity with extracellular components. Immunohistochemically, myofibroblasts exhibit variable immunophenotypes, including vimentin (V) positivity, vimentin and actin (VA) and vimentin and desmin (VD) positivity, and vimentin, actin and desmin (VAD). The VA is the most common (2, 7). In addition, myofibroblasts can be positive for actin isoforms, e.g. specific muscle actin (HHF35) (2). Other useful markers for myofibroblasts are fibronectin with a positive cell surface reaction and calponin, which is sensitive but not specific (8). Recently a new marker, h-caldesmon, was found useful in differentiating between myofibroblasts and smooth muscle cells (9).

As well as the physiological functions in the wound healing process, myofibroblasts have been described as the predominant cells in different lesions, some

recognized as reactive lesions and others as true benign and malignant neoplasms (3, 4). Myofibroblastic lesions can be classified into four main groups, i.e. reactive lesions, benign tumors, locally aggressive (borderline) fibromatoses, and sarcomas with myofibroblastic differentiation (7). In reactive lesions, the fasciitis family constitutes the principal type, with nodular fasciitis (NF) as the most common.

Initially NF was defined as pseudosarcomatous fibromatosis (10), because of its clinical rapid growth and histological rich cellularity and common mitotic figures. However an abundance of data have confirmed its benign nature. The NF is a soft tissue lesion and up to 20% of cases has been recorded in the head and neck region, mostly in infants and children (11). Although the cause of NF is unknown, trauma is believed to be important. In a review of NF cases from the head and neck region, approximately 50% were located in the subcutaneous tissues overlying bony prominences, e.g. the angle of the mandible, the inferior border of the mandible the zygomatic arch, and the anterior mandible (12). Oral cases of NF have been considered rare, with several being summarized in a letter to the editor (13).

The present study reports five new cases of oral mucosa NF, reviews the English language literature for cases of oral NF, and analyses them with regard to their clinico-pathologic correlations.

Material and methods

A MEDLINE search of the English language literature for cases of oral NF from 1966 to 2004 was carried out, with 31 cases found. Five additional cases were retrieved from the files of the Department of Oral Pathology and Oral Medicine, Tel Aviv University. Patients' demographic data, clinical presentation of the lesions, treatment modality and follow-up information were tabulated and summarized in Table 1 (12, 14–36). Excluded from the study were reported cases of oral NF with missing details (37, 38).

The microscopic features of the reviewed oral mucosa NF cases that provided a detailed histopathologic description and the five new cases were recorded and summarized in Table 2. Results were also recorded for histochemical and/or immunohistochemical stains, and for electron microscopy and flow cytometry findings.

Case 1

A 50-year-old woman presented with an asymptomatic, exophytic lesion of 2-month duration affecting the right cheek. Clinical examination revealed an ulcerated lesion with indurated margins, approximately 2 cm in diameter, in the right buccal mucosa. Medical history revealed a smoking habit. Clinical diagnosis was squamous cell carcinoma (Fig. 1). An incisional biopsy was performed, which included both lesional and adjacent normal appearing tissue. Histologic examination showed a fairly well delineated solid lesion impinging on the adjacent skeletal muscle composed of connective tissue of varying cellularity (Fig. 2). The oral epithelium lining was partly ulcerated. Lesional cells were spindle, displayed uniform, cigar-shaped nuclei and commonly haphazardly oriented in a collageneous stroma. The stroma had a 'tissue culture-like' appearance in several areas, due to the presence of myxomatous, poorly cellular tissue (Fig. 3). Various degrees of diffuse or focal chronic inflammation were observed throughout the lesion. Immunohistochemical stains for alpha smooth muscle actin (α-SMA) (Fig. 4) and vimentin (Fig. 5) revealed strong positivity and confirmed the myofibroblastic nature of the spindle cell lesion. A diagnosis of NF with secondary ulceration was made. Complete excision of the lesion was performed and histologic examination revealed only one focus of infiltration of the lesion into the adjacent skeletal muscle. There was almost complete healing of the surgical site, approximately 5 weeks post-operatively (Fig. 6). The patient has had no recurrence for 4 years.

Case 2

A 37-year-old woman was referred to an oral surgeon because of an asymptomatic mass in the floor of the mouth found during routine dental examination (Fig. 7). The patient was unaware of its presence. Clinically, a dermoid cyst or a salivary gland tumor was suspected. Under local anesthesia, a well-circumscribed mass, $4 \times 3 \times 3$ cm was easily enucleated. Microscopically, it was a well-defined, unencapsulated mass characterized by a high degree of cellularity and low fibrillar density. The mass consisted of spindle-shaped cells arranged in irregular bundles or fascicles with plump, oval nuclei presenting slight pleomorphism. Slit-like spaces resembling vascular channels with extravasated red blood cells and well-defined capillaries were seen in proximity to chronic inflammatory cells, denoting a 'granulation tissue-like' appearance to several regions (Fig. 8). Infrequent, normal appearing mitotic figures were evenly distributed throughout the lesion. Small areas of loose, myxoid stroma were also present. There was no recurrence during a 7-year follow up.

