Retrospective analysis of oral peripheral nerve sheath tumors in Brazilians

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Abstract: Traumatic neuroma, neurofibroma, neurilemmoma, palisaded encapsulated neuroma and malignant peripheral nerve sheath tumor (MPNST) are peripheral nerve sheath tumors and present neural origin. The goal of this study was to describe the epidemiological data of oral peripheral nerve sheath tumors in a sample of the Brazilian population. Biopsies requested from the Oral Pathology Service, School of Dentistry, Federal University of Minas Gerais (MG, Brazil), between 1966 and 2006 were evaluated. Lesions diagnosed as peripheral nerve sheath tumors were submitted to morphologic and to immunohistochemical analyses. All cases were immunopositive to the S-100 protein. Thirty-five oral peripheral nerve sheath tumors were found, representing 0.16% of all lesions archived in the Oral Pathology Service. Traumatic neuroma (15 cases) most frequently affected the mental foramen. Solitary neurofibroma (10 cases) was more frequently observed in the palate. Neurofibroma associated with neurofibromatosis type I (2 cases) was observed in the gingival and alveolar mucosa. Neurilemmoma (4 cases) was more commonly observed in the buccal mucosa. Malignant peripheral nerve sheath tumors (3 cases) occurred in the mandible, palate, and tongue. Palisaded encapsulated neuroma (1 case) occurred in the buccal mucosa. The data confirmed that oral peripheral nerve sheath tumors are uncommon in the oral region, with some lesions presenting a predilection for a specific gender or site. This study may be useful in clinical dentistry and oral pathology practice and may be used as baseline data regarding oral peripheral nerve sheath tumors in other populations.

Descriptors: Neuroma; Neurofibroma; Nerve sheath neoplasms; Mouth; Epidemiology.

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Introduction

Peripheral nerve sheath tumors may be classified in benign and malignant. The first category includes traumatic neuroma, neurofibroma, neurilemmoma, and palisaded encapsulated neuroma (PEN) whereas the second category consists of malignant peripheral nerve sheath tumor (MPNST). These tumors share a common neural origin but present microscopic and clinical heterogeneity.[1,2]

The traumatic neuroma is a non-neoplastic lesion characterized by the proliferation of schwann cells and nerve fibers that arise following injury to a nerve.[3-5] Jones, Franklin[6] (2006), in a series of 44,007 oral and maxillofacial pathologies, observed that 0.34% of the cases were of traumatic neuroma. In studies of oral peripheral nerve sheath tumor cases, the following frequencies of traumatic neuroma were observed: 16%[7] and 29.9%.[1]

Neurofibroma is a circumscribed but non-encapsulated tumor consisting of a mixture of schwann cells, perineurial cells, and endoneurial fibroblasts.[1,2,4] Jones, Franklin[6] (2006) found the frequency of this lesion to be 0.43%. In oral peripheral nerve sheath tumors, the frequencies identified for neurofibroma were 20.8%[1] and 32%.[7]

Neurilemmoma is an encapsulated neoplasm composed of schwann cells arranged in two patterns: Antoni type A and Antoni type B.[1,5] Although they can occur in any region, 25 to 48% of the lesions occur in the head and neck region.[8] One study regarding oral and maxillofacial pathologies reported a 0.1% frequency for this lesion.[6] The frequencies of 16.9%[1] and 22%[7] for neurilemmoma were recorded in studies of the oral peripheral nerve sheath tumors.

PEN is characterized by a bundle of nerves interposed to schwann cells, which characteristically aggregate in palisades.[1,2,9] This is a well-circumscribed tumor that represents 0.05% of the oral biopsy specimens.[10] The frequency of PEN found in a study of oral peripheral nerve sheath tumors was 20.8%.[1]

MPNSTs are spindle-cell sarcomas that arise from nerve, neurofibroma, neurilemmoma, or tissue containing nerves.[2,11] Although 8 to 16% of MPNSTs develop in the head and neck region, this lesion is extremely rare in the oral cavity.[12] A similar frequency (8%) of this lesion was described in a study on oral peripheral nerve sheath tumors.[7]

Epidemiologic studies on oral lesions have been conducted, being important sources of knowledge and contributing to the practice of clinical dentistry and oral pathology.[13,14] However, few authors have assessed the epidemiological features of oral peripheral nerve sheath tumors to date.[1,5-7] The aim of this paper was to describe the epidemiological data on the peripheral nerve sheath tumors recorded in the archives of the Oral Pathology Service, School of Dentistry, Federal University of Minas Gerais (UFMG), MG, Brazil.

Material and Methods

The protocol of this study was approved by the Committee for Bioethics in Research, UFMG (016/03).

All files regarding oral peripheral nerve sheath tumors submitted to the Oral Pathology Service, School of Dentistry, UFMG (FO-UFMG) from 1966 to 2006 were reviewed. These files were classified in accordance with histological and immunohistochemical criteria. Histological sections stained with haematoxilin and eosin were analyzed using an optic microscope (Axiostar 1122-110, Carl Zeiss, Oberkochen, Baden-Württemberg, Germany). Patient clinical data and lesion location were recorded. The histological criteria used to classify the peripheral nerve sheath tumors were in accordance with Enzinger, Weiss[2] (1995).

