On Pseudo-Onion Bulb Intranearal Proliferations of the Non-Major Nerves of the Oral Mucosa

Ioannis G. Koutlas · Bernd W. Scheithauer

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Abstract Perineurial cells (PCs) participate in reactive and neoplastic processes, of the latter pure perineurial being intraneural (IP) and soft tissue perineuriomas with oral examples being reported in both. In our review of over 500 peripheral nerve sheath tumors including granular cell tumor, we identified a single ostensible case of IP occurring on the tongue of a 45-year-old African-American male that was characterized by classic perineurial pseudo-onion bulbs (PsOb), proliferating PCs among these PsOb, sclerosis apparently due to long term duration and a plexiform pattern. We have also encountered 37 examples of apparently reactive, hyperplastic or traumatic, PsOb intraneural pseudoperineuriomatous proliferation (IPP) simulating microscopically some of the properties of IP. The majority of the lesions occurred in women and close to 80 % affected the tongue. Three microscopic patterns were appreciated. Type I lesions were those where IPP was seen only focally, type II where it was seen in roughly half of the lesion, and type III where the majority of the lesional tissue or the lesion itself was characterized by IPP. Immunohistochemically, IPP featured PsOb with generally a single layer of PCs decorated by epithelial membrane antigen, glut-1 or claudin-1, and decreased numbers of S-100 positive Schwann cells. The number of axons was not apparently altered. A prominent collagenous intraneural component was occasionally

evident among PsOb and the affected nerve featured discontinuous or absent perineurial envelop. While type I and II IPP can be distinguished from IP, the distinction from type III lesions can be problematic. However, the discontinuity of the perineurium of the affected nerve, the spacing and collagenization among PsOb, the limited perineurial cell layer defining the pseudo-onion bulbs, the absence of proliferating PCs between PsOb and the decreasing number of Schwann cells may be of help in the distinction from IP.

Keywords Perineurial cells · Perineurioma · Pseudo-onion bulbs · Intraneural

Introduction

Originally described by Henle, perineurium and perineurial cells (PCs) were first studied in detail in 1873 by Key and Retzius who referred to the perineurial ensheathment as “Perineuralhäutchen,” literally “delicate perineurial skin” [1]. There is evidence that PCs originate from fibroblasts stimulated by *Desert Hedgehog*, an intercellular signaling molecule secreted by Schwann cells, prompting perineurial surrounding fibroblasts to form a cellular sheath, the perineurial barrier [2]. Perineurial cells with typical immunohistochemical and ultrastructural features contribute to the formation of reactive traumatic neuromas, as well as peripheral nerve sheath tumors such as neurofibromas and so-called “benign mixed nerve sheath tumors” i.e. hybrid schwannoma/perineuriomas [3]. They are the sole constituent of perineuriomas which occur in two forms, the intraneural (IP) (hypertrophic neuropathy or neoplasm) and the far more common extra neural or soft tissue (STP) neoplastic type.

Intraneural perineurial (IP) involves, generally, major nerves of primarily young adults and is associated with

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

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

motor or, less often, sensorimotor disturbances [4]. Grossly, IP is characterized by fusiform or nodular enlargement of nerve fascicles, featuring, histologically,

layers of concentric proliferation of PCs (onion bulbs) around nerve fibers. These structures have been dubbed “pseudo-onion bulbs” (PsOb) to distinguish them from

Fig. 1 **a** Low power microphotograph depicting mucosal mass characterized by serpentine or plexiform proliferation of peripheral nerve sheath origin. (H&E, original magnification $\times 5$). **b** Medium power microphotograph featuring plexiform pattern and sclerosis. (H&E, original magnification $\times 20$). **c** PsOb proliferation in a collagenized and vascular stroma. (H&E, original magnification $\times 200$). **d** Short streams of perineurial cells in juxtaposition of PsObs. (H&E, original magnification $\times 200$). **e** The center of this microphotograph reveals small peripheral nerves exhibiting PsOb proliferation. On the right is portion of the IP (H&E, original magnification $\times 100$). **f** Cytoplasmic vacuolization of perineurial cells (H&E, original magnification $\times 200$). **g** Prominent sclerosis and artifactual cracking. The lesion most likely was longstanding. (H&E, original magnification $\times 140$). **h** EMA decorated proliferating perineurial cells. (ABC, hematoxylin counterstain, original magnification $\times 320$). **i** EMA decorated perineurial cells with cytoplasmic vacuolization. These cells were negative for S100. (ABC, hematoxylin counterstain, original magnification $\times 400$). **j** S100 protein revealed rare scattered Schwann cells. (ABC, hematoxylin counterstain, original magnification, $\times 200$)

“true onion bulbs,” architecturally similar Schwannian proliferations encountered in certain reactive/demyelinating processes such as the inherited polyneuropathies of the Charcot-Marie-Tooth and Dejerine-Sottas types [4].

