Clin Oral Invest (2011) 15:329–335
DOI 10.1007/s00784-010-0389-7

ORIGINAL ARTICLE

A 38-year review of oral schwannomas and neurofibromas in a Brazilian population: clinical, histopathological and immunohistochemical study

George João Ferreira do Nascimento · Danielle de Albuquerque Pires Rocha · Hébel Cavalcanti Galvão · Antônio de Lisboa Lopes Costa · Lélia Batista de Souza

Received: 20 July 2009 / Accepted: 9 February 2010 / Published online: 9 March 2010

Abstract The benign peripheral nerve sheath tumours are rare lesions mainly represented by schwannoma and neurofibroma. The present work evaluated the clinical and histopathological features of schwannomas and neurofibromas of the oral cavity diagnosed in a Brazilian population. Among 9.000 cases of oral lesions archived from 1970 to 2008, four schwannomas and 12 neurofibromas were identified, microscopically revised and immunohistochemically certified through a panel including monoclonal antibodies (anti-S100, vimentin, HHF-35 and desmin). From biopsy and histological sections records, clinical and histopathological data were retrieved, reviewed and statistically analysed. Predominantly, schwannomas affected non-white males (3:1), with an age and size averages of 34.7 years and 2.8 cm, respectively. Neurofibromas preferentially occurred on the gingival/alveolar ridge of white females (5:1), with 35.7-year mean age, peak of incidence between 3rd and 5th decade, and size average of 1.7 cm. (12 cases, 75%). The studied tumours exhibited more frequently as a painless, sessile and slow growth very similar to other oral lesions, but their microscopic features differed significantly. Schwannomas and neurofibromas are extremely uncommon in the oral cavity, exhibiting clinical features very similar but specific and peculiar microscopic findings that are useful in the establishment of the diagnosis, which in some particular cases must be confirmed by immunohistochemistry.

Keywords Schwannoma · Neurofibroma · Benign peripheral nerve sheath tumours · Epidemiology · Oral diseases

Introduction

The benign peripheral nerve sheath tumours (BPNSTs) are mainly represented by schwannoma and neurofibroma, and although these tumours are the most common neurogenic tumours, they rarely affect the oral cavity [1-9]. Schwannoma (neurilemmoma or neurinoma) is exclusively composed by neoplastic Schwann cells, and its first description was done by Verocay at 1910 [3]. It is very uncommon, but about 25% to 48% of all cases affect the head and neck region. Preferentially, schwannoma is a solitary, asymptomatic and slow-growth lesion affecting both genders equally, and the average age is between 20 and 50 years [10-12]. Some diseases such as the neurofibromatosis type 2 and the schwannomatosis may present several uni- or bilateral schwannomas of the vestibular nerve as a peculiar feature [8, 13]. In the oral cavity, schwannomas affect the

G. J. F. do Nascimento · H. C. Galvão · A. de Lisboa Lopes Costa · L. B. de Souza
Oral Pathology Post-Graduation Program, Dentistry Department, Federal University of Rio Grande do Norte, Natal, Rio Grande do Norte, Brazil

D. de Albuquerque Pires Rocha
Department of General Pathology, Histology and Embryology, Federal University of Amazonas, Coari, Amazonas, Brazil

L. B. de Souza (✉)
Programa de Pós-Graduação em Patologia Oral, Departamento de Odontologia, Universidade Federal do Rio Grande do Norte-UFRN, Avenida Senador Salgado Filho, 1787, Lagoa Nova, Natal, RN CEP: 59056-000, Brazil
e-mail: lelia.souza@pesquisador.cnpq.br

tongue preferentially [10, 12, 14]. Microscopically, schwannoma is generally encapsulated, and the neoplastic cells compose two different patterns of organisation: (1) Antoni A, which is consisted by spindle-shaped cells exhibiting elongated nucleus and indistinct cytoplasmatic borders that are arranged in palisade or parallel rows generally separated by an acellular and eosinophilic area called Verocay bodies [3, 10, 12]; and (2) Antoni B, which is characterised by oval or spindle-shaped cells that are distributed on a disorganised way within a loose connective tissue matrix where the microcystic degeneration and inflammatory cells can be found [3, 10, 12].

