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ORIGINAL ARTICLE

Sporadic and multiple neurofibromas in the head and neck region: a retrospective study of 33 years

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Abstract The neurofibroma occurs as isolated or multiple lesions frequently associated with neurofibromatosis type 1 (NF-1). The aim of this study was to analyze the clinical and histopathological features of neurofibromas, particularly the plexiform variant, in the skin and oral mucosa, discussing their pathogenesis as well as clinical management of isolated lesion unassociated with NF1. The clinicopathologic features of 66 neurofibromas in the head and neck region diagnosed at the pathology laboratories of the Bauru Dentistry School and Lauro de Souza Lima Research Institute from 1970 to 2003 were reviewed. The clinical data, therapy, and follow-up information were obtained from the medical records. The results showed a high frequency of cutaneous lesions (81.8%) occurring mainly in females older than 40 years. Isolated neurofibromas were found in 51.2% of patients, and multiple lesions were often associated with the NF-1. The histopathological analysis demonstrated that diffused neurofibromas occur more frequently than the plexiform type. However, one case of plexiform neurofibroma was detected in the oral mucosa as an isolated lesion non-associated with the NF-1. The indolent clinical behavior of isolated neurofibromas in the head and neck region and the absence of NF-1 association reinforce that sporadic lesion could be hyperplastic or hamartomatous rather than neoplastic in nature.

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Introduction

Neurofibroma is a benign peripheral nerve sheath tumor composed of a variable mixture of Schwann, perineurial-like, and fibroblastic cells, as well as ones with features intermediate between these various cells, immersed in a collagenous or myxoid matrix [11, 19, 27, 36].

Approximately, 25% of all neurofibromas are found in the head and neck region [18, 20] and 6.5% occur in the oral cavity [28] as solitary or multiple lesions associated with neurofibromatosis type 1 (NF-1) [9, 28, 36]. This syndrome is linked on a large gene on chromosome band 17q11.2, whose expression produces a protein named neurofibromin that has been shown to act as a tumor suppressor [14]. This genetically inherited condition, characterized by an autosomal dominant pattern with complete penetrance and variable expression, affects approximately 1 in 2,190 to 7,800 individuals [8, 14].

The real frequency of isolated neurofibromas unassociated with neurofibromatosis in the oral cavity is uncertain, but these tumors have been described in the tongue [5, 24, 28, 30, 32, 38], gingiva [5, 24, 28], palate [22, 24, 31], major salivary glands [2, 6, 34], and maxillary bones [23, 24, 32].

Plexiform neurofibromas are the least common variant considered pathognomonic of the NF-1 [9, 13, 16, 17, 19, 27, 38]. They are poorly circumscribed tumors forming tortuous cords along the segments and branches of a nerve with a tendency to develop centripetally along a nerve course [30]. When associated with NF-1, plexiform variant is commonly disfiguring, causing cosmetic abnormalities, pain, functional deficits, and neurologic manifestations [19]

with a significant rate of malignant transformation [9, 13, 16, 19, 21, 27].

The purpose of the present study was to review the clinical and histopathological features of neurofibromas, particularly the plexiform subtype, located in the skin of the head and neck region and oral mucosa, discussing their pathogenesis as well as the clinical management of isolated lesions unassociated with NF-1.

Materials and methods

Sixty-six surgically excised specimens of neurofibromas in the head and neck region from the files of the pathology laboratories of the Bauru Dentistry School and Lauro de Souza Lima Research Institute from 1970 to 2003 were retrospectively reviewed. The inclusion criteria were:

1. Neurofibromas located in the head and neck region confirmed by biopsy and classified according to the World Health Organization [37];
2. Tumor tissue available for microscopic analysis (glass slides and/or paraffin blocks);
3. Medical records with essential information.

Clinical data (anatomic distribution, gender, age, ethnic group, multiple or isolated lesion, association with NF-1, duration, and size), therapy, and follow-up information were extracted, tabulated, and expressed in percentage.

The qualitative analysis of tumor microscopic features was performed by two observers (L.S.M. and D.T.O.) from the routine sections stained with hematoxylin–eosin (H & E). Some features such as cellular morphology, tissue organization, distribution of inflammatory infiltrate, presence of mast cells, and tactile-like bodies were reported.

Results

The clinical, demographic, and histopathological features of patients with neurofibromas in the head and neck region are summarized in Tables 1 and 2.