Case 3

A 43-year-old woman attended the Oral and Maxillofacial Surgery Department, Tel Aviv University, because of an asymptomatic swelling in the posterior part of the right cheek that grew slowly during the last 3 weeks. Clinical examination revealed a firm, submucosal mass in the right cheek close to the retromolar pad, measuring approximately 2 cm in diameter. A salivary gland tumor was suspected. Under local anesthesia, the mass was separated from the adjacent tissues. Histopathologic examination revealed a well-circumscribed, unencapsulated mass with pushing margins into the adjacent skeletal muscle tissue. The stroma was partially hyalinized and partially myxoid and contained spindle cells, some with vesicular nuclei and others with slightly hyperchromatic nuclei. Cells were arranged in short untidy bundles that included scattered chronic inflammatory cells and extravasated red blood cells. No recurrence was reported during 1-year follow up.

Table 1 Demographic data, clinical presentation, treatment, and follow up information

Author (ref)	*Age/gender*	*Site*	*Duration of lesion*	*Size*[a] *(cm)/depth*	*Signs and symptoms*	*Rate of growth*	*Clinical diagnosis*	*Treatment*	*Follow up*
Smith (14)	42/M	BM	9 months	NM/deep	Tenderness	Progressive (doubled in size last 3 months)	NM	Complete excision	NM
Abulafia et al. (15)	65/M	Lower lip	NM	2.0/exophytic	Asymptomatic	NM	NM	Complete excision	NM
Rakawer (16)	48/M	AlvM upper canine	1.5 months	1.5/exophytic	NM	NM	Apical granuloma[b]	Excision + apicoectomy	3 years
Allen (17)	NM	BM	NM	NM/NM	NM	NM	NM	NM	NM
Allen (17)	25/M	BM	2 months	3.0/NM	NM	NM	NM	NM	2 months – recurrence
Lummerman et al. (18)	31/F	BM	3 days	2.0/exophytic	Tenderness	Progressive	Sebaceous cyst	Complete excision	2.5 years
Solomon et al. (19)	47/M	BM	3 months	2.5/exophytic	Painless	Gradually	Salivary gland tumor	Complete excision	1 month
Larsson and Svartz (20)	25/F	BM	3 days	1.0/deep	Slight pain	Suddenly	NM	Complete excision	4 years
Werning (12)	NM	BM	NM	NM/NM	NM	NM	NM	NM	NM
Werning (12)	NM	BM	NM	NM/NM	NM	NM	NM	NM	NM
Werning (12)	NM	BM	NM	NM/NM	NM	NM	NM	NM	NM
Werning (12)	NM	Tongue	NM	NM/NM	NM	NM	NM	NM	NM
Sato et al. (21)	31/M	AlvM upper premolar and molar	2 months	4.0/exophytic	Slight pain	NM	Salivary gland tumor – malignant[b]	Complete excision	1 year
Dahl and Akerman (22)	36/F	BM	3 months	NM/NM	NM	NM	NM	NM	5 year
Takagi and Ishikawa (23)	46/F	Palate	>1 month	1.0/exophytic	Asymptomatic	NM	NM	Complete excision	NM
Takagi and Ishikawa (23)	34/M	Tongue	>1 month	1.5/exophytic	Asymptomatic	NM	NM	Complete excision	NM
Freedman and Lummerman (24)	19/M	AlvM lower first molar	3 months	2.5/exophytic	NM	NM	NM	Complete excision	NM
Freedman and Lummerman (24)	53/M	BM	2 months	2.0/deep	NM	NM	NM	Complete excision	NM
Kawana et al. (25)	42/M	Upper lip	1 month	1.0/exophytic	Painless	Slowly; rapidly after incisional biopsy	Benign tumor	Complete excision	NM
Mostofi et al. (26)	46/M	AlvM lower molar area	10 days	3.0/exophytic	NM	Rapidly	Pyogenic granuloma[b]	Complete excision	2.5 years
Kahn et al. (27)	20/F	Lower lip (comissu re)	3 months	1.5/deep	Painless	Slowly	Benign salivary gland tumor	Complete excision	3 months
Davies et al. (28)	15/M	Chin and AlvM lower incisors	1 month	1.0/exophytic	Painful	Very rapidly after incisional biopsy	NM	Complete excision	6 months
Bodner and Dayan (29)	20/M	Upper lip	1 month	2.0/exiphytic	NM	Slowly	Salivary gland tumor; nasolabial cyst; mucocele sebaceous cyst	Complete excision	1 year
Badia et al. (30)	76/F	BM	6 months	1.8/exophytic	NM	NM	NM	Complete excision	1.5 years
Shlomi et al. (31)	30/F	BM	2 months	2.0/exophytic	Discomfort last 2 weeks	Sudden enlargement	NM	Complete excision	6 months