The most detailed reviews on IP were authored by Boyanton et al. [5] and Mauerman et al. [6], the former group of investigators regarding them neoplasms, the latter group supporting a hyperplastic process as a pathogenetic mechanism. Alleged examples of oral IPs have affected the inferior alveolar nerve [7, 8] and non-major nerves of the tongue [5, 9–11], lower lip [12] and buccal mucosa [12, 13]. In one patient with hemifacial hyperplasia, multiple lesions were encountered [13]. An unusual multifocal perineurial proliferation affecting the tongue of a horse with features “reminiscent of but not identical to IP” has also been described [14]. When it comes to non-major nerves, a peculiar intraneural tumor sharing features of intraneural and reticular perineurioma has also been described [15]. In March 2013, the first example of cutaneous intraneural perineurioma was reported [16].

In our review of oral peripheral nerve sheath tumors we have encountered 38 cases that featured PsOb intraneural proliferations. Among them, we identified an apparent

example of IP, however, the vast majority of them comprise what we perceive as being reactive lesions. In that the characteristics of these distinctive IP-like lesions have not been previously described, we report their clinical, histologic, and immunophenotypic features.

Methods and Materials

One case of oral IP, initially diagnosed as a plexiform neurofibroma and 37 cases of what will be thereafter referred to as intraneural pseudoperineuriomatous proliferation (IPP) were identified among over 500 tumefactive, oral peripheral nerve sheath tumors, including granular cell tumors, and spanning a period of 50 years. Prior to establishing the IPP concept, 30 examples were diagnosed as follows: 17 as pure traumatic neuromas, 6 as fibrous hyperplastic polyps (fibromas, traumatic fibromas) being the primary diagnosis with traumatic neuroma a secondary feature, and 7 as neurofibromas including one of plexiform type.

Demographic and clinical data were obtained from pathology reports. Hematoxylin and eosin preparations of surgically resected tissues, formalin-fixed, routinely processed and paraffin-embedded, cut at 5 μ m were available in all cases. For IPP, parameters evaluated in all lesions included (a) the level of participation of IPP in the lesion, type I lesions being those where IPP was seen only focally, type II where it comprised roughly half of the lesion, and type III where the majority of the lesional tissue or the lesion itself was characterized by IPP, (b) collagen deposition both within the lesion and in surrounding connective tissue, (c) semiquantitative evaluation of nerve fibers (axons and Schwann sheaths), (d) presence or absence of overlying epithelial hyperplasia, and (e) stromal inflammation.

Immunohistochemical stains were performed upon the one oral IP and 29 IPPs using the streptavidin–biotin peroxidase complex method. Applied antisera were directed against S-100 protein (Dako, Carpinteria, CA; 1:1600, polyclonal), neurofilament protein (NFP) (Dako, 1:800, 2F11) and epithelial membrane antigen (EMA) (Dako,

Fig. 2 **a** Polypoid lesion of the right buccal mucosa. **b** Nodular lesion of the left lateral border of the tongue

Fig. 3 **a** Type I lesion featuring predominantly fibrous hyperplastic connective tissue with only focal serpiginous IPP proliferation [square area, see **(b)**]. (H&E, original magnification $\times 25$). **b** Area in

square depicting hyperplastic nerve with PsOb proliferation. (H&E, original magnification $\times 100$)

Fig. 4 Type II lesion characterized by roughly equal parts of fibrous hyperplasia and IPP. (H&E, original magnification $\times 20$)

1:50, E29). In instances wherein EMA reactivity was unsatisfactory or weak, immunostains for glut-1 (Dako, 1:200, polyclonal) and claudin 1 (Invitrogen, Carlsbad, CA; 1:50, polyclonal) were also performed.

