# Nerve Sheath Myxoma of the Tongue

***Francesco Spadari[1], Gianpaolo Guzzi[2], Gian Paolo Bombeccari[1], Umberto Mariani[3], Andrea Gianatti[4], Diego Ruffoni[1], Dario Costantino[1]***

[1]Department of Biomedical, Surgical and Dental Sciences, University of Milan; [2]Italian Association for Metals and Biocompatibility Research – A.I.R.M.E.B., Milan, Italy; [3]Unit of Oral Pathology and Medicine; [4]Unit of Histology and Pathology, Ospedale Papa Giovanni XXIII, Bergamo, Italy

**Corresponding Author:**
Gian Paolo Bombeccari, DDS
Department of Biomedical, Surgical
and Dental Sciences
Ospedale Maggiore Policlinico Fondazione
Ca' Granda IRCCS
University of Milan
Via Della Commenda 10,
20122 Milan
Italy
*gpbombeccari@libero.it*

Received June 13, 2013
Accepted: September 15, 2013

**SUMMARY** Nerve sheath myxoma (NSM) of the oral mucosa is a slow-growing, benign, often asymptomatic submucosal mass. We report on a case of classical NSM of the tongue, with diagnostic and therapeutic approach to the case.
Many NSM arise within the endoneurium of a peripheral nerve. It is a rare condition with no apparent differences between sexes in its prealence. It can occur at any age.

**KEY WORDS:** benign neoplasm, neurothekeoma, male, oral myxomas, oral pathology, peripheral nervous system.

## INTRODUCTION

Nerve sheath myxoma (NSM) of the oral mucosa is a slow-growing, benign, often asymptomatic submucosal mass. Many NSM arise within the endoneurium of a peripheral nerve (1). It is a rare condition with no apparent differences between sexes in its prevalence. It can occur at any age (2). In this report, we describe a case of classical NSM of the tongue.

## CASE REPORT

In August 2011, a 69-year-old male came to our oral pathology department with a painless nodular tongue lesion, without antecedent trauma. He reported that the tongue lesion had appeared approximately 8 months earlier. His chief complaint was speech impediment, pain on mastication, and difficulty swallowing. He had hypertension. He did not smoke cigarettes or drink alcohol.

Intraoral examination revealed a sessile nodule on the anterior one-third of the tongue, sized 1.0×0.8 cm. The surface was smooth and slightly whitish in appearance Figure 1). An excisional biopsy of the lesion was performed using a diode laser (Figures 2, 3).

Histopathological examination showed a multilobular cellular growth included in the muscular tissue of the tongue with acanthosis of the squamous epithelium. The mucosal connective tissue was composed of myxoid stroma containing round and spindle cells (Figure 4). The tissue specimen was examined for tumor markers by immunohistochemical analysis. The immunophenotype of the tumour cells was positive for S-100 protein and vimentin, suggesting Schwann cell origin (3). (Figures 5, 6, 7) The lesional tissue was negative for CD34 antigen expression and

Acta Dermatovenerol Croat
2014;22(1):52-56

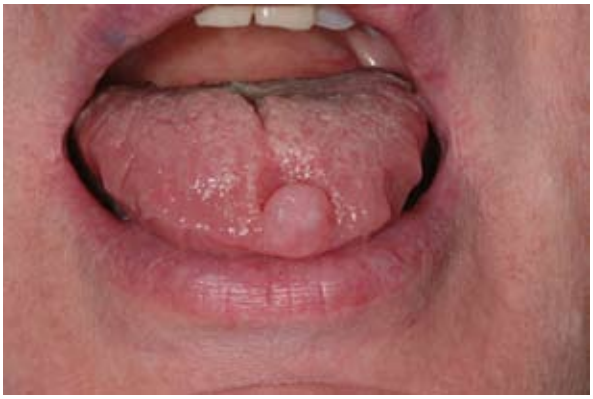

**Figure 1.** Nerve sheath myxoma of the tongue at admission.

**Figure 2.** Intraoperative picture of nerve sheath myxoma during the surgical procedure.

epithelial membrane antigen (EMA) antibodies. Immunostaining for the proliferation the Ki-67 antigen was at 2-3%. The lesion was diagnosed as a classical nerve sheath myxoma (NSM). At 8 months of follow-up there was no evidence of recurrence.