Table 1 Continued

Author (ref)	*Age/gender*	*Site*	*Duration of lesion*	*Size[a] (cm)/depth*	*Signs and symptoms*	*Rate of growth*	*Clinical diagnosis*	*Treatment*	*Follow up*
Chartier (32)	39/M	Upper lip	NM	NM/deep	Painless	Rapidly	NM	Wait and see	6 months (residual induration)
Alkan et al. (33)	35/F	BM	4 months	1.7/exophytic	Painful	NM	Benign tumor	Complete excision	1.25 years
Haddad et al. (34)	9/F	Upper lip	3 weeks	1.0/exophytic	Painless	NM	NM	Complete excision	NM
Martinez-Blanco et al. (35)	73/M	FOM	1 month	2.0/exophytic	Painless	NM	NM	Complete excision	4 years
Martinez-Blanco et al. (35)	53/M	Tongue	3 weeks	2.5/exophytic	Painless	Progressive	NM	Complete excision	2.5 years
Nair et al. (36)	37/F	BM	2 months	1.5/exophytic	Painless	Progressive	NM	Complete excision	1.5 years
Case 1	50/F	BM	2 months	2.0/exophytic	Asymptomatic	NM	SCC	Complete excision	4 years
Case 2	37/F	FOM	Unaware of lesion	4.0/exophytic	Asymptomatic	NM	Salivary gland tumor; dermoid cyst	Complete excision	7 years
Case 3	43/F	BM	3 weeks	2.0/exophytic	Asymptomatic	NM	Salivary gland tumor	Complete excision	1 year
Case 4	42/F	BM	2 years	0.8/exophytic	Slight tenderness	NM	Salivary gland tumor	Complete excision	2 years
Case 5	38/M	BM	NM	NM/NM	Asymptomatic	Suddenly	NM	Complete excision	5 years

[a]Greatest diameter.
[b]Involvement of cortical bone.
BM, buccal mucosa; AlvM, alveolar mucosa; FOM, floor of mouth; FH, fibrous histiocytoma; SCC, squamous cell carcinoma; NM, not mentioned.

Table 2 Histopathologic features of oral mucosa NF

Lesion borders		*Lesion cell arrangement*			*Mitotic features*		*Stromal features*		*Vascular components (including slit-like spaces)*		*Inflammatory infiltrate*		*Multinucleatead giant cells*
Well defined	*Focally infiltrative*	*Bundles*	*Haphazard*	*Combined (bundles and haphazard)*	*Numerous*	*Absent-few*	*Tissue culture-like (myxoid)*	*Granulation tissue-like*	*Prominent blood vessels*	*Extravasated RBC*	*Present*	*Absent*	*Present*
10	11	11	4	6	6	7	18	2	12	12	20	1	5

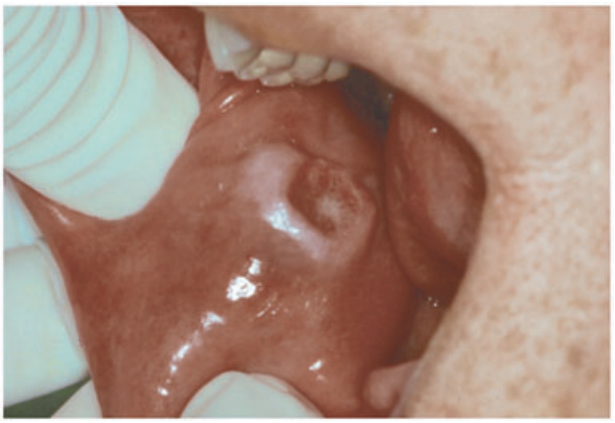

Figure 1 Exophytic lesion on the right buccal mucosa with central ulceration and raised margins suggesting a clinical diagnosis of chronic ulceration or squamous cell carcinoma.

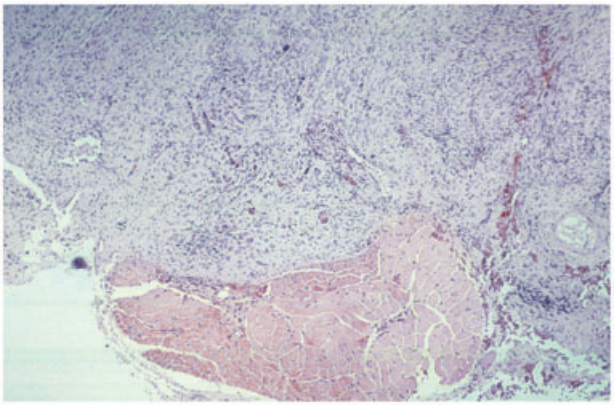

Figure 2 Photomicrograph showing pushing margins of the lesion into the adjacent muscle tissue (hematoxylin and eosin, original magnification ×40).