Results

Oral Intra-neural Perineurioma (IP)

The one IP encountered occurred on the left lateral aspect of the tongue of a 45-year-old African-American male. It measured 2.2 cm and was asymptomatic, there being no sensorimotor disturbance. No history of trauma was related and no reference was made to the presence or absence of neurofibromatosis, type 1. Histologically, the tumor exhibited a serpiginous or plexiform pattern of growth and occupied nearly the entire bulk of the specimen (Figs. 1a, b). Perineurial cells formed primarily PsOb characterized of few layers in thickness and, focally, short aggregates of occasionally parallel lined cells (Figs. 1c, d). Of particular interest was the presence of multifocal areas at the base of the lesion wherein nerve fascicle(s) was/were undergoing intra-neural perineuriomatous PsOb transformation featuring close packed PCs (Fig. 1e). The cytoplasm of PCs was eosinophilic and

cytoplasmic membranes were ill-defined. Occasional cells exhibited cytoplasmic vacuolization giving them an adipocytic- or signet-ring-like appearance (Fig. 1f). Prominent lesional sclerosis and areas of cracking artifact were noted, the latter being a feature occasionally seen in STP (Fig. 1g). Immunostaining for EMA was diffusely positive, clearly delineating pseudo-onion bulbs (Fig. 1h) as well as the above-noted cells with cytoplasmic vacuolization which were S-100 protein-negative, thus supporting their origin in apparent degenerative lipidization (Fig. 1i). Small sheets of EMA positive PCs bridged, occasionally, adjacent onion bulbs. S-100 protein disclosed the presence of few scattered Schwann cells (Fig. 1j). The perineurial envelop of the affected nerve(s) featured layers of PCs in parallel. NFP stain revealed axons at the centers of some pseudo-onion bulbs. One should note that in areas of prominent sclerosis the presence of axons was very scarce. The patient after removal of the lesion has been lost to follow up for the last 10 years.

Intra-neural Pseudoperineuriomatous Proliferation (IPP)

Of the 37 patients with what we are referring to as IPP, 22 (59.5 %) were females and 15 males (40.5 %). The age at diagnosis was known in 35 patients, the youngest being 4 months and the oldest 91 years old (mean = 25.6 ± 17.8 ; median = 21); 27 patients were younger than 30 (~ 73 %). The race was known in 35 cases; 29 patients were Caucasians (~ 83 %), 4 African-Americans, 1 Asian and 1 Hispanic. Of 7 patients where symptomatology was recorded, 2 described their lesions as “bothersome” or “annoying”, while no evidence of pain was stated by 5. In two instances patients reported trauma, and one patient denied it. The duration of the lesions was recorded as unknown in one patient, while in 12 it varied from 2 months to more 29 years. Nine lesions had been present for more than 1 year.

Clinically, all lesions were nodular or polypoid in configuration (Figs. 2a, b) and the clinicians’ impression at surgery was generally that of fibrous hyperplasia (“fibroma or traumatic fibroma”). Of the 29 involving the tongue (78.4 %), 12 cases affected its lateral border (9 right- and 3

Fig. 5 **a** Type III lesion exhibiting a plexiform IPP that occupied the majority of the lesion. Fibrosis is evident in the stroma. (H&E, original magnification $\times 40$). **b** Type III lesion where the IPP is

characterized by single hyperplastic nerve featuring PsOb. (H&E, original magnification $\times 40$)

Fig. 6 The characteristic and defining PsOb. Concentric single layer of perineurial cells surrounding an axon. Fibrosis between individual PsOb. Blending of the periphery of the PsOb with the surrounding connective tissue is seen especially in the lower right area of the PsOb (H&E, original magnification $\times 200$)

left-sided), 9 occurred at or close to its tip, 6 arose in the dorsum and in 2 instances the location was designated as the tongue anterior. Of the remaining lesions, 5 originated on the lower lip (13.5 %), two in buccal mucosa (5.4 %) and one on the floor of the mouth (2.7 %).

Histologically, 13 lesions (35.1 %) were of type I in which the IPP was present focally (Fig. 3a and insert), its pattern varying from round or ovoid pseudo-onion bulb nests (9 lesions) to serpiginous or somewhat plexiform (4 lesions). In either case, the affected nerve exhibited pseudo-onion bulbs (Fig. 3b). Ten type II lesions (~ 27 %) had roughly equal parts of stromal fibrous hyperplasia with interspersed IPP (Fig. 4). A somewhat serpiginous plexiform pattern was most frequently encountered (8 lesions). Fourteen type III lesions (37.8 %) were seen primarily on the tip and dorsal areas of the tongue as well as in 2 out of the 3 buccal mucosal lesions. In four lesions, a serpiginous pattern was present (Fig. 5a), while the remaining lesions, which consisted predominantly of small ones, featured a prominent core of a hyperplastic nerve exhibiting pseudo-onion bulb proliferation (Fig. 5b).

