



Demographic, Clinical and Histopathological Features of Oral Neural Neoplasms: A Retrospective Study

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Abstract

Intraoral neural neoplasms though unusual may be clinically significant. The aim of this study was to categorize and evaluate oral neural tumors in a large oral pathology biopsy service. With IRB approval, a retrospective search of all neural neoplasms of the oral cavity in the archives of the University of Florida Oral Pathology Biopsy Service spanning from 1994 to 2015 was performed. Extraoral cases as well as cases with insufficient patient information were excluded. A total of 340 out of 164,578 submitted specimens in a 22 year period (0.2%) were included with a mean age of 43.3 years (range: 6–89), and 44% male and 56% female. The most commonly affected locations were: tongue (37.5%), palate (22%), lip (19%), and gingiva (14%). The microscopic diagnoses rendered, in descending order of frequency were: neurofibromas (NFs): 123 (36%), granular cell tumor (GCT): 108 (32%), schwannomas: 61 (17%), palisaded encapsulated neuromas: 39 (11%), benign neural lesion not otherwise specified: 8 (2%), and mucosal neuroma c/w multiple endocrine neoplasia type 2B (MEN 2B): 1 (<0.5%). Six cases of NF reported a history of neurofibromatosis Type 1 (NF 1). Four cases showed multifocal lesions. Immunohistochemical staining was performed on equivocal cases (25% of the lesions) and all were confirmed by their S-100 positivity. Intraoral neural neoplasms, though uncommon should be in the differential diagnosis of oral soft tissue entities and specific consideration to syndromal linkage is paramount as this may impact patient management.

Keywords Oral neural lesions · Peripheral nerve sheath tumor · Neurofibroma · Schwannoma · Palisaded encapsulated neuroma · Granular cell tumor

Introduction

In the oral and maxillofacial region, lesions of neural origin are rare and represent 0.2–0.6% of cases submitted to oral pathology laboratories [1, 2]. Oral neural lesions may often appear as bland non-ulcerated tissue proliferations and can be mistaken for reactive fibrous proliferations with the potential for biopsy follow-up to be missed. However, the true significance of accurate diagnosis of neural neoplasms lies in their association with potentially life-threatening

syndromes and malignant transformation such as seen in neurofibromatosis type 1 (NF1) and multiple endocrine neoplasia type 2B (MEN2B) [3]. Biopsied oral neural lesions have been reported as the first recognized sign leading to diagnosis of neural related syndromes, particularly in regards to MEN2B where mucosal neuromas are an early and common development which may occur prior to other manifestations [4]. In addition, significant histologic overlap in these lesions may sometimes lead to difficulty differentiating oral neural lesions with no syndromic significance from those with such associations.

The volume of literature related to neural lesions of the oral cavity is sparse due to the rarity of these lesions [1–3, 5]. The aim of this study is to examine details on the demographics, clinical, and histologic features of a large series of neurogenic neoplasms in order to assist clinicians and pathologists in the accurate diagnosis and identification of such lesions.

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Materials and Methods

With IRB approval, all intraoral neural neoplasms were retrieved from the University of Florida Oral Pathology Service archive spanning 1994 to 2015. These lesions included diagnoses of: neurofibroma (NF), schwannoma, granular cell tumor (GCT), palisaded encapsulated neuroma (PEN), oral mucosal neuroma consistent with MEN 2B syndrome, and malignant peripheral nerve sheath tumor (MPNST). Exclusion criteria included extraoral location including vermilion side of lip, incomplete patient information, or lesions for which a neural origin was uncertain. Non neoplastic neural lesions such as traumatic neuroma and subgemmal neurogenous plaques were excluded. All diagnoses were initially signed out by one board certified oral pathologist and reviewed during quality assurance exercises by secondary oral pathologists and residents. The cases with available slides were retrieved and reviewed by one board certified oral pathologist and one senior oral pathology resident for consensus (SF and FA). Diagnostic criteria of neural lesions according to the most recent WHO classification were utilized [6]. All the cases that met inclusion criteria were reviewed in terms of the patient’s age, gender, location of the lesion, any known syndrome history, clinical appearance, submitting clinician’s impression of the lesion, histologic diagnosis, and immunohistochemistry (IHC) results if available. For S-100 staining, nuclear and cytoplasmic staining was required for positivity. The results were aggregated and described qualitatively using Microsoft Excel 2013.