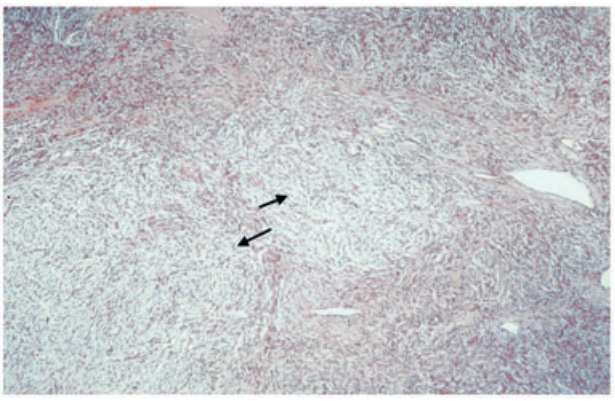

Figure 3 Photomicrograph demonstrating the varying degrees of cellularity that range from highly cellular to myxomatous, poorly cellular regions (black arrows) (hematoxylin and eosin, original magnification ×100).

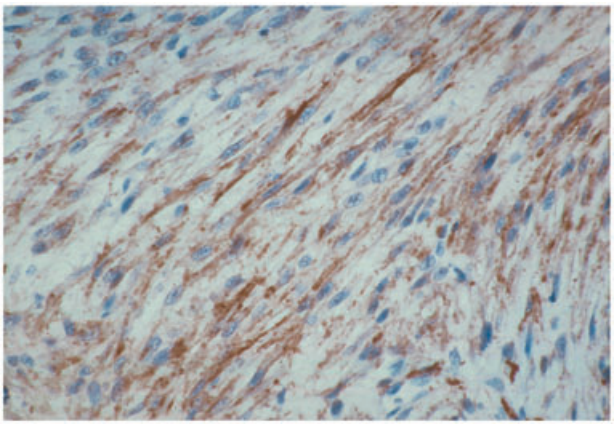

Figure 4 Photomicrograph of immunohistochemical stain with antibody to alpha smooth muscle actin that shows strong and diffuse cytoplasmic positivity of the lesional spindle cells. Staining is either granular or homogeneous (ABC immunostain, original magnification ×200).

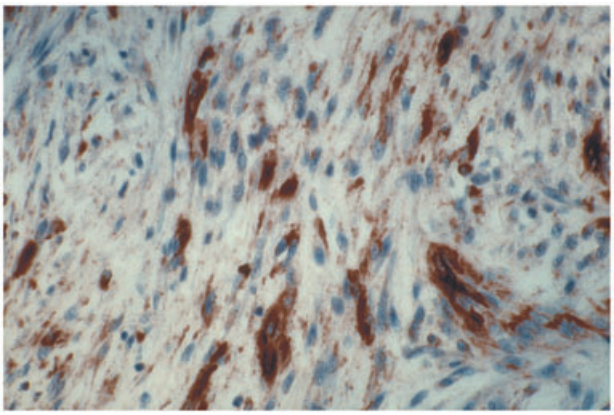

Figure 5 Photomicrograph of immunohistochemical stain with antibody to vimentin that shows strong and diffuse cytoplasmic positivity of the lesional spindle cells (ABC immunostain, original magnification ×200).

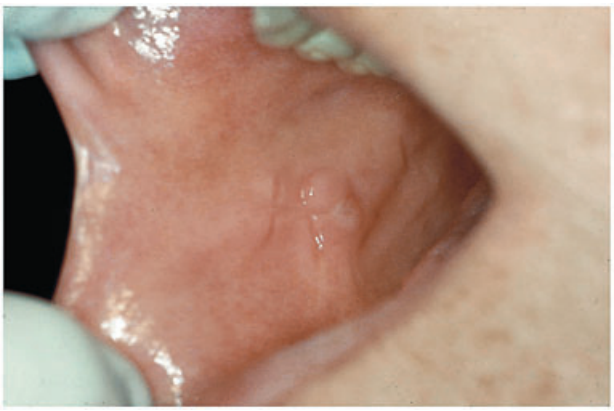

Figure 6 The same lesion as in Fig. 1. Five weeks after excision, healing is almost complete but for a residual surgical wound.