Neurofibromas are the most frequent benign neoplasms originating from the peripheral nerve sheath and occur as solitary or multiple tumours when associated to the von Recklinghausen disease, better known as neurofibromatosis type 1 (NF-1) [15-21]. Preferentially, these neoplasms affect persons between 20 and 40 years old or younger when associated to the NF-1 [15-21]. Solitary neurofibromas are superficial, painless and slow growth reaching variable sizes [22, 23] and, particularly, they clinically present after the puberty and remain their progressive growth throughout life [19-23]. As part of the NF-1, deeper and visceral or plexiform neurofibromas as well as their malignant transformation, which is more common in neurofibromas than schwannomas, may be observed [11, 19-27]. Oral sites more affected are the tongue, buccal mucosa and lips. Due to the neurofibromas arising from Schwann cells and other cells, such as perineural cells and endoneural fibroblasts, they present a great cellular heterogeneity in their microscopic aspects [3, 4, 8, 11, 18]. Nevertheless, basically, they exhibit as well-circumscribed tumours characterised by intermingled sheaves of elongated spindle-shaped cells with wavy or comma-shaped nucleus within a myxoid matrix consisting of dispersed and delicate collagen fibres and presenting variable number of mast cells [3, 10, 12, 22]. The aim of this paper was to describe the clinical, histopathological and immunohistochemical profiles of the oral schwannomas and neurofibromas diagnosed in a Brazilian single centre.

Material and methods

After approval by the National Bioethics Committee, four cases of sporadic schwannomas and 12 cases of neurofibromas (nine sporadic cases and three NF-1-associated cases) were found and selected for this study among 9.000 oral lesions diagnosed in the Oral Pathology Laboratory, School of Dentistry, Federal University of Rio Grande do Norte, Natal, Brazil. The biopsy records were used to retrieve the clinical data related to the patients such as gender, age and race and the data concerning the tumours such as the anatomical site, size, symptomatology and type of implantation and growth besides the first clinical diagnostic hypothesis.

Three micrometre-thick serial sections were taken from the archived paraffin blocks of the selected cases and processed routinely for the morphological and immunohistochemical studies. For morphological analysis, these sections were stained with haematoxylin and eosin and examined under light microscopy. In an attempt to certify the histopathological diagnosis, the immunohistochemistry study through the streptoavidin–biotin–peroxidase complex (SABC, Dako, Glostrup, Denmark) was performed for all cases. The antigen retrieval, dilution and clone of the monoclonal antibodies anti-S-100, desmin, vimentin and HHF-35 used in this study are shown in the Table 1.

The microscopic features of schwannomas and neurofibromas related to the pattern of organisation and morphology of the neoplastic cells, to the stroma type and to the secondary aspects such as the presence of inflammatory infiltrate and bleeding were analysed and recorded by two observers separately. The immunohistochemical assessment was mainly utilised for the diagnosis confirmation by mean of the intensity of the immunoexpression presented by the tumour cells under light microscopy and scored as follows: + focal/mild immunoexpression; ++ intense immunoexpression. The obtained data were statistically treated by means of the SPSS 10.0 software (SPSS, EUA).

Results

The main clinical features of the studied schwannomas and neurofibromas may be observed in the Table 2. Predominantly, schwannomas affected non-white males (3:1 ratio) with an age average of 34.7 years and mean size of 2.8 cm, whereas the neurofibromas occurred with more frequency on the gingival/alveolar ridge of white females (5:1 ratio) with 35.7-year mean age, peak of incidence between 3rd and 5th decade and size average of 1.7 cm. The majority of the studied neurofibromas (n=4; 33.3%) exhibited concor-

Table 1 Technical protocol for use of monoclonal antibodies anti-S-100, vimentin, HHF-35 and desmin

