Extraneural Sclerosing Perineurioma of the Buccal Mucosa: A Case Report and Clinicopathologic Review

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Abstract The perineurioma is an infrequently encountered benign peripheral nerve sheath tumor composed of a clonal proliferation of perineurial cells. Rare cases of perineurioma have been reported in the oral cavity. An extraneural sclerosing perineurioma arising in the buccal mucosa of a 17-year-old male is presented. Histopathologically, the tumor is composed of a well circumscribed nodular proliferation of spindle cells arranged in a storiform growth pattern, in some areas subtly arranged around vascular channels. The tumor cells reveal positive immunostaining for epithelial membrane antigen (EMA), collagen type IV and vimentin, and negative immunostaining for S-100 protein, consistent with a perineurial origin. To the best of our knowledge, this case represents the first report of an extraneural sclerosing perineurioma involving the oral cavity.

Keywords Extraneural perineurioma ·
Sclerosing perineurioma ·
Benign peripheral nerve sheath tumor

Introduction

Originally described on the basis of ultrastructural studies by Lazarus and Trombetta in 1978, [1] the perineurioma is

an infrequently encountered benign peripheral nerve-sheath lesion arising from perineurial cells [2]. Typically divided into either the intraneural or the extraneural (soft tissue) variants, the perineurioma is thought to represent a clonal proliferation of perineurial cells that surround the periphery of nerve fascicles. Unlike the intraneural form of perineurioma which is notable for enlargement of the involved nerve together with associated sensorimotor deficits, the extraneural perineurioma is typically unassociated with peripheral nerves and presents as a solitary nodule or subcutaneous mass. Rare occurrences have been reported in the oral cavity; including the present case, at the time of this publication 16 intraoral cases of perineurioma were identified in the English-language literature [3–16]. The sclerosing perineurioma represents an unusual variant of the extraneural perineurioma, thought to exclusively arise as a solitary lesion in the hands of young adults [2]. To the best of our knowledge, this case represents the first report of a sclerosing extraneural perineurioma involving the oral cavity.

Case Report

A 17-year-old male presented with a firm, painless nodule of several months duration involving the right buccal mucosa situated between the commissure and Stensen's duct. There was no history of trauma or previous surgery. The nodule was not fixed, but easily moveable and appeared to be midway in depth between the buccal mucosa and the external cutaneous surface of the cheek. The lesion was approximately 7–8 mm in greatest dimension and the overlying surface was smooth and pink. An excisional biopsy of the nodule was performed under general anesthesia at the same time as the removal of his

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impacted third molars. The postoperative course was unremarkable and no evidence of recurrence is appreciated eight months post excision.

Microscopic Examination

Histopathologic evaluation showed a well-circumscribed, nodular proliferation of densely collagenized fibrous tissue (Fig. 1) revealing spindle cells exhibiting a subtle whorled growth pattern. (Fig. 2) Scattered vascular elements were appreciated throughout with whorls of spindle cells arranged in a vague perivascular configuration.

Fig. 1 Low-power view showing a well-circumscribed densely collagenized proliferation of spindle cells exhibiting a vague storiform arrangement. (Hematoxylin and eosin [H&E], original magnification, 20×)

Fig. 2 Hypercellular areas composed of spindle-shaped mesenchymal cells juxtaposed with hypocellular areas (H&E, original magnification, 100×)

Immunohistochemistry

Immunohistochemical studies revealed strong reactivity to epithelial membrane antigen (EMA) within the population of spindle shaped cells suggesting a perineurial origin. Additionally, immunohistochemical stains for collagen type IV were positive within the tumor cell population and vimentin positivity was appreciated throughout. (Fig. 3) Immunohistochemical stains for smooth muscle actin, claudin-1, CD31, CD34, HMB-45, pan-cytokeratin, and S-100 protein were noncontributory in the presence of appropriate controls.

Discussion

Serving as a barrier positioned between the epineurium and endoneurium of peripheral nerve fascicles, the perineurium is populated by perineurial cells and is in continuity with the pia arachnoid membrane of the central nervous system [17]. The perineurioma represents a neoplastic proliferation of these perineurial cells and is notable for a unique morphological, immunohistochemical, and ultrastructural profile that distinguishes these lesions from the more commonly encountered peripheral nerve tumors such as the schwannoma and neurofibroma. Including the present case, only 16 intraoral cases have been reported (Table 1); of these ten were the extraneural variant whereas the remaining six were associated with both major and small unnamed nerve branches [4–7, 10, 16]. While the intra-neural perineurioma is often symptomatic with sensory and motor deficits reported in cases involving major nerves, extraneural lesions are typically asymptomatic [9, 10].