Case 4

A 42-year-old woman presented with an exophytic lesion on the right buccal mucosa, present for approximately 2-year duration. The patient complained of mild tenderness due to lesion biting. Clinical examination revealed a 1 cm diameter mass in the right buccal

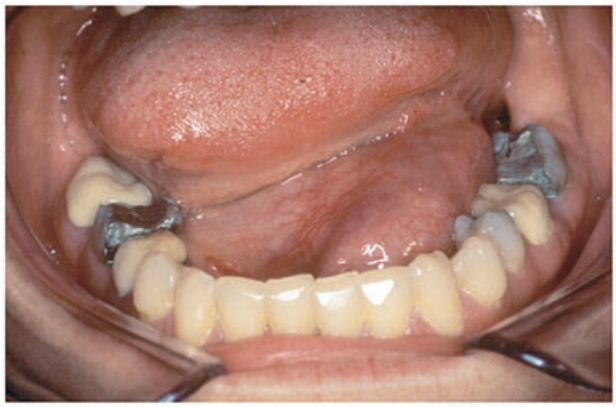

Figure 7 An exophytic lesion in the floor of the mouth, extending from the midline to the lingual aspect of the left premolar area. Lining mucosa is of normal color.

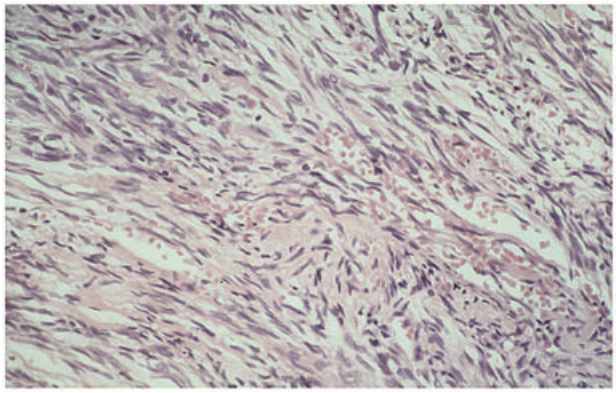

Figure 8 Photomicrograph showing an area reminiscent of granulation tissue with slit-like vascular spaces extravasated red blood cells and dispersed lymphocytes (hematoxylin and eosin, original magnification ×200).

mucosa close to the commisure. The mucosa lining was of normal color. The mass had a rubbery consistency, which was easily and completely excised. Clinical diagnosis was a salivary gland tumor or other inflammatory conditions of the minor salivary glands. Histopathologic examination showed a cellular, well-delineated, unencapsulated lesion composed of spindle-shaped cells arranged either haphazardly or in short bundles. Cells had uniform, plump, vesicular nuclei and a few scattered chronic inflammatory cells and extravasated red blood cells could be observed (Fig. 9). There was no recurrence after follow up of 2 years.

Case 5

The histopathologic hematoxylin and eosin stained slides of a 38-year-old man were sent for consultation to the Department of Oral Pathology, Tel Aviv University. The patient had a right buccal mass of sudden appearance. Clinically, the mass was fixed to adjacent muscular tissue. Histopathologic examination revealed a well-demarcated, unencapsulated mass composed of spindle cells arranged in bundles without definite orientation. Cells had uniform, plump vesicular nuclei. Several slit-like vascular spaces were observed. In a few areas, the stroma was myxoid and poorly cellular, reminiscent of tissue culture. Chronic inflammatory cells were scattered within the lesion. The lesion was easily and completely enucleated and no recurrence was recorded after a 5-year follow up.

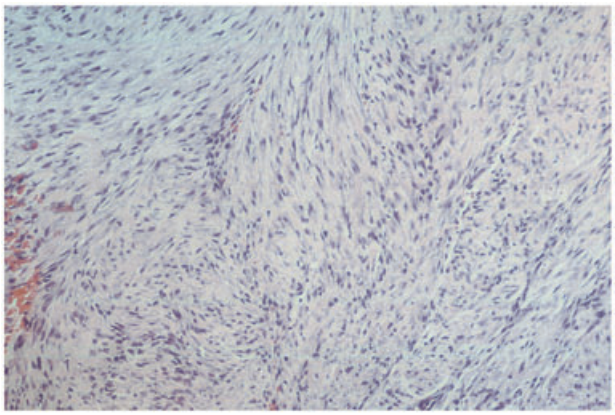

Figure 9 Photomicrograph demonstrating the arrangement of the spindle-shaped cells into short intersecting bundles reminiscent of storiform pattern. Extravasated red blood cells are present at the left and scattered lymphocytes throughout the section (hematoxylin and eosin, original magnification ×200).

Immunohistochemistry

All presented cases were immunohistochemically stained for determining the nature of the spindle-shaped cells. Antibodies for vimentin, α-SMA and HHF-35 were used as the main markers for myofibroblast cells. Desmin, a marker for striated muscle cells was also used as some myofibroblast cells may also show positivity (7). Antibodies for cytokeratins and S-100 were used for ruling out spindle-shaped lesions of epithelial or neurogenic origin, respectively. Results are summarized in Table 3.

