Neurothekeoma of the Oral Cavity: Report of two cases of a distinctive variant and review of the literature

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Neurothekeoma (NT) including nerve sheath myxoma (NSM), is a benign neoplasm derived from the peripheral nerve sheath that occurs very rarely in the oral cavity. We describe two cases of a distinctive variant of NT arising in the buccal mucosa and the tongue. Histologically, one of the lesions showed the coexistence of ill-circumscribed hypocellular and myxoid lobules and hypercellular fibrous fascicles, and the other demonstrated a scattered distribution of the tumor cells in myxoid matrix in various sizes of nests. These findings, together with immunohistochemical characteristics, suggest that the former lesion is a mixed variant of NT, and the latter is a myxoid variant of it. A review of the literature revealed 16 previous reports of NTs arising in the oral cavity.

Key words: neurothekeoma (nerve sheath myxoma), buccal mucosa, tongue, immunohistochemical analysis

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Introduction

Neurothekeoma (NT) including nerve sheath myxoma (NSM), is a rare neoplasm arising from the endoneurium of the peripheral nerves. In 1969, Harkin and Reed (1) were the first to report on this tumor in the dermis, and they termed it “myxoma of the nerve sheath”. The tumor was characterized by a lobular proliferation of myxomatous tissue separated by fibrous septa. Subsequently, Gallager and Helwig (2) reported 53 cases of a benign tumor of the dermis and subcutaneous tissue that was histologically suggestive of “Schwann cell tumor”, which they called NT. Since then, the differential diagnosis between NSM and NT has been controversial. Generally, the prevailing view has been that NSM and NT are predominantly myxoid and cellular variants of the same tumor (3), and Pulitzer and Reed (4) accepted these two lesions as synonymous in a broad sense. However, Laskin et al. (5) stated that NSM is only a hypocellular variant in the myxoid type of NT. In 1996, the World Health Organization “Histological Typing of Skin Tumours” (6) stated that NSM may represent a variant of NT with increased mucin deposition associated with greater age, and NT may be subdivided into cellular and myxoid variants. Recently, immunohistochemical analysis has been performed to determine the subdivision of NT, but there is no consistency of immunoreaction in some cases. Thus, the precise relationship between NSM and NT has not yet been completely established due to disagreement among investigators. NT often develops in the dermis and subcutis of the face, extremities, trunk and the shoulders (6), and very rarely in underlying mucous membranes. Previously, only 16 cases of intraoral NT have been reported (2, 4, 7-18). We describe the clinical and pathologic features of two cases of NT as a distinctive variant: a mixed variant arising in the buccal mucosa and a myxoid variant arising in the inferior surface of the tongue. In addition, previously reported intraoral lesions of this tumor are reviewed.

Case Reports

Case 1

A 59-year-old man visited our outpatient clinic on May 20, 1992, with a chief complaint of a gradually enlarging mass in the buccal mucosa. The patient had repeated formation of a submucosal hematoma in the left buccal mucosa during the previous two years, due to biting. Physical examination revealed a pedunculated polypous mass measuring 10 × 14 × 7 mm in size on the left buccal mucosa corresponding to the bite-surface of the
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was observed in the stroma of the fibrous fascicles, and a small amount of loose myxoid materials was partly present (Fig. 1C). Additionally, a few calcifications as deposition of microgranules were observed in a part of the stromal fibrous connective tissue.

For immunohistochemical staining, the streptavidin-biotin peroxidase complex method (Histofine, SAB-PO kit, Nichirei, Tokyo) was employed on paraffin-sections. Primary antibodies against S-100 protein (pre-diluted, Biomeda, Foster CA, USA), neuron specific enolase (NSE), epithelial membrane antigen (EMA), vimentin, \(-\)smooth muscle actin (\(-\)SMA) and glial fibrillary acidic protein (GFAP) (each pre-diluted, Immunotech, Marseille, France) and CD34 (pre-diluted, Immunotech, Marseille, France) and CD57 (Leu 7, 1: 50, Novoceastra, Newcastle, UK) were used for this examination. The stellate and spindle-shaped tumor cells showed a diffusely positive immunoreaction for NSE (D; 200).