## DISCUSSION

Nerve sheath myxoma (NSM) is a benign neoplasm of the peripheral nervous system, usually found in the dermal and subcutaneous tissues of head, neck, and limbs (2,3-6). Harkin and Reed were the first to define the disease nerve sheath myxoma in 1969 (1). Subsequently, in 1980, Gallager and Helwing named the lesion neurothekeoma (NTK) (2). The nerve sheath derivation of NSM is still debated because the immunohistochemical profile of the three variants has not been established. We are aware of only 41 case reports of NSM of the oral mucosa published between 1974 to 2013 (7) and retrievable through PubMed's Medline. (Table 1). Locations of NSM in the oral cavity were: tongue (n=11), buccal mucosae (n=7), lips (n=6), palate (n=1), retromolar area (n=1), gingiva (n=1). Epidemiological data indicates a wide range of age from 1 to 73 years (mean age 32.7 years), and a female/male ratio of 1.4:1 (4).

The current classification of NSM is based on the amount of myxoid stroma: classical, cellular, and mixed types (8), although some authors disagree with the existing classification (9,10). Histologically, the "classic type" presents as a multinodular/multilobular lesion with an abundant myxoid matrix outlined by thin condensed fibrous tissue (4). The lesion usually shows stellate and spindle-shaped cells typically grouped in cords, nests, and/or syncytial aggregates, randomly scattered in a predominantly edematous and myxomatous stroma (4,9). The "cellular type" is characterized by spindle and epithelioid cells proliferating in the fibromyxoid stroma, which form lobular aggregates and sheet-like areas exhibiting a cellular appearance. The cells have round nuclei with eosinophilic cytoplasm (4). Histology of the "mixed type" frequently shows an aggregate of stellate and spindle-shaped cells with basophilic ovoid vesicular nuclei scattered mainly in myxoid stroma, which can be identified as mucoid using Alcian blue staining (4,11).

There are conflicting reports in the literature about the expression of S-100 protein in most of the tumor cells. A recent analysis of 178 patients with neurothekeoma – including myxoid NTK/NSM – provides no evidence of expression of the S-100 protein (9).

Another study has shown that positive staining for S-100 protein was over-expressed in 22 tumors, of which 11 were diagnosed as myxoid NTK/NSM and expressed S-100 (10).

Other reported cases have also shown a positive S-100 protein antigen immunoprofile in the mixed variants of NSM (5,12,-14), although it appears that no immunoreactivity for S-100 protein is detectable in myxoid NTK/NSM when cells are less differentiated (10). Immunohistochemical profiles seem differ in the classic and cellular types of NSM.

The NSM "classic type" displays frequent findings of Schwann cells that are immunoreactive for S-100 protein in the tumor tissues (3,4,7).

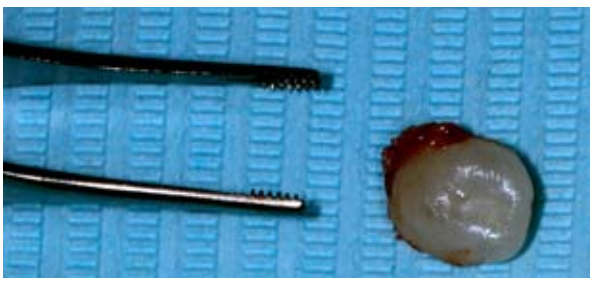

**Figure 3.** The gross specimen showing a round mass, 1.0 × 0.8 cm in size.

Acta Dermatovenerol Croat
2014;22(1):52-56

**Table 1.** Clinical characteristics of 41 nerve sheath myxoma (NSM) found in the literature, modified from Vered *et al.*(7). BM, buccal mucosa; NR, not reported.

