Intraoral Perineurioma, Soft Tissue Type: Report of Five Cases, Including 3 Intraosseous Examples, and Review of the Literature

Ioannis G. Koutlas · Bernd W. Scheithauer ·
Andrew L. Folpe

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Abstract Soft tissue type perineuriomas (STP) are uncommon tumors, oral examples being very rare. They have been described in the mandible, gingiva, lips, retromolar mucosa and maxillary vestibule. Herein, we report the clinicopathologic features of five STP, two affecting the buccal mucosa and three the mandible. Three patients were women and two men. All tumors were characterized by a proliferation of cytologically bland, mitotically inactive spindled cells with round, ovoid or spindled nuclei, embedded in a variably collagenous and myxoid matrix. Interestingly, two mandibular tumors featured psammoma bodies and one, in addition, contained irregular calcifications. Tumor cells showed the immunohistochemical profile of perineurial cells including epithelial membrane antigen, Glut-1, claudin-1 and collagen type IV. S100 and neurofilament proteins were not expressed by the tumor cells. A few minute, peripherally situated, entrapped nerves were identified. All tumors were reported gross-totally excised and no recurrences have taken place. The clinical characteristics of STP are summarized and its differential diagnosis relative to other spindle cells tumors and meningioma is discussed.

Keywords Soft tissue type perineurioma · Oral cavity · Jaw

Introduction

Detailed descriptions of perineurium and perineurial cells were first published in 1873 by Key and Retzius [1]. It has been suggested that three very different cell types are histogenetically related to perineurial cells. These include Schwann cells [2], and fibroblasts [3], both components of endoneurium, and even arachnoid cap cells [4]. Microscopically, obvious perineurial cells with typical immunohistochemical and ultrastructural features may be a conspicuous component of so-called mixed or “hybrid” peripheral nerve tumors, including neurofibroma [5] and schwannoma [6, 7]. Perineurial cells have also been encountered in a rare example of multiple granular cell tumors [8].

Peripheral nerve and soft tissue tumors composed of perineurial cells are termed perineuriomas. Pure perineuriomas fall into two principal categories; intraneural perineuriomas once termed “localized hypertrophic neuropathy,” and soft tissue type perineuriomas (STP) [9]. Whereas the former are entirely intraneural, the latter are generally unassociated with a visible nerve. The first case of a soft tissue perineurioma was published by Lazarus and Trombetta [10] and arose in the calf of a 45-year-old male. Thereafter, numerous case reports and a single very large series by Hornick and Fletcher [11] have been reported. Since their original description, STP of the sclerosing [12] and reticular (retiform) [13] subtypes have also been described. Lastly, rare granular cell [14] and epithelioid cell [15] variants have also been proposed.

Oral STP are rare. Examples have been reported to occur in the mandible [16, 17], gingiva [13, 18], tongue [11], upper lip [11], lower lip [19], nasolabial fold [20] and retromolar region [11]. Yet another mandibular case example was presented at the annual meeting of the Western Society of Teachers in Oral Pathology [21].

I. G. Koutlas (✉)
Division of Oral and Maxillofacial Pathology, University of
Minnesota, School of Dentistry, 515 Delaware Street
SE #16-206B, Minneapolis, MN 55455, USA
e-mail: koutl001@umn.edu

B. W. Scheithauer · A. L. Folpe
Department of Laboratory Medicine and Pathology,
Mayo Clinic, Rochester, MN, USA

In our review of over 350 cases of oral peripheral nerve sheath tumors, exclusive of granular cell tumors, all accessioned to the files of the Division of Oral Pathology, University of Minnesota, School of Dentistry, we encountered 2 STP, one affecting the buccal mucosa and the other the mandible. Three further cases, two affecting the mandible and one the buccal mucosa were identified in the consultation files of two of the authors (BWS,ALF). Features described in soft tissue perineuriomas characterized all mandibular examples. Herein we present the clinical, histologic and immunohistochemical characteristics of these five cases and summarize the characteristics of the relatively few other oral STP reported to date.

