Palisaded Encapsulated (“Solitary Circumscribed”) Neuroma of the Oral Cavity: A Review of 55 Cases

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Abstract We describe the clinicopathologic characteristics of 55 oral palisaded encapsulated (solitary circumscribed) neuromas (PEN/SCN). Fifty-five cases of PEN/SCN in 54 patients were reviewed. Lesions were categorized according to their histologic pattern, partial or complete encapsulation, presence of Verocay bodies and presence of a parent peripheral nerve. In 13 selected cases immunohistochemical evaluation for neuronal markers (S-100, GFAP, NFP, EMA) was performed. When immunoreaction with EMA was weak, claudin-1 and glut-1 stains were utilized. Thirty-eight patients were men and 16 were women. Mean patient age was 48 years (SD: ± 14). The vast majority involved the masticatory (palate and gingiva) mucosa (76.4%) followed by the labial mucosa, the tongue and buccal mucosa. Recurrence was recorded in only one case. Histologically, 34 lesions had a lobular pattern, 10 were plexiform, 7 fungating and 4 multilobular. Stroma was limited, but focal myxoid changes were seen at the periphery of the lobules. Only one predominantly myxoid lesion was encountered. The number of intralesional axons varied, but the ratio of Schwann cells to axons was generally less than 1:2. Most lesions (89%) were only partially surrounded by perineurium. Tumor cells were S-100 positive and GFAP negative. The parent nerve was identified in 50% of the

cases. Overlying epithelium was generally atrophic. Peritumoral connective tissue was generally unremarkable, but chronic inflammation was present in five cases. PEN/SCN is a relatively common peripheral nerve sheath tumor. Generally, its diagnosis is simple. GFAP may be of help to distinguish PEN/SCN from other peripheral nerve sheath tumors (schwannoma, neurofibroma, traumatic neuroma) in cases where histomorphologic features may be confusing. Finally, pathologists should be aware of the occurrence of plexiform and multilobular PEN/SCN variants, to avoid misinterpretation as plexiform neurofibroma or schwannoma.

Keywords Palisaded · Encapsulated · Solitary · Circumscribed · Neuroma · Oral · Mouth

Introduction

Since the original 1972 report of Reed et al. [1] of palisaded encapsulated neuroma (PEN), several series have detailed its clinicopathologic and immunohistochemical features [2–8]. That of Fletcher [2] noted that most lesions are not fully encapsulated and show only focally palisading at best. He proposed the alternate designation solitary circumscribed neuroma (SCN). Irrespective of terminology, PEN/SCN are regarded as reactive, hyperplastic processes akin to traumatic (amputation) neuroma. Infrequency of an antecedent traumatic event and the general absence of histologic changes suggestive of trauma [9] weaken this notion [10].

Although the majority of PEN/SCNs occur in skin, mucosal sites such as the glans penis [11, 12], nasal fossa [13] and mouth [14, 15] are also affected, oral lesions being the second most frequent. Clinically, the superficially

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situated nodules are small and most often painless. Histologically, they consist of a proliferation of aligned, infrequently palisaded Schwann cells accompanied by a variable number of axons and they are most frequently partially enveloped by a delicate layer of perineurium. Thus, PEN/SCN are “true neuromas.” Fungating, plexiform and multinodular forms [16] have been described in detail, as have epithelioid [17], vascular [18] and myxoid [19] examples. Multifocal lesions are rare. Butterworth and Coyne reported a 56-year-old female patient with two cutaneous lesions affecting the skin of the cheek and forehead, respectively [20]. All reported PEN/SCN have been surgically excised, thus only a single recurrence is documented [5].

Herein, we present the clinicopathologic features of a large series of oral PEN/SCNs archived in the Division of Oral and Maxillofacial Pathology of the University of Minnesota over a period of 63 years (1945–2008). The lesions included ones arising in the vermilion border of the lips. Cutaneous or facial tumors were excluded.