Antibody specificity	Dilution	Antigen retrieval	Incubation
S-100	1:400	Citrate pH 6.0, Pascal	1 h, at 37°C
Vimentin	1:50		1 h, at 37°C
HHF-35	1:40		Overnight, at 37°C
Desmin	1:40		Overnight, at 37°C

Table 2 Clinical characteristics of the schwannomas and neurofibromas

Case	Gender	Age (years)	Race	Anatomical site	Size (cm)	Clinical hypothesis
Schwannoma	M	53	Black	Palate	3	Pleomorphic adenoma
Schwannoma	F	46	White	Mandible	3.5	Central giant cell lesion
Schwannoma	M	18	Other	Tongue	2	Neurofibroma
Schwannoma	M	22	Other	Floor of mouth	–	Epidermoid cyst
Neurofibroma	F	28	White	Maxillary vestibulum	3	Lipoma
Neurofibroma	M	58	White	Buccal mucosa	1.5	Fibroma
Neurofibroma	F	78	White	Retromolar area	–	Pleomorphic adenoma
NF-1 neurofibroma	F	24	White	Low lip	3	NF-1 neurofibroma
NF-1 neurofibroma	F	22	White	Mental region	1.2	NF-1 neurofibroma
Neurofibroma	M	6	White	Alveolar ridge	3.5	Fibroma
Neurofibroma	F	21	White	Alveolar ridge	1.5	Fibrous hyperplasia
NF-1 neurofibroma	F	44	Black	Low lip	0.4	NF-1 neurofibroma
Neurofibroma	F	19	–	Maxilla	–	Myxoma
Neurofibroma	F	47	White	Gingiva	0.5	Fibrous hyperplasia
Neurofibroma	F	41	–	Retromolar	–	Fibrous hyperplasia
Neurofibroma	F	37	White	Tongue	1.0	Neurofibroma

dance between the clinical diagnostic hypothesis and the microscopic diagnosis, and these tumours were more clinically confused with fibrous hyperplasias (n=3; 25%). With relation to the schwannomas, it was not observed any diagnostic concordance. Only two (neurofibromas) of all studied cases exhibited as a painful lesion and about 60% of all cases (n=9) presented as a sessile nodule, whereas 93.7% of the schwannomas and neurofibromas displayed a slow growth (n=15). The three NF-1 patients studied in the present work were previously diagnosed by clinicians, and they were sent to our service only when the oral neurofibromas appeared.

The predominant histopathological findings and immunohistochemical profiles of the schwannomas and neurofibromas are listed in the Tables 3 and 4, respectively. The schwannomas predominantly exhibited spindle-shaped cells with variable nucleus morphology arranged in the Antoni B pattern with scarce Antoni A areas presenting few Verocay bodies and perivascular hyalinisation. The solitary and syndromic neurofibromas were composed to spindle-shaped, homogeneous nucleus cells forming short interwoven sheaves in a myxoid stroma mixed to variable amounts of mast cells. The Figs. 1 and 2 show the peculiar microscopic features of the studied cases. There was a variable staining to the S-100 protein both in neurofibromas and schwannomas, but it was more evident in this latter tumour (Tables 3 and 4, Fig. 3). Desmin and HHF-35 immunoexpression was not evidenced in the evaluated cases, and the vimentin staining was stronger in the neurofibromas than schwannomas (Tables 3 and 4).

Table 3 Histopathological features and immunohistochemical profile of the schwannomas

Case	Cell and nucleus morphology	Organisation pattern	Stroma	Secondary features	Immunohistochemical profile	
					S100	Vimentin
1	Spindle-shaped, variable nucleus	↑Antoni B, ↓Antoni A/↑Verocay bodies	Dense fibrous	Haemorrhage	++	+
2	Round, spindle-shaped, variable nucleus	↑Antoni B, ↓Antoni A/↓Verocay bodies	Loose fibrous, myxoid	Perivascular hyalinisation	++	+
3	Spindle-shaped, mild pleomorphism, variable nucleus, mitoses figures	↑ Antoni B, ↓Antoni A/↓Verocay bodies	Dense fibrous	Perivascular hyalinisation, inflammation, melanin deposits	++	+
4	Spindle-shaped, vesicular nucleus	↑Antoni A/↑Verocay bodies, ↓Antoni B	Dense fibrous	Inflammation	++	+