Immunohistochemistry staining to detect S-100 proteins was performed for all lesions using the standard streptavidin-biotin-peroxidase method on deparaffinized tissue sections. The sections were incubated with an S-100 primary antibody (Z0311, Dako Corporation® Carpinteria, CA, USA) at a 1:700 dilution for 18 hours at 4°C. Mayers hematoxilin was used as a counterstain. All lesions were positive for S-100. In MPNST lesions, immunohistochemistry staining for AE1/AE3 (M3515, Dako Corporation® Carpinteria, CA, USA; at a 1:100 dilution), HHF35 (M0635, Dako Corporation® Carpinteria, CA, USA; at a 1:100 dilution), and α-smooth muscle actin (M0851, Dako Corporation® Carpinteria, CA, USA; at a 1:50 dilution) were also

performed. An antigen retrieval was also performed using a 10 mM citrate buffer (pH = 6.0, 30 min at 98°C) in stains testing AE1/AE3 and α- smooth muscle actin. The primary antibody was also incubated for 18 hours at 4°C. MPNST showed a negative stain for AE1/AE3, HHF35, and α- smooth muscle actin.

Results

Oral peripheral nerve sheath tumors represented 35 (0.2%) of 21,476 specimens biopsied from 1966 to 2006 in the Oral Pathology Service, FO-UFMG. The cases diagnosed included 15 (42.9%) traumatic neuromas, 10 (28.6%) solitary neurofibromas, 2 (5.6%) neurofibromas associated with neurofibromatosis type I, 4 (11.4%) neurilemmomas, 1 (2.9%) PEN, and 3 (8.6%) MPNSTs. The clinical data are presented in Table 1.

The neurilemmomas presented 50% of the lesions composed of Antoni type A pattern and 50% composed of a mixture of both patterns, Antoni type A and type B. All of these tumors were encapsulated.

Discussion

The oral peripheral nerve sheath tumors were considered rare as they occurred in only 35 cases among 21,476 biopsied lesions from FO-UFMG, representing 0.2% of all lesions. Studies regarding oral peripheral nerve sheath tumors reported the frequencies of these lesions, without immunohistochemical evaluation.[6,7] However, Chrysomali *et al.*[1] (1997) evaluated 77 oral peripheral nerve sheath tumors using immunohistochemistry to detect the S-100 protein, CD57, epithelial membrane antigen (EMA), factor XIIIa, CD34, CD68, and collagen IV. Likewise, Magnusson[10] (1996) studied 12 cases of oral PEN evaluating the expression of S-100, neurofilament and EMA.

Used as an auxiliary method in the diagnosis of the peripheral nerve sheath tumors, the most common immunohistochemical markers described in the literature include: S-100, CD34, and EMA. In the present study, S-100 was used because it represented an easy marker, has been widely used in the identification of schwann cells, and aids greatly in the diagnostic process.[1,15-17] The neural origin of all lesions of this study was confirmed by the immuno-

Table 1 - Clinical data of oral peripheral nerve sheath tumors (FO-UFMG, 1966 - 2006).

Tumor	Mean age (Range)	Gender (cases)	Sites
Traumatic neuroma (n = 15)	33.5 (10-80)	M (5) F (10)	Mental foramen (6) Lower lip (3) Buccal mucosa (2) Tongue (2) Hard/soft palate (2)
Solitary neurofibroma (n = 10)	31.2 (9-50)	M (1) F (9)	Hard palate (4) Gingiva, anterior region (2) Tongue (2) Mandibular symphysis (1) Lower lip (1)
Neurofibroma associated with neurofibromatosis type 1 (n = 2)	23.0 (10-36)	M (1) F (1)	Gingiva, anterior region (1) Alveolar Mucosa (1)
Neurilemmoma (n = 4)	23.7 (12-31)	M (0) F (4)	Buccal mucosa (2) Hard palate (1) Tongue (1)
MPNST (n = 3)	45.0 (37-61)	M (3) F (0)	Mandible, anterior region (1) Hard palate (1) Tongue (1)
PEN (n = 1)	*	M (0) F (1)	Buccal mucosa (1)

F: Female; M: Male; *: no data; MPNST: malignant peripheral nerve sheath tumor, PEN: palisaded encapsulated neuroma.