Methods and Materials

Fifty-five oral PEN/SCN affecting 54 patients were identified among over 350 cases of peripheral nerve sheath tumors, excluding granular cell tumors, affecting the mouth. Thus, PEN/SCN ranked third in frequency among oral nerve sheath lesions after neurofibromas and traumatic neuromas, the latter including associations with other reactive lesions. One PEN/SCN patient experienced a recurrence. Hematoxylin and eosin (H & E) stained preparations were available in all instances. In thirteen selected cases, immunohistochemical investigation (streptavidin–biotin peroxidase complex method) was performed. Applied antisera were directed against S-100 protein (Dako, Carpinteria, CA; 1:1,600, polyclonal), neurofilament protein (NFP) (Dako, 1:800, 2F11), GFAP (Dako, 1:4,000, polyclonal) epithelial membrane antigen (EMA) (Dako, 1:50, E29) and, in four cases where EMA was weak, both glut-1 (Dako, 1:200, polyclonal) and claudin-1 (Invitrogen, Carlsbad, CA; 1:50, polyclonal). Selection criteria included lesions with typical and unusual architectural patterns. Histologic features systematically sought included: (a) pattern of proliferation (lobular, fungating, multilobular, and plexiform taking into consideration the classification of Argenyi et al. [16]), (b) partial or complete encapsulation, (c) presence of Schwann cell regimentation or Verocay body formation, (d) presence of a parent peripheral nerve (defined as a small fascicle at the base of the lesion, often in continuity with the perineurium and featuring early histopathologic changes of PEN/SCN and (e) PEN/SCN with the unusual characteristics. GFAP

immunostain was performed to verify previous studies that have reported negative staining for this marker.

Results

All pathology reports were available. The original diagnosis in the report in 26 out of 55 cases was some other type of peripheral nerve sheath tumor. Specifically, 13 cases were diagnosed as neurofibromas, 10 as schwannomas including one of plexiform type, and three as traumatic neuromas. The single recurrent case was originally diagnosed as schwannoma but the recurrent lesion correctly as PEN/SCN.

Clinical Features

Of the 54 patients, 38 (70.3%) were men and 16 (29.7%) were women. Patient age ranged from 20 to 73 years (mean and median: 48; SD: ± 14). Tumor locations were as follows: palate-31, maxillary or palatal gingiva-8 (including one example on an edentulous maxillary alveolar ridge), tongue-4, mandibular gingiva-3, upper lip vermilion border-3, mucosal part of the lower lip-3, lower lip vermilion border-2, and buccal mucosa-1. Viewed somewhat differently, the masticatory mucosa (palate and gingiva) was affected in 42 cases (76.4%) followed by 8 labial lesions. Lesion duration was recorded in 19 cases; of these, 13 had been present between 1–20 years and 6 between 1–6 months. In 4 cases, the lesion duration was recorded as unknown. Symptoms were commented upon in 11 instances (20%), 7 patients being asymptomatic and 4 reporting pain upon “drinking hot beverages” or “after irritation”. Only 3 patients were aware of prior trauma to the area, one stating that the lesion resulted from orthodontic treatment. Clinically, all PEN/SCN presented as small, rarely ulcerated nodules the size of which never exceeded 1.0 cm in greatest dimension. All were gross totally excised. As previously mentioned, only 1 example, a lesion of the palatal gingiva, recurred after an interval of 8 years (Fig. 1). Interestingly, the initial tumor histologically appeared to have been completely excised.

Macroscopic Features

Grossly, all tumors were nodular in appearance. It is of note that one was a component of a fibromatous hyperplastic palatal lesion; it was a feature of the overall process and was entirely contained within the field of a 20 $\times$ objective.

Microscopic Features

At low power magnification, 34 cases presented a classic lobular pattern of growth, 10 were plexiform, 7 fungating

Fig. 1 Recurred lesion on the palatal gingiva between the second premolar and molar eight years after excision

and 4 multilobular in architecture (Fig. 2a–d). Of the lobular lesions, 2 had a dumbbell configuration apparently unassociated with surgical compression. Of note was the fact that the multilobular pattern was artifactual in some cases and the result of tissue sectioning. Similarly, the plexiform pattern appeared to be the result of tortuosity of the tumor (Fig. 3).

All tumors were composed of proliferating Schwann cells forming fascicles or microfascicles that often coursed in various directions (Fig. 4a). Fascicles were occasionally separated by very limited myxoid tissue. Also noted was artificial cleaving within lesions, the result of tissue shrinkage (Fig. 4b). Individual Schwann cells exhibited elongated, oftentimes sinuous to ovoid nuclei with occasional

nuclear holes (“Lochkerne”). Round nuclear shape was seen mainly in cross-sectioned fascicles. No epithelioid cells were encountered. Focal and subtle nuclear pleomorphism or hyperchromasia were infrequent features. No mitoses were identified. Although the majority of tumor cells was confirmed as being Schwannian in nature (Fig. 4c), there were occasional S-100 negative spindled endoneurial cells, presumably fibroblasts. In all examples studied, tumor cells were GFAP negative (Fig. 4d).

In 31 (56.4%) cases, subtle and generally focal regimentation of Schwann cells was seen (Fig. 5a). A pattern indistinguishable from Verocay bodies was encountered in another 11 cases (Fig. 5b). This finding was generally focal, however, 4 cases exhibited this finding very prominently and in several areas and were reminiscent of schwannoma. Initially, such lesions were thought to be schwannomas but, after noting a microfascicular growth pattern, multiple axons, a delicate, often discontinuous distribution of EMA immunoreactivity at the periphery, and GFAP negative immunostaining, the diagnosis of PEN/SCN was favored.