↑ predominant, ↓ scarce, + focal/mild immunoexpression, ++ intense immunoexpression

Table 4 Histopathological features and immunohistochemical profile of the neurofibromas

Case	Cell and nucleus morphology	Organisation pattern	Stroma	Secondary features	Histological typing	Immunohistochemical profile	
						S100	Vimentin
1	Spindle-shaped, homogeneous nucleus	Short sheaves	Myxoid	Mast cells	Conventional	+	++
2	Spindle-shaped, homogeneous nucleus	Short sheaves, vater-pacini corpuscles	Myxoid	Mast cells	Pacinian	++	+
3	Spindle-shaped, variable nucleus	Short sheaves	Myxoid	Mast cells	Conventional	++	++
4	Spindle-shaped, variable nucleus	Mixed sheaves	Myxoid	Mast cells	Conventional	++	+
5	Spindle-shaped, homogeneous nucleus	Short sheaves	Dense fibrous	Mast cells	Conventional	++	+
6	Spindle-shaped, light pleomorphism, vesicular nucleus	Long sheaves	Loose fibrous	Mast cells	Cellular	++	++
7	Spindle-shaped, homogeneous nucleus	Long sheaves	Dense fibrous	Mast cells	Conventional	+	++
8	Spindle-shaped, homogeneous nucleus	Long sheaves	Myxoid	Perivascular hyalinisation, inflammation, ulceration	Conventional	+	++
9	Spindle-shaped, light pleomorphism, mitoses figures	Short sheaves	Myxoid	Mast cells	Cellular	++	++
10	Oval, spindle-shaped, variable nucleus	Short sheaves	Dense fibrous	Mast cells	Conventional	+	++
11	Spindle-shaped, homogeneous nucleus	Long sheaves	Myxoid	Mast cells	Conventional	+	+
12	Spindle-shaped, homogeneous nucleus	Long sheaves	Myxoid	Mast cells	Conventional	+	++

+ focal/mild immunoexpression, ++ intense immunoexpression

Discussion

Only about 0.17% of all assessed oral lesions records from our service were diagnosed as solitary schwannomas and sporadic- and NF-1-associated neurofibromas, and this result is in line with several works concerning to the rare prevalence of these tumours in the oral cavity [4, 8, 15, 16]. In the head and neck region, schwannomas are more prevalent than neurofibromas [3, 28], whereas in the oral cavity, this latter tumour seems to be more frequent than the former [8, 29]. In the present work, we also found a higher prevalence of neurofibromas. Additionally, only three cases of neurofibroma were associated to NF-1 that is one of the most common inherited disorders in humans occurring in

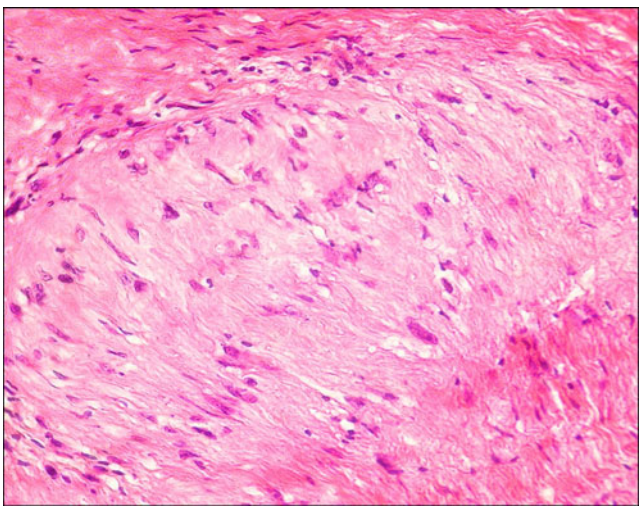

Fig. 1 Schwannoma. Classical feature of the tumour with the Antoni A areas centrally disposed within the predominant Antoni B areas [H&E, ×200]