The analysis of 43 patients with neurofibromas revealed a female predominance (60.5%) over males (39.5%). Age varied from 9 to 86 years old (mean=47.5 years), with the majority of cases occurring in patients older than 40 years (62.8%) as shown in Table 1.

A total of 22 patients (51.2%) present isolated neurofibromas in the head and neck region, and multiple lesions detected in 16 patients (37.2%) were often associated with the NF-1 (Table 1). Only three NF-1-affected individuals have a familiar history of the disorder.

Clinically, the neurofibromas were soft, slightly elevated, and uncommonly exceed 2 cm in maximum dimension (Table 1). The tumor in our sample developed in later life, and only three patients confirmed that it was present at birth.

Table 1 Distribution of the clinical features of patients with neurofibromas in the head and neck region

Clinical features		Number of cases	Percentage (%)
Age	≤40 years	16	37.2
	>40 years	27	62.8
Gender	Male	17	39.5
	Female	26	60.5
Ethnic group	White	33	76.8
	Non-white	08	18.6
	Non-specified	02	4.6
Location	Face	27	62.8
	Neck	02	4.6
	Scalp	02	4.6
	Gingiva/alveolar ridge	05	11.6
	Tongue	02	4.6
	Buccal mucosa	01	2.3
	Chin	01	2.3
	Floor of the mouth	01	2.3
	Mandible	01	2.3
	Upper lip	01	2.3
Distribution	Multiple	16	37.2
	Isolated	22	51.2
	Non-specified	05	11.6
Association with NF-1	Yes	12	28.0
	No	16	37.2
	Non-specified	15	34.8
Size	<2 cm	33	76.7
	≥2 cm	06	14.0
	Non-specified	04	9.3
Recurrence	No	14	32.6
	Yes	0	0.0
	Non-specified	29	67.4
TOTAL		43	100

Follow-up time ranged from 3 to 230 months for 14 patients with neurofibroma (32.6% of the sample), and most of them (10 patients) were NF-1 affected. As shown in Table 1, no recurrence of the neurofibromas was detected after surgical treatment.

Higher frequency of cutaneous lesions (81.8%) was observed compared to those of the oral mucosa (18.2%). The most frequent intra-oral sites involved were gingiva and/or alveolar ridge (7.6%) as demonstrated in Table 1.

The microscopic features of the neurofibromas located in the skin or oral mucosa were essentially the same. Most of lesions were composed of widely spaced cells with ovoid to thin, elongate nuclei, and scant cytoplasm embedded in a variably collagenous matrix (Fig. 1). Tactile-like bodies resembling Meisnner and Pacinian corpuscles were detected in two neurofibromas of this study (Fig. 2), one of them was plexiform variant. Although relatively circum-

Table 2 Distribution of the microscopic features of patients with neurofibromas in the head and neck region

Microscopic features		Number of lesions	Percentage (%)
Microscopic classification	Plexiform	2	3.0
	Diffuse	64	97.0
Histopathological pattern	Multinodular	2	3.0
	Fasciculated	9	13.6
	Diffuse	55	83.4
Peripheral nerve fibers	Yes	41	62.1
	No	25	37.9
Tecidual distribution	Circumscribed	53	80.3
	Diffused	13	19.7
Chronic Inflammatory infiltrate	Yes	29	44.0
	No	37	56.0
Mast cells	Yes	40	60.6
	No	26	39.4
Blood vessels	Central areas	20	30.3
	Peripheral areas	04	6.1
	Both	42	63.6
Vascularization intensity	Mild	10	15.2
	Moderate	38	57.5
	Intense	18	27.3
TOTAL		66	100

scribed (80.3% of neurofibromas), they are not encapsulated and peripheral nerve fibers were often noted (Table 2).

Diffuse neurofibromas occur more frequently than the plexiform variant, as shown in Table 2. Both cases of plexiform neurofibroma were located in the oral cavity that presented classical histologic pattern characterized by tortuous mass of expanded nerve branches with an abundant mucoid matrix and bundles of wavy, spindle cells (Fig. 3).

Mononuclear inflammatory infiltrate surrounding the blood vessels were seen in 44% of the neurofibromas in the head and neck region. In addition, a moderate to intense vascularity was noted in tumor stroma, and numerous mast cells were frequently observed in cutaneous neurofibromas, mainly in the perivascular region (Table 2).