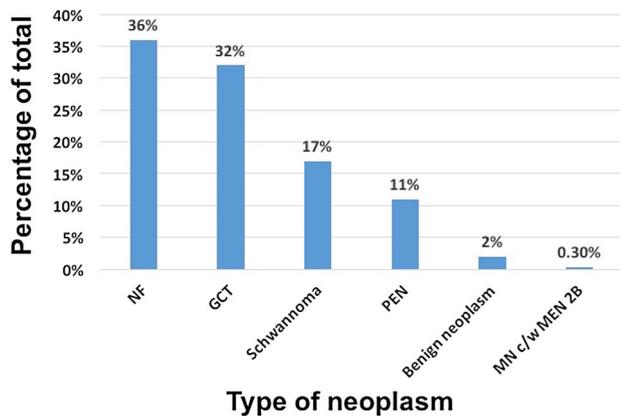


Fig. 1 Distribution of intraoral neural neoplasms. *NF* neurofibroma, *GCT* granular cell tumor, *PEN* palisaded encapsulated neuroma, *MN c/w MEN2B* mucosal neuroma consistent with multiple endocrine neoplasia type 2B

Results

A total of 340 intraoral neural neoplasms were included in the study. Figure 1 lists the diagnoses. Of these 340 cases, females were affected more than males (56 vs 44%). These lesions occurred over a wide age range (6–89 years) with an average age of 43.3 years. The gender predilection and average age among all entities are demonstrated in Figs. 2 and 3. The tongue was the most common site (37.5%) followed by the palate (22%), gingiva (14%), lip (13%), buccal mucosa (6%), and other sites (7.5%) including in descending order mandible (n = 12), maxilla (n = 7), floor of mouth (n = 4), and unspecified oral cavity (n = 1). Four cases (1.2%) were multifocal, including three cases of multifocal GCT and one case of multifocal NF in a patient with known NF1. The clinical appearance of various neural lesions is mentioned in Fig. 4. A comparison

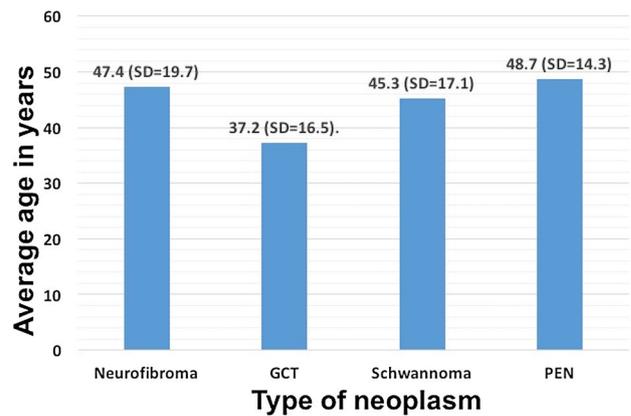


Fig. 2 Age comparison of intraoral neural neoplasms. *GCT* granular cell tumor, *PEN* palisaded encapsulated neuroma, *SD* standard deviation

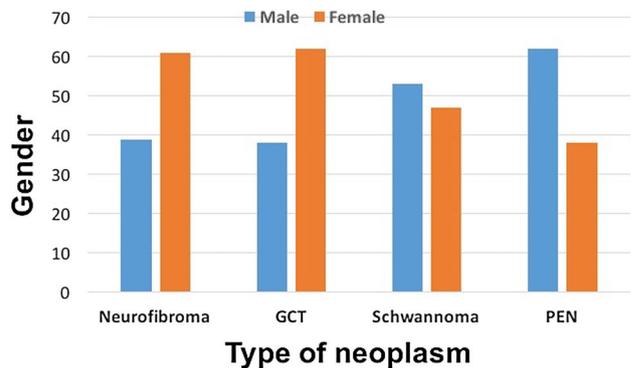


Fig. 3 Gender distribution by diagnosis. *GCT* granular cell tumor, *PEN* palisaded encapsulated neuroma