Delicate axons were identified with great difficulty on hematoxylin and eosin stain, but were clearly evident in all lesions studied by NFP immunostain (Fig. 6). Their number and distribution varied within the tumors. As a rule, the axon to Schwann cell ratio was less than 1:2.

Collagenized connective tissue stroma was generally limited in extent. Seven lesions (12.5%) showed focal, mainly peripheral myxoid change. Only one tumor was predominantly myxoid (Fig. 7a), a lobular lesion featuring a central schwannian, fascicular pattern (Fig. 7b) accompanied by

Fig. 2 **a** Lobular PEN/SCN. Myxoid changes at the lateral aspect of the tumor (H & E, original magnification $\times 20$); **b** Plexiform PEN/SCN. Nerve fascicles arranged in close juxtaposition and presenting in oblique, cross and longitudinal planes. (H & E, original magnification $\times 12$); **c** Fungating PEN/SCN. Note atrophy of the surface epithelium. (H & E, original magnification $\times 20$); **d** Multilobular PEN/SCN. (H & E, original magnification $\times 20$)

Fig. 3 Pseudoplexiform pattern. Irregular but continuous proliferation on the *left* presents as a plexiform pattern in the *right*. (H & E, original magnification $\times 7$)

stromal mucin. As is the rule, it also exhibited discontinuous, delicate perineurial investment (Fig. 7c). Scattered axons were numerous in the fascicular zone (Fig. 7d). Occasional non-dilated capillaries were encountered in nearly all tumors and small numbers of mast cells were evident in some.

Forty-nine tumors (87.2%) were smooth contoured or circumscribed, but unencapsulated. Lack of circumscription was more evident in the superficial aspects of the

lesions underlying surface epithelium. At that site, minute fascicles were seen to blend imperceptibly with connective tissue (Fig. 8). In most tumors, a scant, barely discernible or discontinuous perineurial layer was present on the lateral and basal aspects of the lesion and labeled for EMA, glut-1 and/or claudin-1 (Fig. 9a). Only 6 lesions (10.7%) were entirely surrounded by an intact perineurium consisting of one to several cell layers (Fig. 9b). Among cases evaluated for immunohistochemical markers of perineurium (EMA, glut-1, claudin-1), there were 4 cases wherein minute, crosscut nerve fascicles, perhaps representing more than a single parent fascicle, were noted in the inferior pole of the lesion. In addition, occasional parallel lines of EMA-positive cells were noted in the substance of the lesions. In summary, in 27 cases (49.1%) a parent nerve was clearly present, typically at or just lateral to their base (Fig. 10).

We also evaluated changes in overlying surface epithelium and in peritumoral connective tissue. In 43 cases (78.2%) the epithelium appeared atrophic, while in 5 instances mild basal cell hyperplasia was noted. Three lesions were ulcerated and one exhibited focal pseudoepitheliomatous hyperplasia with brisk mitotic activity. In 5 additional cases, mitoses were present but limited to the basal cell layer. In only 1 case, a Caucasian patient, were increased numbers of melanocytes noted in overlying epithelium. Peritumoral connective tissue was generally unremarkable; but in 6 cases (10.7%), vascularity was increased. These lesions lacked both ulceration and inflammation. In 5 instances, peritumoral inflammation was noted: it was chronic in 4 and consisted of a prominent

Fig. 4 **a** Streaming fascicles of proliferating Schwann cells (H & E, original magnification $\times 100$); **b** Exaggerated clefting, apparently the result of tissue shrinkage (H & E, original magnification $\times 100$); **c** S-100 disclosed the Schwann cell proliferation (ABC-hematoxylin, original magnification $\times 200$); **d** Negative immunoreaction for GFAP (ABC-hematoxylin, original magnification $\times 63$)

Fig. 5 **a** Regimentation of Schwann cells (H & E, original magnification $\times 200$); **b** Small Verocay bodies among Schwann cells exhibiting regimentation. (H & E, original magnification $\times 100$)

Fig. 6 Delicate axons appearing as dot or fine fibrils, depending on the plane of fascicular proliferation, were disclosed with NFP (ABC-hematoxylin, original magnification $\times 200$)

eosinophilic infiltrate in one. Lastly, 2 lesions of the lower lip vermilion border exhibited actinic damage.