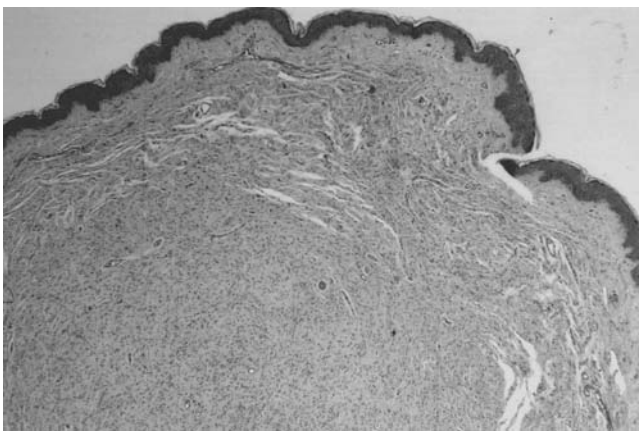

Fig. 1 Neurofibroma localized in the dermis, presenting a diffuse microscopic organization (H & E stain; original magnification ×50)

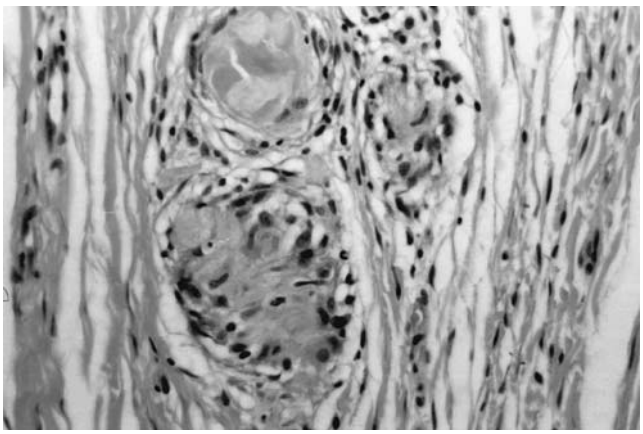

Fig. 2 High-power view of the tactile-like bodies resembling Wagner Meisnner corpuscles (H & E stain; original magnification ×400)

Discussion

In our series, most of the neurofibromas appeared as painless and isolated lesions (51.2%) frequently located in cutaneous region and uncommonly exceed 2 cm in greatest dimension (Table 1). A total of 62.8% of tumors having been present in white women older than 40 years, confirming the findings of Cherrick and Eversole [5] who noted a female predominance in their 19 cases of neurofibromas. This benign clinical course characterized by a slow growing without any apparent symptoms, as observed in our study, delays the search for treatment and contributes for a late diagnosis of the lesion, as frequently described in the literature [9, 10, 27].

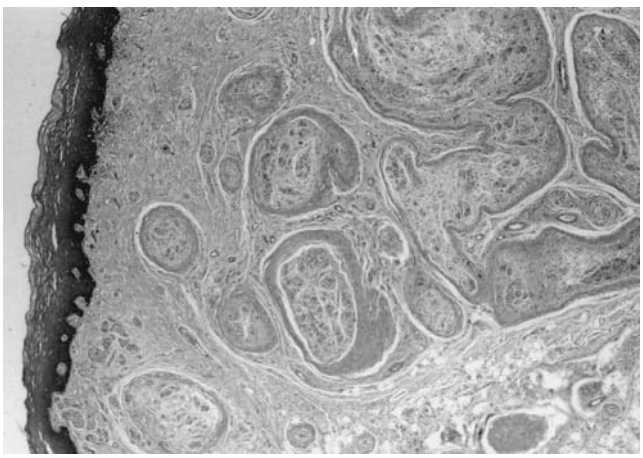

Fig. 3 Low-power view of the plexiform neurofibroma in the oral cavity, showing tortuous nerve fascicles cut in various planes of sections (H & E stain; original magnification ×100)

Multiple neurofibromas were detected in 37.2% of the cases (Table 1). NF-1 was diagnosed in 12 patients and only 3 of them had a positive family history of neurofibromatosis, which reinforces the variability of clinical manifestation of NF-1 [9, 19, 25, 26].

Two of the 12 NF-1 affected patients (16.6% of patients) had neurofibromas within the oral cavity arising in the alveolar ridge and tongue. This frequency of oral neurofibromas in NF-1 patients is higher than that found by previous authors [10] who reported 4 to 7% of oral manifestations in this syndrome. Despite our reduced sample, these results emphasize the importance of a carefully intraoral examination when multiple neurofibromas are detected or NF-1 is clinically diagnosed.