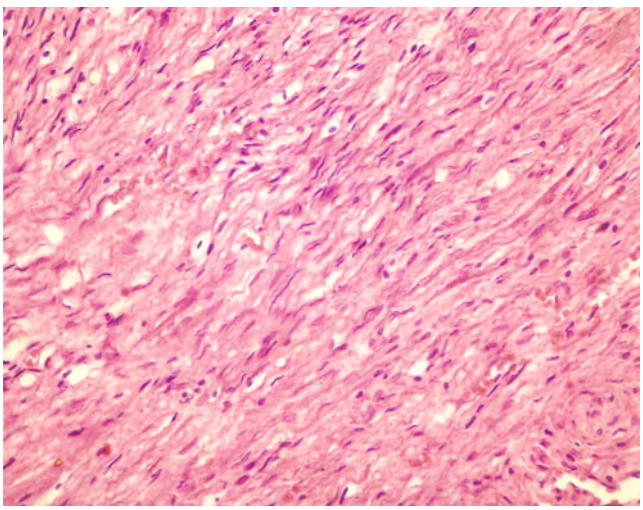

Fig. 2 Neurofibroma. Histopathological aspect presenting the neoplastic spindle-shaped cells arranged in elongated interwoven sheaves within a fibrous connective stroma [H&E, ×200]

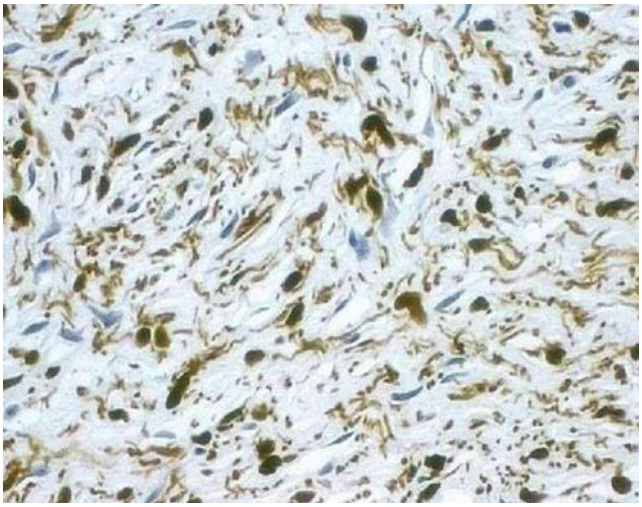

Fig. 3 Variable S-100 immunohistochemical expression in the neoplastic cells of a neurofibroma [SABC, ×400]

one at each 2.000 to 4.000 births [18-21, 24, 25, 30]. These NF-1 patients showed solitary neurofibroma in the oral cavity but multiple tumours throughout the body besides other clinical signs such as iris Lisch nodules (all cases), café-au-lait spots (all cases) and freckling in the axillary region (two cases) that were necessary to fill the diagnostic criteria for this condition [18-21, 25, 30]. Furthermore, although the plexiform neurofibromas are a clinicopathological pathognomonic sign of NF-1 [5, 24, 26], none studied cases presenting this type of tumour growth.

Generally, the relationship between the studied tumours and the gender of patients is considered irrelevant once several works have demonstrated that the difference among the genders is minimal [3, 10, 18, 24]. Adversely, considering all assessed cases, we observed that women were more prevalent than men. However, men represented the majority of schwannomas cases, differing of various reports showing that females are frequently more affected by oral schwannomas [8, 16, 25]. We found that the neurofibromas occurred on an age group older than that mentioned on the literature for the sporadic cases, whereas in those three cases associated to the NF-1 the found average age was in accordance with several reports [18-21, 24, 25, 30]. For sporadic oral schwannomas, our results agree with several works reporting that these neoplasms occur more frequently in young adults between the second and third decades [8, 10, 28]. A high prevalence of neurofibromas in white patients and no relationship between schwannomas and the race were features also found in the present paper. Although these results are consistent with classical reports [3, 10, 12, 22], we believe that they cannot be a reliable finding because of the difficulty in managing the individuals by ethnic group once the Brazilian population is a result of large miscegenation.