Discussion

Historic Background and Clinical Characteristics of Oral PEN/SCN

The first purported example in the oral pathology literature was that of Tomich and Moll [21] who in 1976 described a lesion of the vermilion border of the lower lip. Based on their histologic description and the figures provided, the lesion featured prominent myxoid and cellular components, as well as organoid structures reminiscent of Meissnerian corpuscles. No mention of axons was made. The lesion may have represented the uncommon myxoid variant of PCN/SCN or, alternatively, a neurofibroma or schwannoma. The first convincing intraoral PCN/SCN arising on the tongue was included in the series by Fletcher [2]. Many

years passed before the first series of oral examples was reported by Chauvin et al. [14]. Prior to general and oral pathologists becoming familiar with PEN/SCN, examples were variously reported as schwannomas, neurofibromas or lesions intermediate between the two. Indeed, in the 1963 report of McMillan [22], the purported “partially encapsulated neurilemmoma” (case 2) would now be considered a PEN/SCN. A subsequent 1980 review paper by Wright and Jackson [23] on neural tumors of the oral cavity and the jaws made reference to PEN, considering them rare lesions. Jordan and Regezi [24], in their 2003 review of oral spindle cell tumors, revised 15 original diagnoses of schwannoma and neurofibroma to PEN/SCN. In our files, the diagnosis of PEN/SCN became consistent only in the year 2000. Until then all cases of PEN/SCN were diagnosed as some other form of peripheral nerve sheath tumor, i.e. neurofibroma, schwannoma or traumatic neuroma. Nonetheless, we occasionally encounter difficulties in distinguishing PEN/SCN from other benign peripheral nerve tumors. For example, in our present review, 10 original diagnoses of PEN/SCN were revised to neurofibroma ($n = 4$), traumatic neuroma ($n = 3$), probable schwannoma ($n = 1$), solitary ganglioneuroma ($n = 1$), and a case of “unusual Schwann cell proliferation” lacking axons or a perineurial cell component.

The series by Chauvin et al. [14] was followed by the studies of Magnusson [15], Chrysomali et al. [25], the latter being part of a review of oral peripheral nerve sheath tumors, and that of Lombardi et al. [26]. The clinical data of those series as well as ours are summarized in Table 1.

Histopathologic Characteristics of PEN/SCN

PEN/SCN are most often unilobular and exhibit smooth contours. Argenyi et al. [16] introduced the plexiform, multilobular and fungating forms, plexiform examples being relatively common. These morphologic variations are neither clinically nor biologically relevant, but familiarity with them minimizes their confusion with other peripheral nerve sheath tumors, especially plexiform

Fig. 7 **a** Myxoid PEN/SCN (H & E, original magnification $\times 2$); **b** Streaming fascicles intermixed with prominent myxoid material (H & E, original magnification $\times 5$); **c** Delicate but interrupted perineurium surrounded this tumor and was disclosed by glut-1 (ABC-hematoxylin, original magnification $\times 4$); **d** Axons were disclosed by NFP and were present in the Schwannian fascicular areas. There were no axons identified in the myxoid areas. (ABC-hematoxylin, original magnification $\times 200$)

Fig. 8 Minute fascicles blending with the connective tissue subjacent to the epithelium. (H & E, original magnification $\times 200$)

schwannoma and neurofibroma. In many cases, plexiform lesions are difficult to distinguish from ones multilobular. Argenyi et al. [16] defined plexiform tumors by “the repetitive appearance of cross, oblique, and longitudinal sections of markedly expanded, sometimes nodular nerve fascicles arranged in close juxtaposition” and multinodular lesions as “arrangements in a perpendicular fashion.” In our series the definition of multilobular was more liberal i.e. the identification of distinct lobules, regardless of whether their arrangement was perpendicular or not. In

actuality these perceived patterns are highly dependent on vagaries of tissue processing. Indeed, step sectioning confirms the continuity of what appear to be individual nodules [2, 4, 16]. This was certainly the case in several of our tumors. The plexiform pattern was second most frequent in our series, a finding in keeping with those of Chrysomali et al. [25] who encountered 5 such lesions among their 16 cases. Lombardi et al. [26] also encountered the pattern once. Chauvin et al. [14] undertook no pattern subtyping. Less common than uninodular or plexiform lesions are ones fungating. With respect to the “dumbbell” pattern of PEN/SCN, it is our opinion that it is not the result of artifactual surgical compression.