The frequency of solitary neurofibroma in the oral cavity and maxillary bones is uncertain [24]. Some clinical cases have been reported in the literature [1, 2, 15, 22, 23, 29–34], and the tongue is the most common site involved by the tumor [5, 24, 28, 38]. In our series, two cases occurred in the tongue, but the most frequent intra-oral region compromised by neurofibromas was the alveolar ridge/gingiva (Table 1).

The clinical behavior of neurofibromas is characterized by a benign course with a low frequency of recurrence after surgical excision [4, 27]. Large lesions located in critical areas, generally associated with NF-1, have a high recurrence rate [16, 27]. Our sample was basically composed of small and superficial lesions. Fourteen patients (32.6%), 10 of whom affected by NF-1, were followed up for a period that ranged from 3 to 320 months, during which no case displayed recurrence after surgical resection, confirming previous findings [4, 16, 27].

There is an approximately 2 to 6% risk of malignancy arising from the tumor, in individuals with NF-1 [11, 27]. The frequency of malignant transformation that occurs in solitary lesions unassociated with the disorder is not known [9, 11] but some authors [9, 17, 27, 35, 36] have reported that NF-1-associated plexiform neurofibromas seem to have an increased incidence of malignant change. In our study, none of the lesions in the head and neck region underwent malignant transformation.

In spite of plexiform neurofibromas presenting a benign clinical behavior, they are poorly circumscribed, diffused enlargement of neural sheaths that can become distorted into convoluted masses. Dysfunctions including cosmetics abnormalities, pain, and neurologic deficits can be caused by these lesions [19, 27]. In addition, the plexiform variant associated with NF-1 exhibit a higher risk of malignant transformation [9, 17, 27, 35, 36]. Two of the 66 neurofibromas of our sample analyzed in H & E stain presented the plexiform arrangement (Fig. 3), both located in the oral cavity and only one of them was associated with NF-1.

Microscopically, the tumors were composed of a variable mixture of Schwann, perineurial-like, and fibroblastic cells. Tactile-like bodies resembling Meisnner and Pacinian corpuscles are very uncommon microscopic findings, but they were detected in two neurofibromas of this study (Fig. 2). In addition, numerous mast cells in perivascular region were detected in plexiform and diffuse tumors of our sample but the exact function of mast cell to the development of the neurofibroma is not established [19]. According to Packer et al. [19], further studies will be required to determine whether mast cell plays a direct role in neurofibroma tumor formation, or whether it represents an "innocent bystander" cell trapped within the tumor.

The nature of neurofibroma, whether a neoplasm or a hyperplastic process, remains unsettled [27]. Recent genetic works have suggested that all NF-1 patients harbor one nonfunctional NF-1 gene in every cell in the body, and neurofibromas arise as a result of a second, somatic mutation [27]. This NF-1 loss of heterozygosity seems to be an important stage for the tumorigenesis [11, 12, 19, 21, 25, 26]. Nowadays, more investigations are necessary to demonstrate whether the inactivation of both NF-1 alleles occurs in all sporadic neurofibromas non-associated with NF-1.

Oral cavity involvement by a solitary and peripheral plexiform neurofibroma in patients with no other signs of neurofibromatosis is uncommon, and few cases were described in the submandibular gland [34], tongue [30], or adhered to the periosteum at the mental foramen [1]. In cutaneous region, sporadic neurofibromas without other manifestations of the disease were also rarely reported [3, 7], and the authors [7, 9, 21, 27] have suggested a hyperplastic hamartomatous nature for these lesions.

The exact pathogenesis of the neurofibromas, particularly the plexiform variant, is not completely established, and our results reinforce that sporadic lesions in patients without any other stigmata of NF-1, either cutaneous or mucous, present the benign clinical behavior and seems to be hyperplastic hamartomatous rather than neoplastic in nature. Further studies are necessary to confirm the genetic alterations in sporadic neurofibromas to clarify the exact nature of these lesions in the head and neck region.

Conclusions

The results showed that neurofibromas, particularly the plexiform type, could occur in the skin and oral mucosa as an isolated lesion, not associated with the NF-1, presenting benign clinical behavior. This data reinforces that neurofibroma in the head and neck region seems to have a hyperplastic hamartomatous nature whose pathogenesis needs to be further investigated.

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