Results

Demographic data

Information regarding age (at diagnosis) and gender was available in 31 of the 36 included cases (Table 1). Age ranged from 9 to 73 years (average: 38.9 years, median: 38 years). Most patients ($n = 18$, 58%) were between the fourth and fifth decades of life. There were 16 males

Table 3 Immunohistochemical profile of the spindle-shaped cells in the presented cases

	Vimentin	*α-SMA*	*HHF-35*	*Desmin*	*Cytokeratins*	*S-100*
Case 1	+++	++	++	–	–	–
Case 2	+++	+	+	–	–	–
Case 3	+++	++	++	–	–	–
Case 4	+++	++	+	–	–	–
Case 5	+++	++	++	–	–	–

+++, strong and diffuse stain in majority of spindle cells; ++, strong and diffuse stain in about 50% of the spindle cells; +, weak stain; –, negative stain.

and 15 females. Site of lesions was available for all patients, the most was the buccal mucosa ($n = 19$, 52.8%) followed by the lips ($n = 6$, 16.7%), alveolar mucosa ($n = 5$, 13.9%), tongue ($n = 3$, 8.3%), floor of mouth ($n = 2$, 3.5%), and palate ($n = 1$, 2.8%). Duration of lesions was reported for 27 patients, ranging from 3 days to 2 years. In 17 patients (63%), lesions were present for more than 1 month. Lesion size ranged from 0.8 to 4 cm in their greatest diameter, most ($n = 24$, 89%) were from 1 to 3 cm. Signs and symptoms were described for 22 patients, where a certain degree of pain or tenderness was recorded for 8. Rate of growth was mentioned for 13 patients, where eight lesions grew slowly/progressively, and five suddenly/rapidly. One lesion doubled in size about 2 months before diagnosis and two others grew considerably immediately after incisional biopsy. The tentative clinical diagnosis was usually that of a salivary gland pathology and less commonly a sebaceous or dermoid cyst. Alveolar bone involvement was found in three patients. Treatment was local excision of the whole lesion, except in one patient, in which a 'wait and see' approach was adopted due to esthetic concerns after incisional biopsy and subsequent diagnosis. In most patients, lesions were easily enucleated or dissected from the adjacent tissues. Follow up was recorded for 22 patients, ranging from 1 month to 7 years. There was recurrence in only one patient 2 months after initial treatment, but no further details were available.

Histopathologic data

Documentation of the histopathologic features was usually incomplete and virtually absent for seven cases. The available information is summarized in Table 2, in which it can be seen that the lesion borders were well defined, unencapsulated, and/or focally infiltrative. Constitutional spindle cells were arranged more often in bundles rather than haphazardly or in a combined bundle and haphazard pattern. The number of cases with numerous mitotic figures was almost equal to cases with no or only a few mitotic figures. The stroma was commonly characterized by, myxoid 'tissue culture-like' areas. A considerable vascular network was recorded in 12 cases and extravasated red blood cells also in 12 cases. Most cases had varying degrees of inflammatory cells, frequent lymphocytes and plasma cells. Multinucleated giant cells were found in only five cases.

Histochemical and immunohistochemical stains

Special stains were performed in 15 cases. Histochemical stains were mainly used to demonstrate the presence of a rich fiber network of the lesions' stroma and included silver stains (e.g. reticulin) and Masson's trichrome. Alcian blue was the preferred stain to demonstrate the mucopolysaccharides characteristic of the myxoid areas. Stains with antibodies, such as vimentin, α-SMA, muscle specific actin (MSA), desmin, S-100 protein, CD-34, CD-99, bcl-2, and cytokeratins were applied to differentiate this lesion from other spindle cell lesions. Inflammatory cells were usually stained for anti-chemotrypsin and CD-68, which are histiocyte cell markers. Lesional cells were always positive for vimentin and/or α-SMA/MSA, excluding one case, in which cells were only vimentin positive (34). Lesional cells were constantly found to be negative for S-100 protein and cytokeratins.

Electron microscopy and flow cytometry findings

Lesions were submitted to electron microscope examination in only three cases (25, 26, 29), in which fibroblastic and myofibroblastic cells were found. The latter were characterized by dispersed chromatin, irregular nuclear membranes with indentations and folds, abundant cytoplasmic RER and myofibrils that were immediately beneath the cell borders parallel to the long axis of the cells, occasionally forming focal dense bodies. Desmosome-like junctions were also reported (29). The DNA content of lesional cells of NF from fibrous, myxoid and inflammatory areas was assessed by flow cytometry methods and compared to that of normal gingival fibroblasts (25). The DNA peak of the NF fibrous area was similar to that of the control. The myxoid area was higher and the inflammatory area was between two and threefold higher than the control.

Discussion

The NF is considered a reactive lesion that has been widely reported for different parts of the body since its first description (10). However, the English language literature lacks a comprehensive review on cases of NF originating in the oral cavity. This study presents 36 cases of oral NF that have been analyzed in context to their clinico-pathologic correlations and compared to cases of NF from other regions of the body.