Rare cases of BPNSTs occur within the jaws, and these cases are radiographically visualised as a well-delimited unilocular defect or as an ill-defined, multilocular lesion resembling several types of benign and malignant tumours with or without odontogenic origin [2, 26-28]. We only found two cases occurring intra-osseously: one in the maxilla (neurofibroma) and other in the mandible (schwannoma) that were clinically and radiographically misdiagnosed as odontogenic myxoma and central giant cell lesion, respectively. All cases affected, as it was expected [8, 10, 12, 17, 22], the soft tissues of the oral cavity. Additionally, a lot of papers [1, 4, 7, 10, 12, 14, 17, 22, 29] report that both neurofibromas and schwannomas have the tongue as the main site of occurrence but, adversely, we found more cases affecting the gingival/alveolar ridge followed by the tongue, lower lip and retromolar area. This last result corroborates Salla et al. [8] and Marocchio et al. [15], and, thus, we also believe that the real frequency of sporadic and syndromic neurofibromas in the oral cavity is still uncertain and need further investigation.

Clinically, studied tumours exhibited as small, slow-growth lesions. Two cases of neurofibroma presented mild pain and pedicled implantation while all cases of schwannomas were asymptomatic and sessile. These features are in accordance with several reports, although Neville et al. [10] affirm that, between the neurofibroma and schwannoma, the latter exhibits more symptomatic cases varying from mild pain to paresthesia. In the oral cavity, the clinical aspects of neurofibroma and schwannoma are not specific and, thus, these tumours are very confused with other soft tissue lesions affecting this anatomical site [4, 8, 10, 12, 15, 23]. In our analysis, we observed that these tumours were more clinically misdiagnosed as fibrous hyperplasia, fibroma and lipoma. Only three cases exhibited concordance between the clinical hypothesis and the histopathological diagnosis, and all these cases were of neurofibromas associated to the NF-1, what may have helped in the establishment of their clinical diagnosis once several clinical signs of these disorders are easily identified and found in about 90% of the NF-1 cases [18-21, 24, 25, 30].

Microscopic findings of the analysed cases were also consistent with the literature. With relation to the schwannomas, the Antoni B pattern of organisation was more predominant than the Antoni A, although an equal mixture was expected among them [3, 11, 31, 32]. As the presence of the Verocay bodies was not easily evidenced, we found the diagnosis of schwannoma difficult to establish without especial staining. Additionally, one case of schwannoma exhibited large deposition of melanin. However, we did not classify this case as the histopathological variant called as melanotic schwannoma because this variant presents peculiar clinical and microscopic features such as the frequent association with the Carney syndrome and the presence of

psammoma bodies [3]. The deposition of melanin by tumour cells is possible once the Schwann cells and melanocytes share the same cellular origin: the neural crest cells.

Microscopically, neurofibromas showed variable features in the present work independently of being sporadic or syndromic tumours. This result was expected because these tumours arise mainly from at least two types of cells [3, 4, 8, 11, 31, 32]. Predominantly, we found that the morphology of the cell nuclei was the main difference observed among the neurofibromas. Unlike the schwannomas, it was possible to classify some of the solitary neurofibromas as the variants pacinian and cellular whereas the syndromic cases were diagnosed as conventional neurofibromas. The pacinian neurofibromas, which were firstly described by Prichard and Custer in 1952, exhibits a large amount of nerve structures similar to the tactile bodies of Vater–Pacini that are sparsely distributed to all neoplastic parenchyma resembling a classical neurofibroma within a myxoid stroma [2, 6]. The cellular neurofibromas, whose microscopic findings were described by Weiss and Goldblum [3], were characterised by a large cellularity beside mild pleomorphism of the neoplastic cells exhibiting frequently vesicular nucleus and mitosis figures. These findings suggested malignity, but unlike the malignant peripheral nerve sheath tumours, these lesions were well-encapsulated and exhibited strong S-100 immunoexpression [3, 4, 23, 32].