Methods and Materials

Formalin-fixed, routinely processed and paraffin-embedded, surgically resected tissues were cut at 5 microns for histochemistry (hematoxylin and eosin) and for immunohistochemical staining, utilizing steam heat-induced epitope retrieval and the Dako Envision detection system (Dako Corp., Carpinteria, CA). Applied antisera were directed against S-100 protein (Dako, Carpinteria, CA; polyclonal, 1:1,600), neurofilament protein (NFP) (Dako, clone 2F11, 1:800) and epithelial membrane antigen (EMA) (Dako, clone E29, 1:50). In addition, Glut-1 (Dako, polyclonal, 1:200), claudin-1 (Invitrogen, Carlsbad, CA; polyclonal, 1:50) and type IV collagen (Dako; clone CIV22, 1:25) immunostains were performed in four of the cases. One of the cases (Case 5), had previously been

reported as an example of intra-osseous meningioma of the mandible [22]. We were graciously permitted to review representative tissue sections and favor the diagnosis of intra-osseous perineurioma, soft tissue type.

Results

Clinical Findings

The demographic and clinical features of our five cases including another ten from the literature are summarized in Table 1. Briefly, of all 15 cases, 9 occurred in females and 6 in males. Patient age ranged from 14 to 70 years (mean 42.73 years; SD $\pm 0.17.63$). Nine cases affected oral soft tissues [2-gingiva; 2-buccal mucosa; 2-lip; 1-tongue; 1-retrotonsillar; 1-maxillary vestibule (nasolabial fold)] and 6 involved the mandible.

Two tumors in our series affected the soft tissues of the buccal mucosa and were nodules measuring 0.5 and 2.9 cm, respectively. The mandibular tumors were expansile radiolucent lesions (Fig. 1) varying in size from 1.1 to more than 2 cm. One mandibular tumor caused “lip anesthesia” and according to the surgical description was “wrapped around a nerve”. Also, one of our patients, a 14-year-old male, with a mandibular tumor was diagnosed with nevoid basal cell carcinoma (Gorlin) syndrome. All five lesions were surgically excised. There has been no evidence of recurrence over a follow-up period of 2–10 years.

Table 1 Clinical characteristics of reported oral soft tissue perineuriomas

Reference	Age	Gender	Location	Size (cm)	Duration	Follow-up
Kusama et al. [16]	31	Female	Mandible	2.5	Unknown	NED (12 months)
Barrett et al. [17]	53	Male	Mandible	1	N/A	NED (9 months)
Ide et al. [18]	59	Female	Gingiva	1.5	2 months	N/A
Graadt van Roggen et al. [13]	42	Female	Gingiva	4	4 months	N/A
Hornick and Fletcher [11]	15	Female	Tongue	1.2	5 weeks	N/A
Hornick and Fletcher [11]	44	Male	Upper lip	0.6	3 months	NED (18 months)
Hornick and Fletcher [11]	70	Male	Retrotonsillar	2.5	3 months	N/A
Mentzel and Kutzner [19]	60	Female	Lower lip	0.4	“Since childhood”	NED (21 months)
Meer et al. [20]	46	Female	Nasolabial fold	2.0	3 years	N/A
Morton [21]	58	Male	Mandible	N/A	N/A	N/A
Present case #1	55	Female	Buccal mucosa	0.5	7 years	>3 years
Present case #2	22	Male	Buccal mucosa	2.9	N/A	>2 years
Present case #3*	14	Male	Anterior mandible	2.0	N/A	>2 years
Present case #4	24	Female	Posterior mandible	1.1	Unknown	>10 years
Present case #5 [22]	48	Female	Posterior mandible	>2	>1 year	2 years then LF

* Patient with Gorlin syndrome

N/A, not available; NED, no evidence of disease; LF, lost to follow up

Fig. 1 Radiolucent expansile lesion of the mandible causing divergence of roots. This lesion occurred in a 14-year-old male patient with nevoid basal cell carcinoma (Gorlin) syndrome (Case 3)

Histopathologic Findings

All tumors were well circumscribed with the two tumors from the buccal mucosa featuring focally a partial thin collagenous rim suggestive of a capsule (Fig. 2a). All tumors consisted of spindle cells that were generally arrayed in fascicles (Fig. 2b) or in whorls (Fig. 2c). Frequently, small sclerotic, round to ovoid collagen deposits were seen in the center of whorls. Less often, a vaguely storiform pattern was encountered (Fig. 2d). Alternating cellular and hypocellular areas were present.