Cytologically, PEN/SCN are cellular proliferations of Schwann cells that form microfascicles best appreciated on cross-sections and occasionally separated by artifactual clefts. Alternatively, occasional lesions exhibit a myxoid matrix between fascicles. Schwann cells generally have a sinuous configuration with tapering of nuclei and occasionally “Lochkerns” (nuclear holes). Only rarely and focally are the cells epithelioid in appearance. Although mild nuclear pleomorphism may be seen [3], significant atypia and mitotic activity are generally lacking. Nuclear regimentation, although focal and subtle, is common [1–9, 11, 13, 15, 16, 21, 25, 26], whereas regimentation indistinguishable from Verocay bodies is infrequently seen [5, 16, 25]. In our series from the 11 examples where Verocay-type regimentation was seen, 4 exhibited this finding very prominently and were reminiscent of schwannoma. In

Fig. 9 **a** Discontinuous perineurial envelope highlighted by EMA (ABC-hematoxylin, original magnification $\times 100$); **b** Intact perineurium, a few layers in thickness, was seen in the minority of lesions (EMA, ABC-hematoxylin, original magnification $\times 50$)

Fig. 10 Parent nerve of the lesion (H & E, original magnification $\times 100$)

these cases, the presence of numerous axons, fascicular growth with clefting, incomplete encapsulation and negative GFAP staining supported the diagnosis of PEN/SCN.

Schwann cells in PEN/SCN are strongly immunoreactive for S-100 protein and collagen IV. Interestingly, they have been consistently negative for GFAP [4, 27] as confirmed also by our study; only 1 case in the series by Lombardi et al. [26] showed weak staining. In contrast, schwannomas and neurofibromas show frequent, albeit inconsistent staining for this marker [28]. Thus, negative

GFAP staining may be considered as a helpful distinctive feature between PEN/SCN and schwannoma or neurofibroma.

Aside from Schwann cells, scattered CD34-positive cells of endoneurial origin may also be encountered [25]. Kutzner et al. [7] identified factor XIIIa positive cells, but the observation has not been confirmed by others [9]. Although perineurial cells are not found within the lesions, they rarely do form an EMA-immunoreactive sheath around tumor fascicles within the inferior aspect of the lesion nearby the nerve entry zone. This observation was previously made [4] and was evident in our series.

In keeping with their status as “true neuromas,” PEN/SCN contain axons, the number of which varies, even within individual Schwann cell bundles of the same lesion. Although often numerous, occasional cell bundles contain few or no axons [3, 4, 12, 27]. The suggestion has been made by Kossard et al. [29] that a spectrum of PEN/SCN includes lesions containing numerous axons to ones histologically identical but lacking significant numbers. The authors considered the latter lesions to represent Verocay body-poor schwannomas rather than true neuromas. Semiquantitatively, the ratio of axons to Schwann cells is generally estimated at less than 1:1 and can be as low as 1:10 [27]. Variation in axonal density is observed when using different methods such as immunohistochemistry (NFP, neuron specific enolase) and histochemistry (modified Bielschowsky stain), the latter reportedly being superior [27].

Table 1 Published clinical data on PEN/SCN

Studies	No. of patients	Male	Female	Mean/median age	Location
Chauvin et al. [14]	13	10	3	51/55	10 palate, 2 lip, 1 alveolus
Magnusson [15]	12	5	7	54/58	5 palate, 4 lip, 2 tongue, 1 not stated
Chrysomali et al. [25]	16 ^a	9	6	37.3 ^b	11 palate, 2 tongue, 1 buccal mucosa, 1 lip, 1 gingiva
Lombardi et al. [26]	5	2	3	46/48	3 palate, 1 lip, 1 gingiva
Present study	54	38	16	48/48	31 palate, 11 gingiva, 8 lip, 4 tongue, 1 buccal mucosa

^a Gender unknown in one case

^b Median not provided

The stroma of PEN/SCN is minimal and eosinophilic in appearance [2, 3]. Although Fletcher [2] and Dakin et al. [5] did not encounter myxoid areas, others confirmed their presence, mainly nearby the perineurial capsule [9, 13, 16]. We observed the same in a minority (12.5%) of lesions. It is of note that one group [19] reported an unusual lesion exhibiting features intermediate between PEN/SCN and nerve sheath myxoma, favoring a diagnosis of “myxoid PEN/SCN.” In retrospect, their lesion may represent the recently described “microcystic/reticular variant” of schwannoma [30]. In contrast, our one predominantly myxoid PEN/SCN, lacked a microcystic/reticular pattern, featured fascicular schwannian proliferation, contained scattered axons, and was partially circumscribed by perineurium.

The stroma contains few capillaries. The literature does, however, include a vascular variant [18] of PEN/SCN which features cavernous vessels with occasional thrombosis and perivascular hyalinization such as is seen in so called “ancient schwannoma.” The diagnosis of PEN/SCN was confirmed with identification of axons by both histochemistry and immunohistochemistry. However, schwannomas can contain axons [31], their presence being not as widely distributed as in PEN/SCN.