Although the schwannoma and neurofibroma display peculiar histopathological features, sometimes, the distinction among these tumours is very difficult. In these cases, the use of special staining is necessary to the diagnosis definition [4, 32]. The immunohistochemical assessment performed in the present study confirmed the microscopic diagnosis of the lesions because it permitted exclusion of other tumours also exhibiting spindle-shaped cells in their composition such as leiomyoma, leiomyosarcoma, fibroma, fibrosarcoma, fibrohistiocytoma and malignant peripheral nerve sheath tumours. The negative immunoexpression to desmin and HHF-35 (muscle-specific actin) excluded any muscle lesion, whereas the variable but expressive staining to S-100 defined the neural origin of the studied cases. Vimentin expression was stronger in the neurofibroma cases than in the schwannomas; once in the former neoplasm, there are neural and fibroblastic neoplastic differentiation [3, 4, 8, 11, 32].

Finally, considering our small sample size and other epidemiological biases related to surveys conducted on pathology records, we could conclude that neurofibroma and schwannoma seem to be very uncommon in the oral cavity and at this anatomical site exhibit clinical characteristics extremely similar, but different and peculiar microscopic features. Furthermore, once these tumours are rare and frequently, are associated to syndromes and malignant transformation, this study may sum to others in attempt to better understand their clinical, histopathological and biological behaviours.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Depprich R, Singh DD, Reinecke P, Kübler NR, Handschel J (2009) Solitary submucous neurofibroma of the mandible: review of the literature and report of a rare case. Head Neck Medicine. doi:10.1186/1746-160X-5-24
2. Toth BB, Long WH, Pleasants JE (1975) Central pacinian neurofibroma of the maxilla. Oral Surg 39:630–634
3. Weiss SW, Goldblum JR (2008) Benign tumors of peripheral nerves. In: Weiss SW, Goldblum JR (eds) Enzinger and Weiss´s: Soft tissue tumors, 5th edn. Mosby, St. Louis, pp 825–902
4. Chrysomali E, Papanicolaou SI, Dekker NP, Regezi JA (1997) Benign neural tumors of the oral cavity: a comparative immunohistochemical study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 84:381–390. doi:10.1016/S1079-2104(97)90036-6
5. Oliveira GG et al (2004) Neurofibroma plexiforme en mucosa yugal: presentación de un caso clínico. Med Oral 9:263–267
6. Souza LB, Oliveira JMB, Freitas TMC, Carvalho RA (2003) Neurofibroma paciniano: relato de um caso raro de localização intra-oral. Braz J Otorhinolaryngol 69:1–9
7. Pfeifle R, Baur DA, Paulino A, Helman J (2001) Schwannoma of the tongue: report of 2 cases. J Oral Maxillofac Surg 59:802–804
8. Salla JT, Johann ACBR, Garcia BG, Aguiar MCF, Mesquita RA (2009) Retrospective analysis of oral peripheral nerve sheath tumors in Brazilians. Braz Oral Res 23:43–48
9. Ishida T, Kuroda M, Motoi T, Oka T, Imamura T, Machinami R (1998) Phenotypic diversity of neurofibromatosis 2: association with plexiform schwannoma. Histopathology 32:264–270
10. Neville B, Damm DD, Allen CM, Bouquot J (2008) Soft tissue tumors. In: Neville B, Damm DD, Allen CM, Bouquot J (eds) Oral and maxillofacial pathology, 2nd edn. Elsevier, India, p 843
11. Ferner RE, O'Doherty MJ (2002) Neurofibroma and schwannoma. Curr Opin Neurol. doi:10.10097/01.wco.0000044763.39452.aa
12. Eveson JW (2006) Oral cavity. In: Cardesa A, Slootweg PJ (eds) Pathology of the head and neck. Springer, Berlin, Heidelberg, p 96
13. Baser ME, Friedman JM, Evans DG (2006) Increasing the specificity of diagnostic criteria for schwannomatosis. Neurology 14(66):730–732
14. Arda HN, Akdogan O, Arda N, Sarikaya Y (2003) An unusual site for an intraoral schwannoma: a case report. Am J Otolaryngol 24:348–350
15. Marocchio LS, Oliveira DT, Pereira MC et al (2007) Sporadic and multiple neurofibromas in the head and neck region: a retrospective study of 33 years. Clin Oral Invest. doi:10.1007/s00784-006-0096-6
16. Jordan RC, Regezi JA (2003) Oral spindle cell neoplasms: a review of 307 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 95:717–724
17. Serra E, Ars E, Ravella A, Sánchez A, Puig S (2001) Somatic NF1 mutational spectrum in benign neurofibromas: mRNA splice defects are common among point mutations. Hum Genet. doi:10.1007/s004390100514
18. Gutmann DH, Aylsworth A, Carey JC et al (1997) The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA 278:51–57