Cytologically, the spindle cells revealed either well defined eosinophilic cytoplasm and bipolar processes (Fig. 2e) or indistinct cytoplasmic borders, especially in tumors with a dense collagen stroma (Fig. 2f). Nuclei varied from ovoid to elongate, to triangular, compressed or wavy. Nuclear pseudoinclusions were rare. Atypia, including mitotic activity was not encountered.

Four of the five tumors exhibited collagenous stroma that varied in density. In one tumor the core of the lesion was characterized by a wavy lamellated arrangement of collagenous bands, probably the result of tissue shrinkage due to fixation. The fifth featured prominent mucoid matrix (Fig. 2g). In that lesion, spindle cells with bipolar cytoplasmic processes showed a complex pattern of intercellular cohesiveness which, at low power, resembled a fibroblast tissue culture. Two of the mandibular tumors, including the one with the mucoid stroma, included a few psammoma-like bodies (Fig. 2h) and one of them, in addition, a zone containing dystrophic calcifications. Increased vascularity and foci of microhemorrhage were present in two tumors, one of which also showed central necrosis. Chronic inflammation was noted in one tumor.

Immunohistochemically, all tumors showed staining for perineurial markers (EMA, Glut-1, claudin-1 and type IV collagen), their pattern and intensity varying (Fig. 3a–d). Immunohistochemistry results are summarized in Table 2.

While EMA staining was uniform and noted in all tumors, the pattern and intensity of staining varied with the three other antibodies. For example, in one of the four cases only focal and faint stippled staining was evident in the Glut-1 preparations. Focal and patchy staining was seen with claudin-1 in two instances. In two cases, type IV collagen staining was only focally evident.

In the periphery of two mandibular lesions, a small nerve bundle, entrapped or perhaps parent nerve, was highlighted on S-100 stain (Fig. 3e). Also according to Landini and Kitano (22) (Case 5) the “mandibular nerve was enveloped in the tumor mass”. In 3 of the 5 tumors, S-100 and NFP disclosed only scant entrapped nerve fibers.

Discussion

Based on the studies by Shanthaveerappa and Bourne [4] it was initially thought that perineurial cells originated from ectoderm since they share cytologic, histologic and histochemical characteristics with pia-arachnoid (leptomeninges). Indeed, Shanthaveerappa and Bourne referred to such cells as “perineurial epithelial cells.” With the advent of immunohistochemistry, preliminary observations by Pinkus and Kurtin [23], as well as the more detailed studies of Theaker et al. [24, 25], showed that both perineurium and arachnoidal cells express EMA, an observation again interpreted as evidence of an ectodermal derivation of perineurial cells. On the other hand, Bunge et al. [3] supported a fibroblastic or myofibroblastic derivation, a theory that is currently favored. These authors devised a culture system wherein they investigated the formation of perineurium-like structures after neurons were recombined with Schwann cells or fibroblasts. Prior to in vitro recombination Schwann cells or fibroblasts were labeled with a retroviral marker the gene product of which, β -galactosidase, is detected in the progeny of infected cells. Labeling was retained only in fibroblasts forming perineurium-like structures. Also, Lassmann and Ammerer [26] noted that during the formation of microfascicles resulting from experimental amputation of rat femoral nerve, perineurial cells assume an ultrastructural phenotype indistinguishable from that of fibroblasts. Nonetheless, the latter authors fell short of endorsing a fibroblastic origin of perineurial cells. However, more recently, it was confirmed that *Desert Hedgehog*, an intercellular signaling molecule secreted by Schwann cells signals fibroblasts surrounding developing nerves to form a cellular sheath that becomes the perineurial barrier [27].

As previously noted, at the immunohistochemical and ultrastructural level, perineurial cells may participate substantially in the formation of peripheral nerve sheath tumors, both neurofibromas [5] and schwannomas [6, 7].

Fig. 2 **a** Well-delineated lesion of the buccal mucosa. The tumor was partially encapsulated by a delicate collagenous zone (Case #1; H&E, original magnification $\times 20$). **b** Proliferation of spindle cells occurred in a fascicular pattern (Case 4; H&E, original magnification $\times 100$) or in whorls **c** (Case #2; H&E, original magnification $\times 100$). Dense collagenous deposits were occasionally present in the center of the whorls. **d** Subtle storiform pattern was less frequently appreciated (Case #2; H&E, original magnification $\times 100$). **e** Spindle cells featuring bipolar cytoplasmic processes were present in areas with loose collagenous or mucoid matrix (Case #3; H&E, original magnification $\times 400$). **f** Spindle cells with indistinct cytoplasm and cytoplasmic borders were present in collagenous areas (Case #5; H&E, original magnification $\times 200$). **g** Case #3 was characterized by a fibroblast tissue culture-like pattern mucoid pattern (H&E, original magnification $\times 40$). **h** Psammoma-like and dystrophic calcifications (Case #4; H&E, original magnification $\times 200$)