Fig. 4 Clinical appearance of neural lesions. **a:**Neurofibroma presenting as a diffuse mass of the palate (photo courtesy Dr. Barrett Tolley), **b** Neurofibroma appearing as a small nodule on the dorsal tongue (photo courtesy Dr. Stephen Kotkis), **c** Schwannoma exhibiting a red raised nodular appearance on the hard palate (photo courtesy Dr. Wil-

liam Wood), **d** Granular cell tumor presenting as a yellow macule on the lower lip mucosa (photo courtesy Dr. Pascale Chery), **e** Granular cell tumor presenting as a whitish yellow submucosal nodule on the dorsal tongue (photo courtesy University of Florida oral pathology biopsy service image archives)

of the demographics and histologic variants of different intraoral neural neoplasms can be seen in Table 1.

Six cases of NF (5% of all NF) were associated with neurofibromatosis type 1 (NF1). Six cases were plexiform neurofibroma and three of these reported a history of NF1. All of the plexiform cases were found in females. One case of mucosal neuroma consistent with MEN 2B syndrome was also documented. Examples of histologic patterns of NF, schwannoma, and GCT are depicted in Fig. 5. Adjunctive immunohistochemical staining demonstrating S-100 positivity in 83 cases (24.4%) in descending order of frequency for NF ($n = 65$) followed by schwannoma ($n = 17$) and PEN ($n = 1$). Exclusionary stains were ordered in some cases as well such as CD68, vimentin, smooth muscle actin, muscle specific actin, desmin, and trichrome, and all were noncontributory.

Discussion

To the best of our knowledge, this study included the largest number of intraoral neural neoplasms reported in the literature. Similar to other smaller studies, intraoral neural neoplasms in this study comprised 0.2% of overall submitted specimens to our biopsy service [1, 2]. No malignant neural neoplasms were reported in our study, a relatively unexpected finding.

NF is a benign neurogenic neoplasm that may occur as a sporadic lesion or a component of neurofibromatosis type 1 (NF1) [7]. NF is the most common type of benign peripheral nerve sheath tumor and most frequently involves the skin, although oral lesions are possible [8, 9]. NF are classified into two main types: localized (cutaneous or subcutaneous) or diffuse [8, 9]. Plexiform NF is a distinct multinodular appearing variant highly associated with NF1 [7]. According to the literature, diffuse NF most commonly arise in the head and neck region [10, 11].

In this study, more than one-third of the intraoral neural neoplasms were NF, most frequently affecting gingiva and palate (32 and 29%, respectively). Male to female ratio was 1:1.5 with a wide age range; average age of 47 years. Shekar et al. found that the tongue was the most common location of NF (26%), which differs significantly from our study in which the tongue represents only 12% of all intraoral NF [12]. This difference could be a result of the number of cases studied or the population examined.

For plexiform NF, the most frequently involved nerve in the head and neck region is the trigeminal nerve, particularly ophthalmic and maxillary divisions [13]. In this study, 5% of NF represented the plexiform variant. The lip was the most commonly affected site, followed by tongue and palate. Half of the cases ($n = 3$) reported a known history of NF1, with one of those neoplasms being multifocal in nature. Interestingly, all of the six patients with plexiform NF were female.

Table 1 Demographic and histologic features of the common intraoral neural lesions

Diagnosis	Gender (%)		Age (years)			Location (%)							Comments
	Male	Female	Min	Max	Average	Tongue	Lip	Palate	Gingiva	Buccal Mucosa	Others		
All intra-oral neural neoplasms	44	56	6	89	43.3	37.5	13	22	14	6	7.5	Multifocal = 1.2%	
Neurofibroma	39.3	60.7	7	87	47.4	12.2	7.3	29.3	31.7	6.5	12.2	Plexiform NF = 4.9% Hx of syndrome = 4.9% Multifocal 1%	
Schwannoma	52.5	47.5	10	87	45.3	23.7	28.8	17	6.8	13.6	1	Ancient schwannoma = 5.1% Plexiform schwannoma = 1.7% Intraosseous schwannoma = 1.7%	
PEN	61.5	38.5	23	85	48.7	18	15.5	59	2.5	5	0		
GCT	38	62	6	79	37.2	81.5	9.3	1.9	0.9	1.9	2.8	Multifocal = 2.8% PEH = 6.5%	