Oral mucosa NF occurs at all ages, similar to NF for other body locations. However, in the present study more than half of the oral lesions (58%) developed between the fourth and fifth decades of life, a decade later than NF in general. Only one lesion was reported during the first decade of life (34), which incidence agrees with previous reviews on NF for the whole orofacial region (including the oral cavity) (12, 22). However, this is in contrast to larger reviews of NF in general pathology textbooks, where most lesions in the orofacial region were reported in infants and children (11, 39). An almost equal gender distribution of oral NF cases was found, as was the case with NF in general (12).

Commonly, the clinical presentation of NF is characterized by rapid growth and as such, has a preoperative duration of less than 1 month (11, 39). In contrast, oral lesions of NF display a wide spectrum of clinical presentation. Growth rates in most lesions are slow and progressive but can be also sudden and rapid. Three lesions (14, 25, 28) initially demonstrating a progressive growth rate enlarged rapidly either spontaneously (14) or after incisional biopsy (25, 28). Duration of lesions ranged from 3 days to 2 years, with approximately 60% present for more than 1 month.

The most common location of oral NF lesions was the buccal mucosa. These, together with the ones on the labial mucosa and tongue made up most of the cases ($n = 28$, 78%). Since these locations are frequently

subjected to repeated trauma, it appears that this would support the theory that some local traumatic factors are responsible for NF development (39). However, in the reviewed oral NF cases a history of trauma was certain in one (28) and suspected in four others (14, 27, 32, Case 4), which was only 14% of all cases. This is similar to other body locations, where only about 10–15% of NF lesions are associated with a history of trauma (39). In a review of NF in the orofacial region, approximately 50% of the lesions were situated in proximity to bony prominences of the face (e.g. mandible and zygoma). Therefore, trauma is likely to trigger a proliferative, reactive process of NF in extra-oral (12) rather than in intra-oral locations.

Usually NF occurs at different anatomic depths within the soft tissues. Among the reviewed oral lesions, 22 displayed a degree of bulginess into the oral cavity with some exclusively exophytic, whereas others were located deep in the soft tissues. The clinical differential diagnosis for an exophytic lesion, occasionally secondarily ulcerated, especially when located in the buccal mucosa, should include traumatic ulcer (chronic), traumatic granuloma, salivary gland tumors, various infectious processes (e.g. of bacterial or deep fungal origin) and squamous cell carcinoma. The clinical differential diagnosis of a solitary, deep nodule should include lesions such as salivary gland tumors, solitary fibrous tumor, neurofibroma, schwannoma, intramuscular lipoma, myofibroma, and fibromatosis. The most commonly suggested clinical diagnosis in the reviewed cases was that of salivary gland tumor. Nodules located deeply within the oral submucosal tissues might not be identified by patients immediately after their appearance, thus leading to a remarkable delay in diagnosis.

The difficulty in diagnosing NF at the histopathologic level results from its non-specific features. NF lesions, including those in the oral cavity, are well delineated, unencapsulated with focal areas of infiltration into the adjacent tissues. Intravascular invasion is also found (24, 27). Lesions are composed of uniform, spindle-shaped cells that possess vesicular nuclei and occasional distinct nucleoli, eosinophilic cytoplasm and indistinguishable cell borders (11, 39, 40). These cells are arranged in short intersecting fascicles (storiform pattern) and/or haphazardly scattered. Some areas may even demonstrate a pseudosarcomatous appearance. Zones of varying cellularity and stromal hyalinization or myxoid (mucin-rich) appearance within the same lesion can be observed. Mucin-rich stroma could be abundant and is responsible for the characteristic 'tissue culture-like' or 'feathery' appearance in most cases. Lesions may demonstrate a well-developed vascular network together with slit-like vascular spaces and extravasated red blood cells, which are often accompanied by varying degrees of chronic lymphocytic infiltration. This may render the lesion a 'granulation tissue-like' appearance, mainly in the peripheral areas. In oral mucosa NF lesions, mitotic figures may range from absent to numerous. This is in contrast to what was described for NF lesions from different body locations that frequently show an abundance of mitotic figures (11, 39). In addition, the presence of multinucleated giant cells, characteristic of most of NF lesions, is rather rare among oral lesions.

Due to the wide histopathologic diversity of NF lesions, only just a few other soft tissue lesions cause as many problems in the histopathologic differential diagnosis. Generally, approximately 50% of cases were misdiagnosed as sarcoma or some other malignant neoplasm (39). In the present review, re-evaluation and a correct diagnosis was found in several oral NF cases. Lesions were initially misdiagnosed as fibrosarcoma (16), sarcoma not otherwise specified (38), neurofibroma (28), fibrous histiocytoma (31) and fibromatosis (Case 5). All of these diagnoses consisted of spindle cell lesions, which should be included in the differential diagnosis of NF (41). The NF should be differentiated from fibrosarcoma/sarcoma because sarcomas are far less common than NF, are relatively large lesions (>4 cm in diameter) that lack myxomatous, 'tissue culture-like' areas frequently seen in NF, and are composed of densely packed, interweaving bundles of spindle-shaped cells, which denote the typical 'herring bone' pattern to the tumors. As well, in sarcomas, cells demonstrate a marked degree of pleomorphism and numerous abnormal mitotic figures, which are not found in NF.