19. Yohay K (2006) Neurofibromatosis types 1 and 2. Neurologist 12:86–93
20. Gerber PA, Antal AS, Neumann NJ et al (2009) Neurofibromatosis. Eur J Med Res 14:102–105
21. McClatchey AI (2007) Neurofibromatosis. Annu Rev Pathol 2:191–216
22. Sapp JP, Eversole LR, Wysocki GP (1997) Connective tissue lesions. In: Sapp JP, Eversole LR, Wysocki GP (eds) Contemporary oral and maxillofacial pathology. Mosby, St. Louis, pp 277–318
23. Furniss D, Swan MC, Morritt DG et al (2008) A 10-year review of benign and malignant peripheral nerve sheath tumors in a single center: clinical and radiographic features can help to differentiate benign from malignant lesions. Plast Reconstr Surg. doi:10.1097/01.prs.0000297636.93164.cb
24. Odebode TO, Afolayan EA, Adigun IA, Daramola OO (2005) Clinicopathological study of neurofibromatosis type 1: an experience in Nigeria. Int J Dermatol 44:116–120
25. Ide F, Shimoyama T, Horie N, Kusama K, Ide F (2004) Comparative ultrastructural and immunohistochemical study of perineuroma and neurofibroma of the oral mucosa. Oral Oncol 40:948–953
26. Cortés AR et al (2001) Neurofibroma plexiforme de nervio facial intraparotídeo: revision de la literatura. Anales ORL, Iber-Amer 28:363–370
27. Apostolidis C, Anterriotis D, Rapidis AD, Angelopoulos AP (2001) Solitary intraosseous neurofibroma of the inferior alveolar nerve: report of a case. J Oral Maxillofac Surg 59:232–235
28. Yamazaki H, Kaneko A, Ota Y, Tsukinoki K (2004) Schwannoma of the mental nerve: usefulness of preoperative imaging: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 97:122–126
29. Baden E, Jones JR, Khedekar R, Burns WA (1984) Neurofibromatosis of the tongue: a light and electron microscopic study with review of the literature from 1849 to 1981. J Oral Med 39:157–164
30. Einchenfield LF, Levy ML, Paller AS, Riccardi VM (1997) Guidelines/outcomes committee. Guidelines of care for neurofibromatosis type 1. J Am Acad Dermatol 37:625–630
31. Schmitz KJ, Unkel C, Grabellus F (2005) Melanotic schwannoma of the neck mimicking a malignant melanoma. Eur Arch Otorhinolaryngol. doi:10.1007/s00405-004-0795-z
32. Weiss SW, Langloss JM, Enzinger FM (1983) Value of S-100 protein in the diagnosis of soft tissue tumors with particular reference to benign and malignant Schwann cell tumors. Lab Invest 49:299–308