NF neurofibroma, Hx reported medical history, PEN palisaded encapsulated neuroma, GCT granular cell tumor

NF1 is an autosomal dominant syndrome with neural and cutaneous manifestations and affects approximately 1 in every 2500 individuals. 8–13% of MPNST has been reported in patients with NF1 [14, 15]. In our study, 6 (5%) out of 123 cases of NF reported a history of NF1. No malignant neural neoplasms were reported in the present study. Shapiro et al. reported that 4–7% of NF patients are syndromic [16]. However, the syndromic patients might be underestimated in our retrospective study due to lack of detailed medical history and follow-up results.

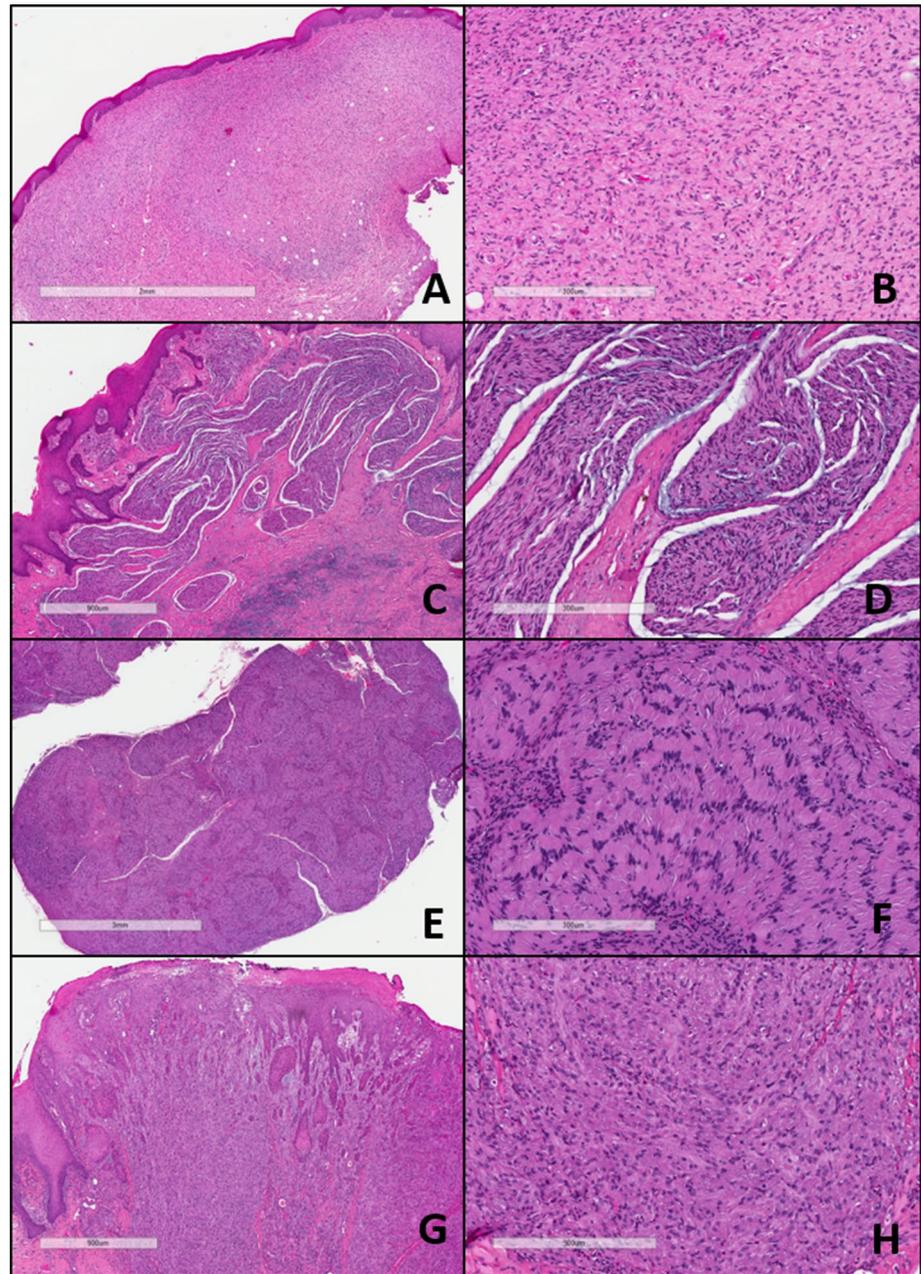
Jouhilahti et al. found that 74% of NF1 patients presented with oral soft tissue changes including mucosal tumors, overgrowths of gingival soft tissue, and prominent lingual papillae [17]. Other studies found that oral manifestations of NF1 are even more common and reported in 72–92% of patients [16, 18]. In this study, we focused only on the oral neural neoplasms and information regarding concurrent oral changes or extraoral tumors was not available for the patients reporting a history of NF1. NF1 can reduce the life expectancy of affected patients [19, 20]. This can be a consequence of malignant transformation (MPNST), vasculopathy such as vascular fibromuscular dysplasia and malformation, and/or hypertension [21–23].