| Study | Case | Gender | Age | Location | Size (cm) |
|---|---|---|---|---|---|
| Mincer *et al.*[11] | 1 | M | 23 | Tongue | 1.0 |
| Tomich[12] | 2 | M & F | NR-45 | BM, Tongue | NR;NR |
| Sist *et al.*[13] | 2 | F | 30-41 | Retromolar, BM | 0.5;NR |
| Wright *et al.*[14] | 1 | F | 15 | Palate | NR |
| Gallager *et al.*[2] | 1 | ? | NR | BM | NR |
| Mason *et al.*[15] | 1 | F | 32 | Lip | 1.0x0.7x0.5 |
| Yamamoto *et al.*[16] | 1 | F | 41 | Tongue | 0.8x0.6x0.4 |
| Terrier *et al.*[17] | 1 | M | 35 | Lip | 5x3 |
| Rodriguez-Peralto *et al.*[18] | 1 | F | 46 | BM | 0.8 |
| Smith *et al.*[19] | 1 | F | 46 | Tongue | NR |
| Tiffee *et al.*[20] | 1 | F | 71 | Lip-BM | 0.9x0.6 |
| Katsourakis *et al.*[21] | 1 | M | 24 | Lip | 2x2x5 |
| Breuer *et al.*[22] | 1 | F | 12 | Tongue | 1.5x2 |
| Pennarocha *et al.*[8] | 1 | F | 1 | Tongue | 3x2.5 |
| Schortinghuis[23] | 1 | M | 73 | Tongue | 1.2x0.8x0.7 |
| Barret *et al.*[24] | 1 | M | 29 | BM | 1.5x1.2 |
| Makino *et al.*[9] | 1 | M | 8 | Tongue | 0.8x0.5x0.4 |
| Capodiferro *et al.*[10] | 1 | M | 44 | Tongue | 0.5x0.5 |
| Nishioka *et al.*[4] | 3 | F(2), M | 53-2-52 | BM (2), Lower lip | 4.0x2.0; 0.7x0.8; 0.7x0.7 |
| Safadi *et al.*[5] | 1 | F | 32 | Gingiva | 0.8x0.6x0.6 |
| Eksi *et al.*[6] | 1 | F | 28 | Upper lip | NR |
| Green *et al*[28] | 7 | NR | NR | NR | NR |
| Marocchio *et al* [29] | 1 | M | 35 | Palate | NR |
| Prado *et al* [30] | 1 | F | 84 | Mandibular lingual gingiva | 1.0 |
| Kim *et al*[31] | 1 | F | 15 | Tongue | 2.1 |
| Plaza *et al*[32] | 1 | F | 64 | NR | NR |
| Vered *et al*[33] | 4 | F(2), M(2) | 25-12-31-35 | Maxillary buccal gingiva, Mandibular buccal gingiva, Maxillary vestibule, Palatal gingiva | 0.3<br>1.0<br>0.7<br>0.6 |
| Spadari *et al.* | 1 | M | 69 | Tongue | 1.0x0.8 |
| Total | 41 | F (19), M (13) | Mean 34.9 | Tongue (11), BM (7), Lip (6), Others (9) | |

The NSM "cellular type" is consistently positive for S-100A6 and usually S-100 negative (7,15). Nishioka et al. have observed nerve sheath differentiation of mixed and cellular types in 3 oral cases of NSM, which led the authors to support the theory that different types of NSM form a morphologic spectrum rather than distinct disease entities (4). Therefore, the different variants of NSM could have the same origin, closely related to true nerve sheath tumor (4). Fetsch et al. stated that the morphological and immunohistochemical profile of NTK/NSM is distinct from that of true NSM. The authors speculated that NTK/NSM might be derived from fibroblastic cells with the ability to differentiate into myofibroblasts and the pro-

Acta Dermatovenerol Croat
2014;22(1):52-56

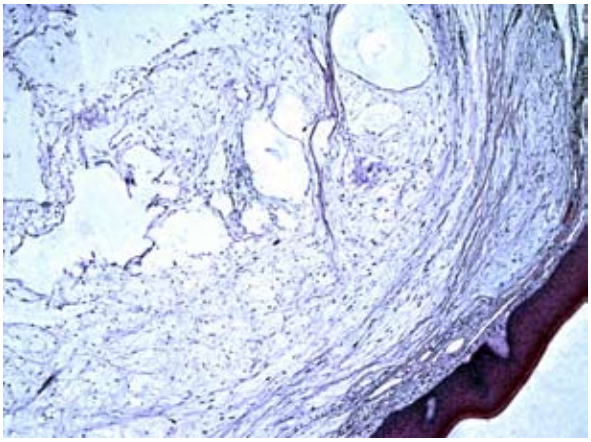

**Figure 4.** Histopathology of nerve sheath myxoma showing a hypocellular tumor with a multinodular pattern and spindle and stellate cells lying within stromal mucin (H&E; x200).

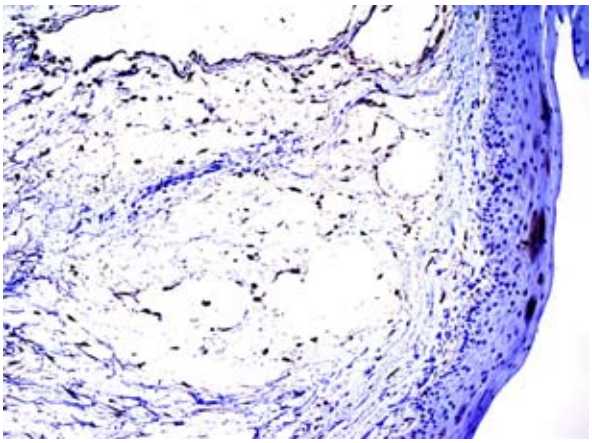

**Figure 5.** Immunohistochemistry of the lesion: Vimentin immunoreactivity in neurothekeoma. Immunoperoxidase: original magnification ×200.