In general, regardless the type, PsOb were characterized by a concentric arrangement of one or rarely two spindle cells with indistinct cytoplasmic borders around an axon (Fig. 6). In some lesions participating IPP had a somewhat sharp demarcation from the surrounding connective tissue surrounded by the apparent perineurial envelop of the affected hyperplastic nerve, while in the majority there was discontinuity or absence of the perineurial sheath. In all lesions, all affected fascicles revealed varying degrees of intrafascicular collagen deposition.

Immunohistochemically, affected fascicles featured generally incomplete perineurium at their periphery and central perineurial onion bulb formation generally 1 to infrequently 2 layers in thickness highlighted by EMA, glut-1 or claudin 1 staining (Fig. 7a–c). On S-100 protein preparations, the pseudo-onion bulbs were seen to surround nerve fibers with same or decreasing numbers Schwann cells when compared to neighboring normal nerve twigs (parent nerve?) (Fig. 8). With NFP, there appeared to be little or no difference in axonal density within onion bulbs when compared to the numbers in neighboring parent peripheral nerve twigs or normal nerves (Fig. 9). Only 2 of the 37 lesions featured perifascicular inflammation. In 24 cases, overlying hyperkeratosis possibly suggestive of prior repeated trauma was appreciated. In two of them superficial hemorrhage and neutrophilic microabscesses were seen.

One type I lesion was accompanied by a nearby or contiguous sclerosing granular cell tumor (Fig. 10a–c). In that case, the IPP occurred mostly in the periphery of the lesion with only a single affected nerve fascicle being present in its center. Lastly, a type III lesion feature at a lateral corner apparent traumatic neuroma.

Discussion

In 1964, da Gama Imaginário et al. [17] described monosymptomatic hypertrophic interstitial neuritis, a localized hypertrophic neuropathy characterized by concentric proliferation of PCs forming small whorls (“onion bulbs”).

Fig. 7 **a** EMA defining the single layer of perineurial cells forming PsOb. Note absence of perineurium around the nerve. (ABC, hematoxylin counterstain, original magnification $\times 400$). **b** PsOb highlighted by glut-1. Note the incomplete perineurial envelop of the

affected nerve. (ABC, hematoxylin counterstain, original magnification $\times 200$). **c** PsOb highlighted by claudin-1. Note the absence of perineurial envelop of the affected nerve. (ABC, hematoxylin counterstain, original magnification $\times 200$)

Fig. 8 S100 revealed decreasing number of Schwann cells. The number of axons was not decreased. (ABC, hematoxylin counterstain, original magnification $\times 180$)

While their case was presumed to be an example of a restricted form of generalized hypertrophic polyneuropathy, in the broader context of perineurial lesions, it is considered the first example of what, in 1980, Mitsumoto et al. [18] referred to as IP. Various authors have referred to IPs as “localized hypertrophic neuropathy, intraneural concentric perineurial cell tumor, hypertrophic mononeuropathy or hypertrophic interstitial neuritis” [19].

In terms of an etiology, Johnson and Kline [20] supported the concept of a reactive process, i.e. a chronic inflammatory demyelinating polyneuropathy, suggesting the presence of a focal perineurial defect leading to compartmentalized perineurial hyperplasia resulting in onion-bulb formation. In 1995, Emory et al. [21] demonstrated the presence of chromosome 22 aberrations in two IPs studied for chromosomal abnormalities, thus supporting a clonal and apparently neoplastic nature. In line with the opinion of Emory et al. [21], Boyanton et al. [5], have considered them neoplasms. However, Mauerman et al. [6] differ and recognize them as focal hypertrophic neuropathies.

In their systematic review of intraneural perineurioma, Boyanton et al. [5] reported a slight female predilection

(~56 %) and that the majority of lesions affected patients under age 40 years. Mauerman et al. [6] in their series of 32 patients have reported equal gender distribution and confirmed patients’ young age. Among major nerves the ulnar, median and radial nerves of the upper extremities, the peroneal, posterior interosseous and sciatic nerves of the lower extremities, as well as the brachial plexus are most frequently affected [5, 6]. While motor and sensorimotor abnormalities as well as denervation, which correlates with muscular atrophy, have been described in lesions affecting major nerves, alleged IPs of non-major (unnamed) nerves, such as in oral mucosa, are reported as asymptomatic [7, 9–13].