Schwannomas or neurilemmomas are uncommon benign neoplasms arising from supporting Schwann cells of the peripheral nervous system. Even though they are infrequent, one-fourth to the half of these lesions occur in the cervico-facial region. In the oral cavity they generally present as asymptomatic nodules and male and female are equally affected with the peak incident noted in third to fifth decades of life [2, 9]. Most schwannomas are solitary, however, they can be multiple if they are associated with neurofibromatosis [24]. No multifocal schwannoma were found in our study.

Wright and Jackson analyzed 146 cases of intraoral schwannoma and found that more than half of the cases located in the tongue [6]. Approximately 17% of the lesions in the oral cavity in the present study were diagnosed as schwannoma with lip and tongue the most common affected sites (29 and 24% respectively). No significant gender predilection was noted. Among all diagnosed intraoral schwannomas, three cases (5%) had ancient features, while one case was plexiform variant and another one was intraosseous.

Ancient schwannoma is a variant of schwannoma with degenerative changes including myxoid stroma, nuclear hyperchromasia, pleomorphism and calcification. These features might lead to a misdiagnosis of malignancy. Most cases of intraoral ancient schwannoma report an innocuous clinical behavior. The reported cases in the literature demonstrated a striking female to male preponderance (3.5:1) [24]. In contrast, 2 out of 3 ancient schwannomas occurred in males in our study. All of these were located in the lips and buccal mucosa. Plexiform schwannoma is a rare variant (representing approximately 5%) of schwannomas [25].

Fig. 5 Histologic appearance of neural neoplasms. **a** and **b** Neurofibroma, hematoxylin and eosin magnification **a** $\times 2$, **b** $\times 10$. **c** and **d** Plexiform neurofibroma, hematoxylin and eosin magnification **c** $\times 2.4$, **d** $\times 10$. **e** and **f** Schwannoma, hematoxylin and eosin magnification **e** $\times 1$, **f** $\times 10$. **g** and **h** Granular cell tumor with prominent pseudoepitheliomatous hyperplasia, hematoxylin and eosin magnification **g** $\times 2.4$, **h** $\times 10$



It is benign in nature, and might be histologically mistaken as plexiform neurofibroma which is usually associated with NF1 [25, 26]. One plexiform schwannoma was reported in this study in the palatal gingiva in a 25-year-old male without any known history of syndrome. Intraosseous schwannomas are less than 1% of all schwannoma and occur most often in the mandible [27]. In this study, one case of intraosseous schwannoma of the posterior mandible in a 19-year-old female was found.