As a rule, PEN/SCNs are partly surrounded by perineurium. Some tumors appear to be completely ensheathed, particularly deep-seated examples readily separable from surrounding connective tissue [2, 5]. The perineurial envelope is clearly labeled on EMA, claudin-1 or glut-1 immunostains. It is worth mentioning that the EMA reaction is often comparatively weak or lacking entirely with the high antibody dilutions commonly in use. In our experience and in the limited number of cases where both claudin-1 and glut-1 immunostains were performed, glut-1 exhibited

superior results. On occasion, the perineurium surrounding PEN/SCNs is seen to be in continuity with that of the entering nerve, thus confirming the intraneural nature of the lesion. An entering nerve with early PEN/SCNs change is not always present. Indeed, Dover et al. [3] never found continuity of the capsule with peripheral nerve twigs. In contrast, other observers have confirmed continuity [1, 2, 4–6]. Serial sectioning aids in its demonstration. We found a connection in approximately half of our tumors and noted schwannian hyperplasia as well as early microfascicle formation and tortuosity within these near lesional nerves.

Accompaniments of PEN/SCNs include overlying mucosal hyperkeratosis and acanthosis [1, 2, 5], basal cell hyperplasia, pseudoepitheliomatous hyperplasia [2, 6] that may be striking [32], as well as increased number of melanocytes [1]. These findings were infrequent in our series, wherein the majority of lesions revealed epithelial atrophy, presumably due to tumor pressure. Ulceration of surface epithelium is infrequent in oral examples. Surrounding connective tissue is generally unremarkable. Chronic inflammation, increased vascularity and rarely fibrosis may be seen. It is cutaneous lesions that often show traumatic ulceration and, of course, accompanying solar elastosis. In Table 2 we have summarized the histopathologic characteristics of PEN/SCN as seen in our series.

Pathogenesis

The pathogenesis of PEN/SCN remains a matter of debate. Reed et al. (1) considered them a forme fruste of the MEN2B syndrome, since PEN/SCN resemble one of the two histologic forms of hyperplastic mucosal neuroma encountered in this disorder. However, as Fletcher points

Table 2 PEN/SCN: histopathologic and immunohistochemical characteristics

Pattern of growth (in descending order of frequency)	Lobular, plexiform ^a , fungating, multilobular ^a
Schwann cell arrangement	1. Fascicular and microfascicular coursing in various directions; blending of microfascicles with the connective tissue immediately subjacent to the epithelium 2. Regimentation varying from focal and subtle to Verocay-body type; the latter can be prominent in the minority of cases.
Schwann cell immunohistochemical properties	S100 (+) and GFAP (–)
Axons (disclosed by NFP)	Axons to Schwann cell ratio: <1:2
Perineurium (disclosed by EMA, glut-1, claudin-1)	Discontinuous in the majority of cases. Present in the base and lateral aspects of the tumor
Tumor stroma	Limited; generally densely collagenized with only focal myxoid areas; myxoid areas may be seen in the periphery; single example of predominantly myxoid stroma; mast cells may be present
Overlying epithelium	Generally atrophic; rare pseudoepitheliomatous hyperplasia
Peritumoral connective tissue	Generally unremarkable; increased vascularity and, rarely, inflammation may be seen

^a Can be result of tissue sectioning

out (2), the mucosal lesion of MEN2B is simply a hyperplasia of otherwise normal nerves not exhibiting the cardinal features of PEN/SCN.

Interestingly, the literature makes reference to patients with “multiple cutaneous neuromas”, two with oculomucosal neuromas but without other signs of MEN2B [33–35]. If one examines the illustrated histology of these lesions (Figs. 5, 6, 7, 8 in Schnitzler et al. [33], Figs. 2, 3, 4 by Holm et al. [34], and Figs. 4 and 5 by Altmeyer et al. [35]), they are seen to be indistinguishable from PEN/SCN. Altmeyer et al. [35] specifically stated that their patient did not have MEN2B. Thus, it may be that PEN/SCN represents a *forme fruste* of a neurocutaneous disorder, albeit different from MEN2B. Interestingly, there is but a single case report [20] of two simultaneously occurring PEN/SCN. Obviously, the possible likelihood of their concurrence being a chance event is high in that, as pointed out by Theaker [36], PEN/SCN is a relatively common lesion.

The cellular makeup and architecture of PEN/SCN are those of a “true neuroma”, akin to traumatic neuroma. Indeed, most authors discussing PEN/SCN suggest a traumatic etiology [2, 11, 12, 16]. Based on ultrastructural studies, Dover et al. [3] also supported the notion of a regenerative process after minor trauma or local inflammation. Also, a traumatic etiology finds some support in the fact that partially removed PEN/SCNs do not recur [37] an outcome expected if, as suggested by Whimster, remaining lesional tissue lacks viable axons [38]. However, in the vast majority of cases there is no history of trauma. Furthermore, in cutaneous PEN/SCN no scarring or foreign body reaction has been noted and acute/chronic inflammation are infrequent findings [2, 5, 16]. In our series, only 3 of 54 patients related a history of trauma prior to the development of their lesions, while another had undergone orthodontic therapy at the time the lesion became evident. Interestingly, lesions of the buccal mucosa are very rare, it being the most common site of traumatic fibromatous hyperplastic lesions (“traumatic fibromas”). Conversely, the tongue, a common site of oral trauma, is infrequently affected. One must note, though, that the tongue and lips as well as the palatal and gingival areas contain more superficially situated nerve branches compared to the buccal mucosa.