Histopathological findings

Microscopically, the tumor was mainly located in the buccal mucosa partly extending into the submucosa. It showed the coexistence of ill-circumscribed hypocellular and myxoid lobules, as well as hypercellular fibrous fascicles, without obvious encapsulation (Fig. 1A). The lobules were composed of stellate cells and prominently elongated spindle-shaped cells with darkly stained atypical nuclei in an abundant myxoid stroma (Fig. 1B). The peroxidase-digestive periodic acid-Schiff-staining was positive in the myxoid stroma. The hypercellular fibrous fascicles between myxoid lobules were composed of a large-sized epithelioid cells with hyperchromatic and polygonal round or ovoid nuclei and eosinophilic cytoplasm. Mitotic figures were scarce, and atypical mitoses were not seen. A mononuclear inflammatory cell infiltration was observed in the stroma of the fibrous fascicles, and a small amount of loose myxoid materials was partly present (Fig. 1C). Additionally, a few calcifications as deposition of microgranules were observed in a part of the stromal fibrous connective tissue.

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observed in the tumor cells. Based on these histological and immunohistochemical findings, the lesion was diagnosed as a mixed variant of NT (Table 1).

**Case 2**

A 51-year-old man was referred to our clinic on September 26, 1996, with a chief complaint of contact pain on the left inferior surface of the tongue. Oral examination revealed the existence of an erosive white lesion measuring 6 × 15 mm with a slight induration. The left submandibular lymph node was palpable in a pea size, but was painless and mobile. Laboratory data were within normal limits. Because carcinomatous change of leukoplakia was strongly suspected, a biopsy was performed. Histological diagnosis was moderately differentiated squamous cell carcinoma accompanied with mild epithelial dysplasia in the adjacent epithelium. After admission to our hospital, partial glossectomy was performed under general anesthesia on July 25, 1997. Surgical specimen to our hospital, partial glossectomy was performed on September 26, 1996, with a chief complaint of contact pain on the left inferior surface of the tongue. Oral examination revealed the existence of an erosive white lesion measuring 6 × 15 mm with a slight induration. The left submandibular lymph node was palpable in a pea size, but was painless and mobile. Laboratory data were within normal limits. Because carcinomatous change of leukoplakia was strongly suspected, a biopsy was performed. Histological diagnosis was moderately differentiated squamous cell carcinoma accompanied with mild epithelial dysplasia in the adjacent epithelium. After admission to our hospital, partial glossectomy was performed under general anesthesia on July 25, 1997. Surgical specimen to our hospital, partial glossectomy was performed on September 26, 1996, with a chief complaint of contact pain on the left inferior surface of the tongue.

**Histopathological findings**

On microscopic examination, the lesion was located in the submucosa and was well circumscribed and encapsulated with thin fibrous connective tissue. It was composed of a large irregular nest (from center to left upper portion in Fig. 2A) and numerous small and oval nests with abundant myxoid matrices (Fig. 2A). A large irregular nest contained thin fascicles of tumor cells, and some of the small nests included thick fascicles of tumor cells. The bulk of those fascicles showed a tendency to form palisadings, and resembling those of Verocay body, structural elements in schwannoma. Additionally, the scattered distribution of cartilaginous tumor cells was observed in the myxoid matrix (Fig. 2B). These cells had clear cytoplasm and hyperchromatic nuclei, and few multinucleated cells were also present. Minimal cytologic atypia and only rare mitotic figures were seen.

Immunohistochemical staining was performed as described in case 1. In the majority of tumor cells, the Verocay body-like fascicles showed diffusely positive immunoreaction for vimentin, S-100 protein,NSE and CD57 (Fig. 2B-D), and no immunoreactivities for CD34 and -SMA. In contrast, positive immunoreactions for vimentin and CD34 were demonstrated in the cartilagenous tumor cells distributed in the myxoid matrix (Fig. 2F), but no immunoreactivities for S-100 protein, NSE, CD57, -SMA and GFAP were observed. Based on these histological and immunohistochemical findings, the tumor was diagnosed as a myxoid variant of NT (Table 1).