Neurofibroma is another histopathologic differential diagnosis. Both neurofibroma and NF are unencapsulated lesions composed of spindle-shaped cells. However, the constituent cells in the former possess wavy and picnotic nuclei. Neurofibroma lacks an inflammatory component and extravasated red blood cells, frequently encountered in NF. Since myxomatous changes are found in neurofibroma, the presence of myxoid areas is not helpful in distinguishing between these entities.

Fibrous histiocytoma and NF are sometimes impossible to distinguish. Both lesions are composed of spindle-shaped cells, although the former may have a more well-developed, collagenized stroma and, in addition to the spindle cells, rounded, histiocyte-like cells with abundant cytoplasm, which may be prominent in many fibrous histiocytoma, but absent in NF. Multinucleated giant cells may be found in both, but foam cells would favor a diagnosis of fibrous histiocytoma.

Fibromatoses are another group of lesions in the differential diagnosis. However, they are usually larger lesions that commonly infiltrate into the surrounding tissues. They are characterized by slender, spindle-shaped cells arranged in long, sweeping fascicles separated by abundant collagenous stroma, lacking the myxomatous areas and 'granulation tissue-like' appearance, frequently found in NF.

Other possible lesions that can be included in the histopathologic differential diagnosis of NF are myofibroma, solitary fibrous tumor and schwannoma. Myofibroma can be distinguished from NF mainly on the basis of its biphasic 'zoning' phenomenon that refers to the presence of light-staining collageneous, hyalinized areas adjacent to dark-staining hemangiopericytoma-like areas. Solitary fibrous tumor is characterized by a

'patternless' pattern of cell arrangement and a hemangiopericytoma-like vascular network. Schwannoma presents as a mixture of Antoni types A and B structures, which is not a feature of NF. In addition, proliferating capillaries, extravasated red blood cells and inflammatory cells are not typically found in schwannoma.

Immunohistochemical staining can be helpful in diagnosing NF when only small incisional biopsy material is available. Staining with antibodies for S-100 excludes neural tumors and staining with antibodies for CD-34, CD-99, and bcl-2 excludes solitary fibrous tumor. However, immunohistochemistry is of little use in distinguishing NF from other lesions that belong to the group of fibroblastic and myofibroblastic tumors, both benign and malignant (e.g. myofibroma, fibromatosis, fibrous histiocytoma, fibrosarcoma, and myofibrosarcoma) since all may stain for smooth muscle actin and muscle-specific actin. Electron microscopy confirms the myofibroblastic nature of cells in this group, and may be of value in some cases. The DNA content of myofibroblasts in NF was studied in only one oral lesion and it was found to be abnormally higher as compared to normal control tissue (25). Although most NF lesions are generally considered to be diploid (42), several case reports on NF from different body locations describe chromosomal aberrations (43–46), thus raising the question of whether NF is a reactive lesion or a benign tumor. Further studied are needed to resolve this issue.

The clinical course in patients with NF in this series was entirely benign. Complete local excision, with as much tissue sparing as possible is considered as the treatment of choice. Even in lesions, where the deep margins were involved with lesional tissue (19, 26), no recurrence has been reported. Furthermore, in one patient, where there was no surgical excision of the lesion after the diagnosis was made on incisional biopsy material (32), the lesion had almost completely regressed after 6 months. Recurrence was reported in only one patient (2.8%), soon after the first excision (17). This is in accordance with NF lesions in the orofacial region and the entire body where the recurrence rate is approximately 4% (12) and 2% (39), respectively.

In summary, oral mucosa NF is a group of lesions that have a peak incidence in adults (fourth and fifth decades) and a preference for the buccal mucosa. Etiology remains unsolved and trauma seems to play a minor role for the oral NF lesions. Biological behavior is typical for a long-standing exophytic solitary nodule, but deep submucosal located lesions may also occur. Histologically, these are myofibroblastic spindle cell lesions with varying degrees of cellularity that often display some infiltration into the adjacent tissues. In spite of this, constituent cells are uniform and their mitotic rate usually ranges from absent to moderately high. Local excision is the treatment of choice. Immunohistochemistry can be useful in small incisional biopsies to differentiate the myofibroblastic nature of the spindle cells from other spindle cell lesions. Extensive, mutilating surgical procedures are unnecessary, since lesions could resolve even when surgical margins are partly involved.

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