Occasionally, PEN/SCNs do include areas that can be encountered in traumatic neuroma. For example, there is occasional fibrosis among Schwann cell bundles and focal myxoid changes within them [16]. Furthermore, occasional bundles, particularly in superficial portions of the lesion resemble the proliferating microfascicles of traumatic neuroma. In any event, as stated by Argenyi et al. [9], substantial histomorphologic differences exist between PEN/SCN and traumatic neuroma. These include the presence of perineurial cells surrounding individual microfascicles in traumatic neuroma, the greater abundance

of interstitial collagen, mucoid matrix and myelin components within them, and, lastly, the more orderly, parallel arrangement of axons in their microfascicles.

Unlike traumatic neuroma in which myelination is prominent [9], PEN/SCN features only focal and poorly preserved myelin [3, 9]. Furthering the comparison with traumatic neuroma, one might expect upregulation of GFAP in PEN/SCN, as GFAP is upregulated in myelin forming and non-myelin forming Schwann cells in the proximal stump of transected nerves [39]. As previously noted, this is not the case in PEN/SCN. The absence of GFAP staining in PEN/SCN is intriguing and may highlight an altered Schwann cell phenotype. Also, it has been found that loss of GFAP can impair Schwann cell proliferation and delays nerve regeneration after damage [40]. Thus, PEN/SCN, appears to be a GFAP-deficient non-myelin producing intraneural Schwann cell proliferation. Traumatic etiology appears less likely. The focal myelinated axons may represent retained, possibly degenerating ones of the parent nerve.

Differential Diagnosis

The differential diagnosis of oral PEN/SCN includes a variety of benign neurogenic tumors, including schwannoma and neurofibroma, particularly their plexiform variants, and traumatic neuroma. In addition, the dermatopathologic differential diagnosis includes leiomyoma or angioleiomyoma, the distinction being made with immunostains for myoid markers. The common unilobular PEN/SCN is distinguished from conventional schwannomas and neurofibromas, generally without difficulty. Table 3 provides a summary of criteria that may assist the differential diagnosis of PEN/SCN from other peripheral nerve sheath tumors.

It is the plexiform variant of PEN/SCN that prompts confusion and should be distinguished from plexiform schwannoma and plexiform neurofibroma. Plexiform (multinodular) schwannoma is a distinct variant of schwannoma. Representing approximately 4% of all schwannomas, approximately one-quarter arise in the head and neck region [41] and 5% each in the setting of neurofibromatosis type II and schwannomatosis. Histologically, they feature Antoni A and B patterns, Verocay bodies, ectatic and hyalinized vessels, and they are completely surrounded by a perineurial capsule. Occasionally, examples are cellular. Collectively, these features distinguish plexiform schwannoma from PEN/SCN. The presence or absence of axons is again a weak criterion because, according to Nascimento and Fletcher [31], sporadic schwannomas including the plexiform type can contain axons in varying number and distribution. Negative GFAP immunostaining may support the diagnosis of PEN/SCN.

Table 3 Differential diagnosis

	PEN/SCN	Conventional Schwannoma	Conventional Neurofibroma	Intraneural neurofibroma	Traumatic neuroma
Perineurial encapsulation	Mostly partial	Complete	No	Complete	No
Pattern of Schwann cell proliferation	Cellular microfascicles coursing in various directions; superficial fascicles blend with connective tissue	Cellular fascicular Antoni A and less cellular cobweb-like Antoni B areas	Hypocellular sheets	Hypocellular sheets	Microfascicular compartmentalized and haphazard
Schwann cell immunohistochemistry	S100 (+), GFAP (–)	S100 (+), GFAP (+) in ~50% of areas	S100 (+), GFAP varies but usually (+)	As in conventional	S100 (+), GFAP (+)
Verocay bodies	Uncommon and mostly focal	Present in Antoni A areas	Absent	Absent	Absent
Axons	Usually multiple but number can vary; haphazard arrangement	Mostly in the periphery; less frequently in the core	Residual	Residual	Regenerated, parallel to proliferating Schwann cells
Stroma	Limited collagenous with occasional myxoid areas in the periphery Few scattered mast cells	Collagenous in Antoni A, myxoid in Antoni B Prominent vessels Mast cells in Antoni B areas	Usually mucoid with delicate collagen Mast cells in significant numbers	Shreds of collagen bundles resembling “shredded carrots” Mast cells in significant numbers	Mucoid to fibrocollagenous matrix depending on the “age” of the lesion