pensity to recruit histiocytic cells (9). The differential diagnosis of an apparent non-neural NSM includes traumatic fibroma, fibro-papilloma, oral focal mucinosis, soft tissue myxoma, lipoma, ectomesenchymal chondromyxoid tumor, and myxoid malignant fibrous histiocytoma. On the other hand, granular cell tumor, myxoid neurofibroma, true neuroma, neurilemmoma (Schwannoma), and perineurinoma should be considered in the differential diagnosis of NSM of neural origin (5,11,16,17).

Regarding neural lesions, histological diagnosis of NSM overlaps with neurilemmomas, which are rarely myxoid in appearance, and contain areas of increased cellularity (Antoni A tissue) with the formation of Verocay bodies. True encapsulation is seen in nerve sheath myxoma (5,11,14), while true neuromas show nerve axons organized in fascicles (5,11).

Myxoid neurofibromas have been infrequently reported in the oral cavity, but the possible association of these neoplastic diseases with systemic manifestations (e.g. Von Recklinghausen's disease and multiple endocrine neoplasia) makes an accurate diagnosis very important.

Myxoid neurofibromas show a positive immunoreactivity for S-100 protein, but are not capsulated and composed of slender and closely aggregated fascicles of cells placed in loose myxoid stroma (5,11,14). Perineurinomas are positive for EMA, whereas S-100 protein antigen detection is normally negative (18,19).

Other non-neural lesions that may be similar to NSM and should considered in differential diagnosis (within the histological field) are oral focal mucinosis, soft tissue myxoma, myxoid malignant fibrous his-

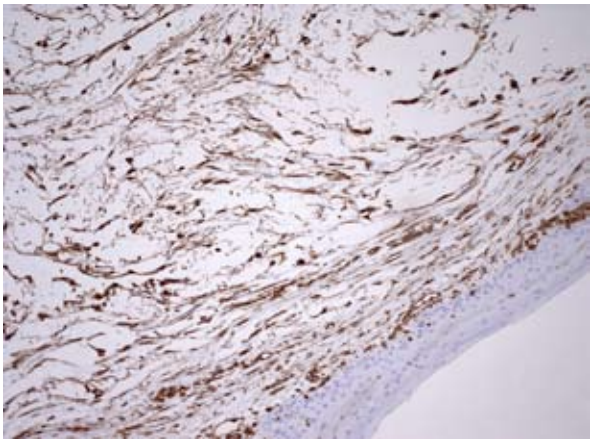

**Figure 6.** Immunohistochemistry of lesion: S100 immunoreactivity in neurothekeoma. Immunoperoxidase: original magnification ×200.

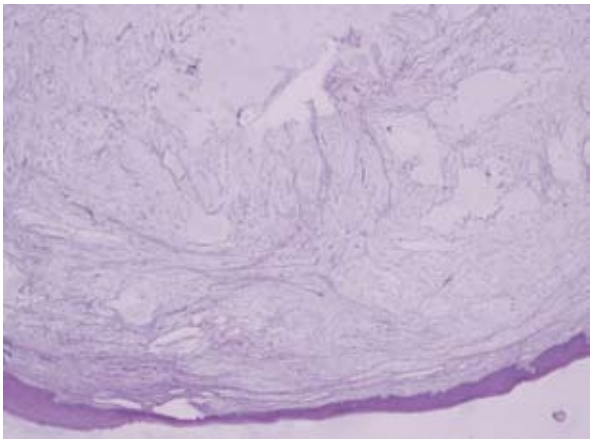

**Figure 7.** Neurothekeoma with distinctive compartmentalized appearance at low power: original magnification ×2.5.

tiocytoma, and ectomesenchymal chondromyxoid tumor. Oral focal mucinosis is not as circumscribed, lobulated, or cellular as NSM and is usually negative for S-100 protein (7,14). Oral myxomas are poorly marginated compared with NSM, and are typically negative for S-100 protein (7,18,19). Myxoid malignant fibrous histiocytoma shows a greater degree of nuclear pleomorphism as well as mitotic activity compared with nerve sheath myxoma (11). In contrast to NSM, ectomesenchymal chondromyxoid tumor displays biphasic myxoid and chondroid patterns and is positive for both glial fibrillary acidic protein (GFAP) and cytokeratin, even if it is infrequently stained with antibodies for smooth muscle actin and S-100 protein (17).