Nine examples of what their authors describe as intraoral IP have been published to date, 2 affecting the inferior alveolar nerve, a major nerve, while the remaining 7 involved non-major nerves. Interestingly, only in the oral mucosa there have been reports on IPs of non-major nerves. The clinicopathologic characteristics of these lesions are summarized in Table 1. Briefly, the 2 tumors of the inferior alveolar nerve occurred in men age 51- and 64-years, while the 7 lesions involving minor nerves of oral soft tissues affected young patients (mean = 15.6 years). The 2 inferior alveolar nerve lesions are classic examples of IP as it occurs in major nerves, the case published by McNamara seen personally by one of us (IGK). The articles by Damm et al. [9], da Cruz Perez et al. [10], and Siponen et al. [13] feature illustrations diagnostic of IP, however, the representative figures by Dundr et al. [12], Case 1 of Boyanton et al. [5] and the cases by Rocha et al. [11] share morphologic characteristics with what we refer to as IPP. For example, there is spacing of and distinct collagenous hyperplasia between individual pseudo-onion bulbs [5, 12] and lack [12] or disruption [5] of the perineurial enveloping of the hyperplastic nerve fascicle. In both of these lesions a plexiform pattern was present, as was the case in more than half of our IPP.

Herein, under the term IPP, also lightheartedly referred by us as “chewies” in our personal communication, we

presented the clinicopathologic characteristics of apparently reactive in nature oral peripheral nerve sheath lesions. They are likely the result of traumatic, non-open mechanical injury, i.e. chronic compression and ischemia of nerve, or of focal loss of the perineurial ensheathment without nerve transection. Korthals et al. [22] have observed a similar pattern of perineurial proliferation in experimentally induced acute ischemic injury of peripheral nerves with replacement of the original fascicle by a collection of minifascicles separated by bands of connective tissue and often surrounded by their own perineurium. Loss of the perineurial barrier resulting from trauma can cause endoneurial fibroblasts to transform into PCs due to the stimulatory effect of *Desert Hedgehog* by Schwann cells ensheathing axons [2]. The result is a newly formed protective barrier surrounding individual Schwann cell-axon nerve units [23]. The process can affect more than one peripheral nerve twig. Collagen deposition between the cell layers comprising PsOb results, apparently, from its secretion by PCs, the effect being fascicular enlargement with no obvious loss of axons. In longstanding lesions, this can be prominent, causing increased spacing of nerve fibers.

Fig. 9 Axonal density was not altered in IPP as disclosed with NFP stain. However, the axons were spaced from each other because of the hypertrophic nerve and the presence of interstitial collagen among PsOb. (ABC, hematoxylin counterstain, original magnification $\times 400$)

The frequent occurrence of IPP on the tongue and lower lip, areas susceptible to trauma, supports our contention of traumatic etiology as does their presence in association with fibrous polyps, a feature observed in type I and II lesions. Of interests is the occurrence of IPP in the tongue of an only 4 month-old patient with a type I lesion. The records were reviewed extensively and there was no indication of a typographical error when it came to the birth date of the patient. The possibility of trauma cannot be excluded.

Chou [24], in his seldom cited but thorough review of peripheral neuropathies with perineurial onion bulbs, was of the opinion that lesions characterized by pseudo-onion bulbs may be of two types, (a) those with central Schwann cells, as seen in what he referred to as “paratraumatic perineurioma” and in some cases of amputation neuroma, and (b) those without or very few Schwann cells, which Chou regarded as hamartomatous. At the time of Chou’s report, there was no evidence of a chromosomal abnormality to suggest a neoplastic nature of IP. It may well be that two fundamentally different intraneural perineurial onion bulb proliferations exist, one neoplastic that may include areas encountered in STP and the other a reactive process. It is also known that at least a subset of STP carry chromosome 22 aberrations [25] as are seen in the two examples of intraneural perineurioma of Emory et al. [21]. Their distinction may be problematic since they share morphologic characteristics and, in histopathologic terms, may focally be indistinguishable. Their distinction becomes more problematic when it comes to clinical/demographic characteristics with both oral IP and IPP generally occurring in young patients with a female predilection and mostly in the tongue.