On the other hand, perineuriomas are entirely perineurial in cell composition. As previously noted, two main types are recognized, STP and intraneural [9]. The former are far more common and, as in intraneural perineuriomas, occasionally show loss of heterozygosity of chromosome 22 [28, 29].

The fact that we encountered only two oral STP among over 350 ($<0.6\%$) peripheral nerve sheath tumors in the oral pathology files of the University of Minnesota is an indication of their rarity at this anatomical location. Although the low frequency may be the result of prior misclassification of these lesions, that is unlikely since we

Fig. 3 **a** Neoplastic spindle cells highlighted by EMA. Also note psammoma-like bodies (Case #3; ABC-hematoxylin, original magnification $\times 100$). **b** Neoplastic spindle cells highlighted by glut-1 (Case #4; ABC-hematoxylin, original magnification $\times 100$). **c** Stippled and membranous staining observed with claudin-1 (Case #2; ABC-hematoxylin, original magnification $\times 200$). **d** Neoplastic cells stained for type IV collagen (Case #4; ABC-hematoxylin, original magnification $\times 100$). **e** Entrapped or parent nerve was seen in the periphery of two mandibular tumors (Case #3; S-100-ABC, original magnification $\times 100$)

Table 2 Immunohistochemical characteristics of lesions for perineurial markers

	EMA	Glut-1	Claudin 1	Type IV collagen
Case #1	+	N/A	N/A	N/A
Case #2	+	Membranous, stippled	Patchy, membranous	Membranous
Case #3	+	Faint stippled	Membranous	Focal
Case #4	+	Membranous	Faint focal	Membranous
Case #5 [22]	+	Membranous	Focal stippled	Focal membranous

examined, immunohistochemically, all examples with features suggestive of perineurioma and still identified only those two perineuriomas. In the comprehensive series by Hornick and Fletcher [11] 3 of 81 cases ($\sim 3.7\%$) were peri- or intraoral, thus the rarity of intraoral STPs is supported.

Conventional STPs occur over a broad age range and tend to involve mainly subcutaneous tissues. Although

grossly discrete, they lack a clear, discernible capsule. Their histologic patterns vary, including storiform or pin-wheel arrangements, interwoven fascicles and/or loose whorls. Although the majority of tumors are relatively hypocellular, some examples are hypercellular or exhibit mixed or alternating cell densities. A lamellated pattern may also be seen. Cytologic features include variations in cell morphology ranging from spindle to oval or

epithelioid. The same is true of nuclear shape, ranging from elongate and curved to disk-shaped and twisted. Nuclear pseudoinclusions are an infrequent feature. Cytologic atypia, often degenerative in nature, resembles that seen in so-called “ancient schwannoma”. Perineuriomas with more concerning degrees of cytological atypia have also been described, as has infiltrative growth. Such tumors have been designed as “atypical perineuriomas” [11]. Frankly malignant perineuriomas have been described [30] but are extremely rare, and although they are included in the spectrum of malignant peripheral nerve sheath tumors, they tend to be of lower grade and behave in a less aggressive manner. The stroma of STP is usually collagen-rich, although a mucoid stroma or a combination of both may be encountered. A mucoid pattern, essentially similar to one of our cases, is a feature of approximately 20% of conventional STP [11].

So-called reticular [12] and sclerosing [13] histologic variants of perineurioma have also been described. The former are characterized by a lace-like growth pattern of anastomosing cords of spindle cells, and are most likely the result of extensive myxoid change in soft tissue perineuriomas, rather than being a truly tumor entity. Sclerosing perineuriomas occur almost exclusively in the hands of young adults, often males, and present as small, painless nodules characterized by proliferation of epithelioid and spindle cells in a trabecular or whorled pattern within a markedly dense sclerotic stroma. Interestingly, deletion of chromosome 10q is a feature of sclerosing perineuriomas [31], a genetic signature different from the chromosome 22 abnormalities often seen in conventional STP. With respect to perineuriomas, only one oral example of reticular perineurioma, a gingival tumor, has been reported [13]. Lastly, one oral STP exhibiting a plexiform pattern of growth has been documented, a lesion of the lower lip [19].