Palisaded encapsulated neuroma (PEN), also known as solitary circumscribed neuroma, was first reported in 1972 by Reed et al. [28]. The oral cavity is the second most frequent location for PEN after the skin. PEN most

often appears as a painless superficial nodule. Koutlas and Scheithauer analyzed 54 cases of PEN and found that 70% of cases were in males and most of the reported lesions were in the palate and maxillary gingiva (70%) [29]. This is consistent with our study where a marked male predilection (61.5%) with an average age of 48 years was found. Similar to previous studies, the majority of cases were located in the palate (59%) followed by the tongue and the lips.

Granular cell tumor (GCT) is a rare tumor that was originally believed to originate from skeletal muscles. However, neural origin has now been accepted as a result of S-100 reactivity of the neoplasm [30, 31]. Lesions can occur at any location, however they are most common in head and

neck with highest occurrence in the tongue. Clinically, they usually present as a small yellowish nodule [32]. Van de Loo et al. found that 75% of intraoral GCT were located in the tongue with a remarkable female predilection (3:1) and average age of 37 years [32]. In our study GCT, which represent 31% of the oral neural lesions, had a 3:2 female: male ratio with average age of 37.2 years. In addition, 81.5% of these were noted on the tongue. These findings are consistent with previous studies [32]. Pseudoepitheliomatous hyperplasia (PEH) is one of the well-known features associated with GCT. This feature might be misdiagnosed as a squamous cell carcinoma by pathologists who are not familiar with the lesion. PEH was noted in 7 cases (6.5%) of GCT in this study. GCT is usually solitary, however, 16 cases of unusual multifocal intraoral GCT have been reported in the literature with 56% of them in the tongue [33]. The mean age of the patient in the previously reported multifocal cases was 29 years. In the present study, 3 cases of GCT with multifocal lesions were reported in female patients with average age of 28.7 years. The tongue was involved in all of the reported cases, with additional lesions affecting the lips and buccal mucosa. Multifocal GCT, especially in young patients have been linked to many disorders, including neurofibromatosis and Noonan's syndrome [33]. Other disorders associated with multiple GCT include lentiginosis, growth retardation and cardiac and pulmonary defects. Syndromes that share these findings are LEOPARD syndrome, LAMB syndrome and NAME syndrome [34]. Multiple GCT have also been described as familial, suggesting a hereditary role [34]. None of patients in the current study with GCT reported a known history of any syndrome.

Mucosal neuroma is a cutaneous neural component of MEN 2B syndrome. MEN 2B is an autosomal dominant disorder associated with multiple endocrine malignancy, especially medullary thyroid carcinoma and pheochromocytoma. Early detection of this syndrome is critical as it affects the prognosis of those affected patients [35]. In this study, a 17-year old boy was reported with multifocal (gingiva and buccal mucosa) mucosal neuroma as a component of MEN 2B syndrome.

Malignant peripheral nerve sheath tumor (MPNST) is an uncommon soft tissue malignant neoplasm with aggressive clinical behavior. They have nonspecific histological features which makes the diagnosis highly challenging. They either arise from preexisting NF or de novo [36, 37]. Up to the half of MPNST cases have a family history of NF1 [37]. Alotaibi and Al Sheddi did not find any MPNST in their series [1]. However, another study conducted in Brazil found 3 cases of MPNST in their cohort, representing 8.6% of their total 35 cases of oral peripheral nerve sheath tumors [2]. In this study no cases of MPNST were reported, an unexpected occurrence. This may be due to the rarity of the neoplasm or the possibility that biopsies of aggressive lesions are less

likely performed in an outpatient setting and submitted to our biopsy service.

The main limitations of this study is due to the retrospective nature of the study which precluded obtaining additional information related to treatment and outcome of the included cases. Moreover, many of the submissions are not accompanied by detailed medical history or reports of any additional lesions or signs in the patients. Additional large studies with follow-up information may be helpful in further understanding of these lesions.

In conclusion, although oral neural neoplasms are uncommon, they should be included in the differential diagnoses for oral soft tissue lesions. Additionally, if diagnosed, the clinician should be mindful of the associated syndromes as this may play an important role in the early diagnosis, prognosis and improved long-term patient outcome. Significant variation exists in demographics, clinical appearance, and histologic findings with regards to these neoplasms therefore both clinicians and pathologists should be sentient in order to best refer and if required manage their patients.

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