**Discussion**

NT is a rare cutaneous neoplasm showing nerve sheath differentiation with a lobulated architecture and variable degree of mucinous changes (6). The patients ranged in age from 2 to 70 years (mean, 24.3 years), and women were affected nearly twice as often as men. The face was the most common site, accounting for almost one-third of the lesions, and a substantial number of lesions also occurred on the extremities and trunk (4). Mincer and Spears (7) had first reported a case in the tongue as NT in the oral cavity. To date, 16 cases (17 lesions) of intraoral NTs have been reported (2, 4, 7-18). The details of the clinicopathological characteristics in the previous cases and our current cases of intraoral NTs were summarized in Table 1 and 2. In the anatomic sites of those cases, there were 6 in the tongue, 5 in the buccal mucosa, 3 in the lip, 2 in the palate, and one each in the retromolar area and the posterior mandible. The mean age was 36.3 years, and woman were more frequently affected. Tumors were typically described as flesh-colored to slightly erythematous nodules with soft consistency. The tumor size ranged from 4 to 18 mm in diameter, with an average of 10 mm in skin lesions (2), whereas intraoral lesions ranged from 5 to 4 mm ("case 2" in ours) to 30 to 25 mm (case No.16) in Table 1 and 2. Clinically, intraoral NTs were often diagnosed as fibroma or mucocele. In our two cases, case 1 was diagnosed as irritation fibroma and case 2 was diagnosed as amputation neuroma.

The histogenesis of NTs has been controversial. Currently, there is equal support for the origin of NT as "Schwann cell" (19) and "perineural cell" (20). The presence of a strong immunoreactivity for S-100 protein and NSE supports the theory that the tumor originates from...
“Schwann cell” (13, 14, 19, 21). In contrast, lack of the immunoreactivity for S-100 protein and EMA in this tumor may indicate a “perineural cell” origin (20). Ultrastructurally, the presence of a basal lamina and spindle-shaped cells support a “Schwann cell” origin, but tight junctions suggest a “perineural cell” derivation (21).

In the histological typing of skin tumors by the World Health Organization (6), this tumor is described as being composed of lobules of spindle-shaped and epitheloid cells embedded in a myxoid stroma, which is more abundant in a tumor predominantly containing spindle cells. Although the tumor is defined in juxtaposition as NSM and NT, NSMs may represent a variant of NT with increased mucin deposition associated with greater age and may be subdivided into cellular or myxoid variants (16). Recently, the two variants of NT have been

Fig. 2: Neurothekeoma, Myxoid variant (Case 2). Excisional biopsy specimen of the right inferior surface of the tongue. The submucosal tumor was well circumscribed and encapsulated with thin fibrous connective tissue, and composed of a large-sized irregular and a numerous small-sized nests with abundant myxoid matrix (A; HE, 200). In the lobulated nest and the aggregated tiny nests, the tumor cells showed a tendency to palisade and the fascicles of the tumor cells resembled those of Varocay bodies. The scattered distribution of some cartilagenous tumor cells were observed in the myxoid matrix (B; arrows, HE, 100). In the bulk of the tumor cells resembling Verocay bodies, the tumor cells showed a diffusely positive staining of immunoreaction for S-100 protein (C; 200), NSE (D; 200) and CD57 (E; 200) and positive immunoreaction for CD34 was demonstrated in the cartilaginous tumor cells distributed with the myxoid matrix (F; 400).
established by an index of the histological features with immunohistochemical characteristics: the myxoid variant is strongly positive for S-100 protein, and the cellular variant fails to express it (16, 22). Argenyi et al. (23) have proposed a three-part histological division of cutaneous NTs into myxoid, cellular and mixed variants. They described that 33% (2 of 6 cases) of myxoid NT were negative for S-100 protein, but weakly and focally positive for smooth muscle specific actin and NSE. More recently, Laskin and coworker’s (5) have shown that both cellular and mixed NT expressed collagen type IV, calponin and SMA, and only in the minority of the cases did they expressed CD57 and S-100 protein, but not nerve growth factor receptor (NFGR), GFAP, or CD34. In our first case, the majority of tumor cells in the myxoid matrix was also positive for NSE. There were also scattered immunoreactivities of CD57 in tumor cells in the marginal region of the myxoid lobes, but no expressions for S-100 protein, CD34 and α-SMA were observed. This evidence strongly suggests that the lesion is a mixed variant of NT. On the other hand, they have demonstrated a clear-cut evidence that myxoid variants of NT show a neurosustentacular (NS) differentiation by exhibiting consistent immunoreactivity for S-100 protein and low-affinity NGFR p75 NGFR, and variable reactivity for GFAP and CD57. They have also revealed that the NT subtype showed pericellular collagen type IV expression, scattered intralesional CD34-positive cells, EMA-positive spindled cells located in the adjacent dense collagen, and calponin (5).