The pathogenesis of the perineurioma is not completely understood. Initial hypotheses suggested that the intraneural variant may represent a non-neoplastic proliferative disorder (localized hypertrophic neuropathy) secondary to trauma or injury; however, such lesions are now considered benign neoplasms. Evidence to suggest a cytogenetic alteration has been demonstrated and many such lesions representing both the intraneural and extraneural variants have shown chromosomal aberrations that may have unique subtype characteristics. For example, alterations on chromosome 22 have been reported to be characteristic for both the intraneural and extraneural perineurioma with an altered tumor suppressor gene thought to give rise to the clonal proliferation of perineurial cells [18, 19]. Although initial reports suggested that no apparent association existed with either neurofibromatosis type 1 (NF1) or neurofibromatosis type 2 (NF2), [20] extraneural perineuriomas have recently been reported in patients with both disorders [21, 22]. Similar to schwannoma and neurofibroma, NF2 deletions (monosomy 22) have been observed in the perineurioma

Fig. 3 Photomicrographs showing positive immunohistochemical staining in the tumor cell population for: **a** epithelial membrane antigen (EMA); **b** vimentin; and **c** collagen type IV. (Original magnification of each photomicrograph, 200×)

including the extraneural sclerosing variant [23, 24] and aberrations in chromosome 10 have been shown to be a feature of the sclerosing perineurioma in particular [25].

Histopathologically, the extraneural perineurioma has a variable appearance which may explain the paucity of

Table 1 Cases of perineurioma involving the oral cavity

Authors	Patient no.	Sex	Age (y)	Location
Kusama et al. [12]	1	F	31	Mandible
Graadt van Roggen et al. [8]	2	F	42	Gingiva
Barrett et al. [3]	3	M	53	Mandible
Meer et al. [13]	4	F	46	Naso-labial
Damm et al. [6]	5	F	26	Tongue
Huguët et al. [10]	6	M	64	Mandible
Ide et al. [11]	7	F	59	Gingiva
Hornick et al. [9]	8	F	15	Tongue
Hornick et al. [9]	9	M	44	Upper lip
Mentzel et al. [14]	10	F	60	Lower lip
Da Cruz Perez et al. [5]	11	M	12	Tongue
Dundr et al. [7]	12	M	16	Buccal mucosa
Boyanton et al. [4]	13	F	6	Tongue
Siponen et al. [15]	14	F	19	Buccal mucosa
Tanaka et al. [16]	15	F	34	Tongue
Noonan et al. (current case)	16	M	17	Buccal mucosa

reported cases in the literature. Most tumors are unencapsulated but well-circumscribed with a whorled (storiform) growth pattern. Occasional lesions exhibit a subtle infiltrative appearance at the periphery [26]. Variable cellularity with nuclear palisading has been infrequently noted and mitotic figures are rarely identified. The spindle-shaped cells typically demonstrate thin, irregular nuclei with some cases notable for cells exhibiting a plump ovoid or epithelioid appearance [26, 27]. The supporting stroma is typically densely collagenized akin to reduplicated basement membrane and may show areas of myxoid change [28]. Artifactual tissue cracking and thick-walled vascular channels are frequently encountered [29]. Anecdotal reports of perineurioma exhibiting osseous metaplasia, calcospherites, and a granular cell component have been described [30–33]. Lesions reported as sclerosing perineurioma are remarkable for either demonstrating a so-called “onion-skin” whorled growth pattern that sometimes gives the appearance of concentric swirls around blood vessels or small nerves [2] or a trabecular growth pattern [29]. Depending on the clinical location of the lesion, cases of sclerosing perineurioma have been likened histopathologically to various adnexal tumors, fibrous histiocytoma, epithelioid glomus tumor, fibroma of tendon sheath and giant cell tumor of tendon sheath, epithelioid hemangi endothelioma, calcifying fibrous pseudotumor, and neurofibroma among others.

As perineurial cells and cells of the arachnoidal cap are most likely derived from a common embryologic origin, this so-called “perineurial epithelium” composed of

perineurial cells shows positive cell membrane immunoreactivity for the high molecular weight transmembrane glycoprotein epithelial membrane antigen (EMA) [34–36]. In addition to EMA, immunoreactivity is also consistently demonstrated for collagen type IV, and vimentin and negative for S-100 protein [29]. Variable immunoreactivity has been demonstrated for cytokeratin cocktail (including AE1, AE3, and CK1), CAM 5.2, claudin-1, muscle specific actin, alpha smooth muscle actin, laminin, and CD99 [9]. Ultrastructurally, lesional cells are notable for thin and widely separated bipolar cytoplasmic processes, [29] discontinuous external lamina, abundant pinocytotic vesicles, and tight junctions [1, 2, 26, 37].

Although perineuriomas typically follow a benign course, in rare instances perineurial features have been described in malignant peripheral nerve sheath tumors [38, 39]. As with conventional perineuriomas, malignant perineurial tumors have been reported to demonstrate a proliferation of spindled cells remarkable for a fascicular or storiform growth pattern, in some instances showing perivascular whorls with variable supporting stromal density. Positive immunoreactivity for EMA and negative S-100 protein profiles are consistently reported in these lesions [38, 39]. Atypical features described include readily identifiable mitotic figures, cytologic atypia, and tumoral necrosis. While such lesions have been termed “low-grade malignant perineuriomas,” due to the propensity for innocuous behavior, long-term follow up is not available in most instances. At least one case of a low-grade malignant perineurioma with multiple metastases 10 years following the initial diagnosis has been cited in the literature [40]. As the clinical behavior of such atypical perineurial lesions is uncertain, further long-term study is indicated.

Clinically, conventional perineuriomas are reported to have an excellent prognosis. Conservative surgical excision with uninvolved margins at histopathologic examination is deemed adequate management and recurrence is not expected.

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