Plexiform neurofibromas occur with high frequency in the setting of neurofibromatosis type 1. In branching nerves, they present as tangled expanded fascicles which in early phase are hypocellular and mucin-rich, their spindle cells being scattered and possessing often curved nuclei smaller than those of schwannoma. Axon bundles are often seen to be centrally placed. Meissnerian corpuscles are occasionally seen, particularly between affected fascicles. Mast cells are also relatively frequent. Over time, the lesions become more cellular and collagenous. The appearance of plexiform neurofibroma is readily distinguished from that of plexiform PEN/SCN. Associated clinical features of often associated neurofibromatosis type 1 further facilitate the differential diagnosis. There is no association of PEN/SCN with neurofibromatosis. Sporadic examples of small plexiform neurofibromas are rarely encountered.

Rare lesions also enter into the differential diagnosis. As previously noted, one ganglioneuroma we encountered had initially been considered a PEN/SCN. It presented as a small nodule on the palate of an 18-year-old male of unknown status with respect to neurofibromatosis. Although ganglion cells were not appreciated in the initial preparation, deeper sections and immunohistochemical staining subsequently disclosed ganglion cells in small number (Fig. 11). Fasciculation of proliferating Schwann cells was inapparent and the loose-textured, collagenous stroma contained scattered capillaries. Immunohistochemically, the lesion shared features with PEN/SCN. A fragmented partial perineurial capsule was present as were scattered axons. Lastly, an unusual solitary, unencapsulated, polypoid Schwann cell proliferation different from subgemmal neurogenous plaques was encountered among our PEN/SCN. It occurred on the anterior dorsal surface of the tongue and featured small fascicles or tufts of aggregated Schwann cells (Fig. 12) separated by slender bands of collagen. The nuclei were generally ovoid. Immunostains for NFP confirmed the presence of scant axons in a few tufts, but EMA, glut-1 and claudin-1 preparations showed no perineurium. The lesion conforms most closely to what Gibson and Hornick recently described as “mucosal Schwann cell hamartoma” of the colon [42].

Treatment

The treatment of choice of PEN/SCN is gross total resection. Only Dakin et al. [5] reported an example of what they considered a recurring PEN/SCN; the authors did not elaborate upon its histopathologic characteristics [10]. A possible recurrent case of PEN/SCN also appears in the article by Lombardi et al. [26] who stated that one of the lesions was submitted for histopathologic evaluation with a clinical diagnosis of recurrent neurofibroma. In our series, we encountered but a single example of recurrent PEN/

Fig. 11 **a** Ganglioneuroma of the oral mucosa. Absence of fascicular proliferation. Few scattered ganglion cells were identified. (H & E, original magnification $\times 10$); **b** Scattered ganglion cells (center of picture) (H & E, original magnification $\times 40$); **c** Perineurial envelope highlighted by EMA (ABC-hematoxylin, original magnification $\times 40$); **d** Scattered axons (NFP, ABC-hematoxylin, original magnification $\times 40$)

Fig. 12 **a** Probable Schwann cell hamartoma. Fascicular proliferation of Schwann cells distributed throughout the connective tissue. (H & E, original magnification $\times 40$); **b** Higher power revealing fan-shaped and fascicular proliferation of Schwann cells. (H & E, original magnification $\times 100$)

SCN, despite the fact that the initial tumor had been “completely excised.”

In summary, we presented a review of oral PEN/SCN, a common mucocutaneous peripheral nerve sheath lesion. The mouth is frequently affected, especially the masticatory mucosa and the lips which in combination account for about 90% of cases. The majority of patients in our study were adult males. Most lesions were histologically unilobular, although plexiform, multinodular and fungating variants were encountered. Although most general and oral pathologists find the diagnosis to be simple, occasional lesions pose a challenge and require distinction from nerve sheath tumors, particularly when it comes to plexiform or multinodular variants. GFAP negative immunoreaction may be of help to distinguish PEN/SCN from other peripheral nerve sheath tumors. The pathogenesis of PEN/SCN is reflected in intraneural, somewhat haphazard proliferation of axons and accompanying Schwann cells. They appear to be reactive, hyperplastic lesions. Traumatic

origin is less likely but this issue remains unsettled. Also, the possibility that PEN/SCN are hamartomatous or forme fruste manifestations of an oculocutaneous disorder different from MEN2b cannot be totally dismissed.

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