## CONCLUSION

Surgical excision is usually the therapy of choice for NSM. Recurrence of NSM has not been reported after surgery. We emphasize the value of immunohistochemistry in the differential diagnosis between nerve sheath myxoma and other oral myxomas.

## References

1. Harkin JC, Reed RJ. Solitary benign nerve sheath tumors. Tumors of the peripheral nervous system. In: Atlas of Tumor Pathology. 2nd edition. Washington DC: Armed Forces Institute of Pathology; 1969. pp.60-4.
2. Gallager RL, Helwig EB. Neurothekeoma - a benign cutaneous tumor of neural origin. Am J Clin Pathol 1980;74:759-64.
3. Perentes E, Nakagawa Y, Ross GW, Stanton C, Rubinstein LJ. Expression of epithelial membrane antigen in perineurial cells and their derivatives. An immunohistochemical study with multiple markers. Acta Neuropathol 1987;75:160-5.
4. Nishioka M, Aguirre RL, Ishikawa A. Nerve sheath myxoma (neurothekeoma) arising in the oral cavity: histological and immunohistochemical features of 3 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;107:28-33.
5. Safadi RA, Hellstein JW, Diab MM, Hammad HM. Nerve sheath myxoma (neurothekeoma) of the gingiva, a case report and review of the literature. Head Neck Pathol 2010;4:242-5.
6. Ekşi E, Oztop I. Nerve sheath myxoma of the upper lip: a case report. Kulak Burun Bogaz Ihtis Derg 2010;20:318-20.
7. Vered M, Fridman E, Carpenter WM, Buchner A. Classic neurothekeoma (nerve sheath myxoma) and cellular neurothekeoma of the oral mucosa: immunohistochemical profiles. J Oral Pathol Med 2011;40:174-180.
8. Argenyi ZB, LeBoit PE, Santa Cruz D, Swanson PE, Kutzner H. Nerve sheath myxoma (neurothekeoma) of the skin: light microscopic and immunohistochemical reappraisal of the cellular variant. J Cutan Pathol 1993;20:294-303
9. Fetsch JF, Laskin WB, Hallman JR, Lupton GP, Miettinen M. Neurothekeoma: an analysis of 178 tumors with detailed immunohistochemical data and long-term patient follow-up information. Am J Surg Pathol 2007;31:1103-4.
10. Laskin WB, Fetsch JF, Miettinen M. The "neurothekeoma": immunohistochemical analysis distinguishes the true nerve sheath myxoma from its mimics. Hum Pathol 2000;31:1230-41.
11. Schortinghuis J, Hille JJ, Singh S. Intraoral myxoid nerve sheath tumour. Oral Dis 2001;7:196-9.
12. Peñarrocha M, Bonet J, Minguez JM, Vera F. Nerve sheath myxoma (neurothekeoma) in the tongue of a newborn. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;90:74-7.
13. Makino T, Utsunomiya T, Kamino Y, Kobayashi R, Fukumoto M, Yamamoto H, *et al.* Nerve sheath myxoma of the tongue in a child. Int J Oral Maxillofac Surg 2002;31:451-4.
14. Capodiferro S, Scully C, Scivetti M, Lacaita MG, Maiorano E. Nerve sheath myxoma (neurothekeoma) of the tongue: case report and literature review. J Oral Maxillofac Surg 2006;64:705-8.
15. Plaza JA, Torres-Cabala C, Evans H, Diwan AH, Prieto VG. Immunohistochemical expression of S100A6 in cellular neurothekeoma: clinicopathologic and immunohistochemical analysis of 31 cases. Am J Dermatopathol 2009;31: 419–22.
16. Katsourakis M, Kapranos N, Papanicolaou SI, Patrikiou A. Nerve sheath myxoma (neurothekeoma) of the oral cavity: A case report and review of related literature. J Oral Maxillofac Surg 1996;54:904-6
17. Smith BC, Ellis GL, Meis-Kindblom JM, Williams SB. Ectomesenchymal chondromyxoid tumor of the anterior tongue. Nineteen cases of a new clinicopathologic entity. Am J Surg Pathol 1995;19:519-30
18. Tiffee JC, Pulitzer DR. Nerve sheath myxoma of the oral cavity: case report and review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;82:423-5.
19. Patil K, Mahima VG, Ambika L. Malignant peripheral nerve sheath tumour: an elusive diagnosis. In-