histochemical tests for the S-100 protein, since all samples were positive to this antigen. In 100% of the cases of traumatic neuroma, schwann cells within the nerve fascicles were immunoreactive toward S-100. This is also reported in the findings from Chrysomali *et al.*[1] (1997) and Weiss *et al.*[17] (1983). The positive stain for S-100 was also observed in 100% of the neurofibroma cases, which is a rate similar to that found in the literature.[1,15,17] However, as indicated by Enzinger, Weiss[2] (1995), the S-100 immunostain in neurofibroma is not as notable as in neurilemmoma. In the present study, all cases of neurilemmoma also showed positive staining for S-100, which is also reported by Hirose *et al.*[15] (2003). However, Weiss *et al.*[17] (1983) found positive immunostains for S-100 in 91% of the cases of neurilemmoma, whereas Chrysomali *et al.*[1] (1997) observed this in only 31% of the cases. The case of PEN, on the other hand, stained positively for S-100. Argenyi[3] (1990) found 100% of the cases to be positive for S-100, in contrast with Chrysomali *et al.*[1] (1997) who found 25% of the cases to be immunopositive. S-100 immunostaining was observed in 100% of the MPNST cases presented in this study, however, the literature described this as varying from 50 to 90% of the cases.[2,17]

Traumatic neuroma is most frequently located in the tongue, lips,[1,18] and mental nerve area.[5] We also found the same neuroma in areas including the buccal mucosa and palate. These tumors affected adults and children from 10 to 80 years of age, with a mean age of 33.5, which is in accordance with Chrysomali *et al.*[1] (1997). The female preponderance noticed in this study is also reported in the findings from Chrysomali *et al.*[1] (1997).

In the solitary neurofibroma, the most common sites found by Shklar, Meyer[7] (1963) and Wright, Jackson[5] (1980) were the tongue, the palate, the buccal mucosa and the floor of the mouth. In contrast, the main site observed by Ellis *et al.*[19] (1977) was the posterior region of the mandible, while Chrysomali *et al.*[1] (1997) reported it in the alveolar mucosa and the palate. In the present study, the palate and the gingiva were the most frequently intraoral and paraoral tissues involved. Also, one case located in the mandibular symphysis was observed in this study. Likewise, neurofibromas of the jaw have been described in the literature.[20,21] As to neurofibromas, it was observed that these lesions affected adults and children from 9 to 50 years of age, with a mean age of 31.2, which is in accordance with the literature.[2,5,11,19] As observed by other authors,[1,5,19] our study also pointed out a female preponderance. However, Enzinger, Weiss[2] (1995) and Pilavaki *et al.*[11] (2004) related no gender dominance to this lesion.

Neurofibromatosis type I is a disorder characterized by the presence of two or more of the following findings: six or more "*café au lait*" macules (> 5 mm in diameter in puberty and > 15 mm in postpuberty patients), two or more neurofibromas of any type or one plexiform, freckling in the axillary or inguinal regions, optic glioma, two or more "Lish" nodules, and a distinctive osseous lesion.[22] Two cases of neurofibroma were associated with neurofibromatosis type I. Association of the oral neurofibroma and neurofibromatosis type I is uncommon.[5] The lesions in the oral soft tissues have been identified with a prevalence of less than 10%,[23] 26%[20] and up to 72% of patients.[21] In addition, neurofibromas associated with neurofibromatosis type I are most frequently found in the tongue, but have also been identified in the gingiva, the alveolar mucosa, the palate, the buccal mucosa, the lip, the floor of the mouth, and the buccal mucosa.[20,22] In this study, these lesions were identified in the gingiva and in the alveolar mucosa and presented no gender predilection.

The cases of neurilemmoma presented a predilection for the buccal mucosa although other authors observed it in the lips,[2] the tongue, the palate[19] and the mandible.[5] These most often occurred in children and young adults with a mean age of 23.7 years. Most reports suggested that the majority of tumors arise between 10 and 40[24,25] and between 20 and 50 years of age.[11] Some studies reported that males and females are equally affected. Shklar, Meyer[7] (1963) reported a male preponderance while other studies showed a female dominance.[24,25] In this study, only women were affected.

The unique occurrence of PEN appeared in a white woman whose age was not duly noted. Some authors reported that this entity may develop anywhere on the face of adults, most frequently in the

5th, 6th, and 7th decades of life, and that both genders are equally affected.[5,10,26] PEN rarely appears in the oral cavity, and when it was diagnosed, it occurred more commonly in the palate and maxillary mucosa.[10,26] This runs in direct contrast with our case, which was found in the buccal mucosa.

Although only three cases of MPNST were observed, it is interesting to note that all occurred in male patients. Enzinger, Weiss[2] (1995) also reported that more males than females were affected by MPNST. The mean age of 45 years was observed in our study. Other authors reported that this malignant lesion affects, most frequently, patients from 20 to 50 years of age.[2] The present lesions occurred in the tongue, the palate and the mandible. The cases of this entity have been reported mostly in soft tissues and less commonly in bones.[27] It can occur in the palate, lips, buccal mucosa, mental foramen, and submandibular triangle.[28]

Conclusions

This paper provides epidemiological data that can be an important auxiliary in clinical dentistry and oral pathology practice, mainly in the diagnosis of the oral peripheral nerve sheath tumors, which rarely occur in the oral cavity. This study may also be used as a data reference of oral peripheral nerve sheath tumors for other populations.

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