An interesting feature in the mandibular tumors we report herein is the presence of peripheral nerves, some minute and others substantial, at the periphery of the tumor. This, which was also evident in the tumor of Morton [21], is often not addressed by other authors. Our observation somewhat challenges the notion that STP are simply soft tissue lesions unassociated with nerve [9]. Instead, an intimate relationship of at least some tumors to otherwise intact peripheral nerve is present. This conclusion seems more reasonable than that STP, tumors of morphologically distinctive, specialized perineurial cells, originate from generic soft tissue.

A very uncommon finding in STP is the presence of calcifications, either in the form of calcospherites resembling the psammoma bodies of meningioma [32] or metaplastic ossifications [11, 33]. Indeed, two of our tumors, both mandibular, revealed well formed, albeit only very few, psammoma bodies. The presence of psammoma

bodies at least suggests a histogenetic link between perineurial and arachnoidal cells and to some extent explains similarities of STP to meningioma [33]. Interestingly, one of our mandibular cases occurred in a patient with nevoid basal cell carcinoma (Gorlin) syndrome, a condition associated with increased frequency of meningiomas. Extracranial meningiomas have been described in the jaws [22, 34, 35], but none in patients with nevoid basal cell carcinoma syndrome. Landini and Kitano [22], suggested their tumor “might have been derived from ectopic arachnoidal villi or perineurial cells of the mandibular nerve”, but preferred a diagnosis of meningioma over perineurioma. We had the opportunity to review their case and prefer a diagnosis of perineurioma based on histologic and immunohistochemical characteristics. Jones and Freedman [34] supported the diagnosis of meningioma over perineurioma in their two cases given the absence of “whorls, rosettes, pseudoinclusions, and psammoma bodies” in perineuriomas. Similarly, Lell et al. [35] preferred the diagnosis of meningioma for their tumor, despite its “intimate” association with the mandibular nerve. They based their opinion on the presence of whorls and fascicles of spindle cells, as well as, psammoma-like bodies. These features, however, have been described in perineuriomas [11] and were variably observed in our series.

Perineuriomas and meningiomas share immunohistochemical characteristics although Yamaguchi et al. [36] reported that Glut-1 was positive in perineuriomas and negative in meningiomas. However, according to Smith et al. [37] and our experience (unpublished data) meningiomas often show Glut-1 expression, varying from focal to diffuse. Similarly, claudin-1 expression is seen in most perineuriomas [38] and in more than 50% of meningiomas [39]. Lastly, collagen IV staining, a regular feature of perineurioma but not of meningiomas has appeared to draw a meaningful distinction between the two tumors. In the three intraosseous cases in our series, the pattern of type IV collagen staining varied. Specifically, in two of the three cases it was only focal. However, we feel that even such distribution supports the diagnosis of perineurioma. Certainly, the likelihood of the derivations of jaw perineuriomas from perineurium of a nearby nerve is greater than from embryonic arachnoidal cell rests. In view of these observations, and although the difference of perineurioma from meningioma may be after all semantic [11], we believe the diagnosis of perineurioma is more reasonable than meningioma in lesions of the jaws.

Two further lesions to be included in the differential diagnosis of oral STP are neurofibroma and solitary fibrous tumor. The former is most readily distinguished by preponderance of S-100 protein, even in so-called “hybrid neurofibroma-perineurioma.” SFT are not expected to stain for perineurial markers. The use of CD34 as a marker of

solitary fibrous tumor has its limitations, since positivity has been documented in 64% of STP [11]. For those tumors occurring in the mandible, the differential diagnosis also includes the epithelial poor variant of odontogenic fibroma or other fibroblastic [S-100(–), CD34(–), EMA(–), glut-1(–), claudin-1(–), collagen IV(–)] or myofibroblastic [SMA(+); EMA(–), glut-1(–), claudin-1(–), collagen IV(–)] tumors.

In summary, we have reported a small series of intraoral SFP and reviewed the relevant literature. Most histologic patterns described in the literature have been encountered among oral STP. General and oral pathologists should be aware of STP as an oral lesion and the utility of a standard immunobattery approach to differential diagnosis.

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