In our second case, the majority of tumor cells resembled the morphology of the Verocay body, which was diffusely positive for vimentin, S-100 protein, NSE and CD57. The positive expression for vimentin and CD34 was prominent in the cartilaginous tumor cells distributed in the myxoid matrix. Based on these histological and immunohistochemical findings, the lesion seems to correspond to a myxoid variant of NT. The above results suggest that the myxoid variant of NT shows NS differentiation and is the bona fide nerve sheath tumor, whereas both cellular and mixed variants of NT fail to show convincing evidence of NS differentiation and therefore probably warrant a separate classification (5).

The histologic differential diagnosis of this tumor should include myxoid schwannoma, neurofibroma, myoepithelioma, mucocoele, oral myxoma, oral focal mucinosis, chondroid (cartilaginous) choristoma, glial choristoma, ectomesenchymal chondromyxoid tumor (ECMT) of the anterior tongue, low-grade myxofibrosarcoma (low-grade myxoid malignant fibrous histiocytoma) and chondrosarcoma (24-26).

In our first case, diagnosed as mixed type of NT, the tumor was predominantly composed of a myxoid component with lobular architecture, and the stellate and spindle-shaped tumor cells were diffusely positive for S-100 protein, and low-affinity NGFR p75 NGFR, and variable reactivity for GFAP and CD57. They have also revealed that the NT subtype showed pericellular collagen type IV expression, scattered intralesional CD34-positive cells, EMA-positive spindled cells located in the adjacent dense collagen, and calponin (5).
bodies against S-100 protein and NSE, in contrast to NT (8, 12, 15, 24, 25). Additionally, occasional myxoid schwannoma mimics NSM in showing remarkable mucin accumulation. Unlike NSM, however, myxoid schwannoma exhibits a collagenous capsule, often with islands of Antoni A tissue (3). In our second case, diagnosed as myxoid type of NT, the tumor was composed of a large irregular nest and numerous small and oval nests with abundant myxoid matrix with the scattered distribution of cartilagenous tumor cells. Those nests contained thin or thick fascicles of tumor cells, and the bulk of those fascicles resembled those of the Verocay body. In the majority of tumor cells, the Verocay body-like fascicles resembled those of the Verocay body. In the thin or thick fascicles of tumor cells, and the bulk of those fascicles are distributed in the cartilagenous tumor cells. Those nests contained thin or thick fascicles of tumor cells, and the bulk of those fascicles resembled those of the Verocay body. In this case, histologic differential diagnosis was needed from tumors with a chondroid component, particularly, chondroid choristoma, glial choristoma, and ECMT of the anterior tongue.

Chondroid choristoma of the oral cavity forms well-differentiated hyaline cartilage that may be surrounded by perichondrium-like connective tissue. This lesion typically does not have a predominant myxoid component (24). Glial choristoma can occur in the anterior tongue; however, it has astrocyte, ganglion cells, and other neural elements (24) that are not present in NT. ECMT exhibits a lobular proliferation of ovoid and fusiform cells, often having multilobulated nuclei that are focally atypical, and chondroid areas. The fibrous septae of NT impart a lobular appearance, which is not characteristic feature of ECMT (26). However, the tumor cells in ECMT are strongly and variably immunoreactive for GFAP, cytokeratin (AE1/AE3) and CD57 (15, 26).

More information is needed to understand the histogenesis of this tumor and to determine the histological division.

References


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