Legitimate arguments can be made against use of the term intraneural perineurioma for what we describe as IPP. Had we considered all our lesions to be IPs, the latter would become a rather common intraoral peripheral nerve neoplasm. For example, in our review of more than 500 oral peripheral nerve sheath tumors inclusive of granular

Fig. 10 **a** Sclerosing granular cell tumor with associated IPP. (Hematoxylin and eosin special stain, original magnification $\times 100$). **b** Sclerosing granular cell tumor highlighted by S100. Note on the right the hyperplastic nerve exhibiting IPP. (ABC, hematoxylin

counterstain, original magnification $\times 100$). **c** EMA highlights the IPP in this granular cell tumor. (ABC, hematoxylin counterstain, original magnification $\times 50$)

Table 1 Clinicopathologic characteristics of cases reported as oral intraneural perineurioma in chronologic order of publication

Authors	Age/ gender	Location	Clinical information	Histologic features	Follow-up
Damm et al. [9]	26/F	Tongue dorsum	Firm nodule; unknown duration; no sensorimotor disturbance	Tortuous, well-circumscribed cellular proliferation with numerous pseudo-onion bulb-like structures	No information provided
Huguet et al. [7]	64/M	Mandible	Mandibular unilocular radiolucent expansion; 6-month duration of expansion	Intersecting fascicles and whorls of proliferating spindle cells; whorls having an onion skin-like arrangement	Complication-free postoperative course
da Cruz Perez et al. [10]	12/M	Tongue dorsum	Symptomless; 10-year duration; inconvenience during chewing and swallowing; no sensorimotor disturbance; trauma denied	Non-encapsulated but well delineated proliferation of spindle cells forming pseudo-onion bulb structures	NED (6 months)
Dundr et al. [12]	16/M	Buccal mucosa	Unknown duration; symptomless; no history of trauma	Tortuous proliferation of spindle cells forming pseudo-onion bulbs	NED (2 years)
Siponen et al. [13]	18/F	Buccal mucosa	Multiple lesions; patient with hemifacial hyperplasia	Hypertrophic proliferation of neural tissue in a pseudo-onion bulb pattern	N/A (the patient underwent surgical procedures to correct deformity)
Boyanton et al. [5]	6/F	Dorsolateral tongue	Symptomless, no trauma, no sensorymotor disturbance	Plexiform pattern of expanded nerve fascicles featuring proliferation of pseudo-onion bulb structures	NED (4 months)
McNamara et al. [8]	51/M	Mandible	Asymptomatic radiolucency	Spindle cell proliferation arranged in variably sized whorls forming a pseudo-onion ring pattern	N/A
Rocha et al. [11]	47/F	Tongue	Painless, present for 27 months, history of bicycle accident	Circumscribed lesion surrounded by fibrous connective tissue composed of layers of spindle-shaped cells around a central axon, forming structures described as onion-bulb-like	
Rocha et al. [11]	37/M	Lower lip	Painless, 20 years duration	Circumscribed lesion surrounded by fibrous connective tissue composed of layers of spindle-shaped cells around a central axon, forming structures described as onion-bulb-like	

cell tumor, IP would account for approximately 7 % of all tumors. Oral IP would also become far more frequent than oral STP [26]. Furthermore, non-major oral nerves would be most often affected and the present study would become the largest series of IP from a single institution, dwarfing the laborious work and literature review of Boyanton et al. [5] and Mauermann et al. [6].

Histologic differences to distinguish IPP from true IP, in our opinion, may exist in their (a) perineurial discontinuity of the affected minor nerve, (b) single layer thickness of the perineurial collar, (c) the collagenous intrafascicular component seen at some level in continuity with the surrounding

stromal collagen and (d) the presence of stromal fibrous hyperplasia as the main bulk of the clinical lesion in the majority of cases. These distinguishing features are summarized in Table 2. To better visualize the PsOb it is suggested that the triad of S-100, EMA and NF immunohistochemical stains be utilized. Immunohistochemical markers MIB-1 and p53 cannot be used to differentiate the two since MIB-1 and p53 expression varies in IP [8].

The most frequently proffered diagnosis of our series of IPP was traumatic neuroma. Although trauma may be the pathogenetic mechanism, IPPs do not resemble ordinary traumatic (amputation) neuromas. Instead, they represent a

Table 2 Comparison of intraneural perineurioma to intraneural pseudoperineuriomatous proliferation

	Intraneural perineurioma	Intraneural pseudoperineuriomatous proliferation
Perineurial cell layer in PsOb	More than 1 perineurial cells	Rarely more than one
Perineurial sheath of the affected nerve	Intact	More frequently disrupted or absent. Continuity of the intrafascicular collagen with the surrounding stroma
Intrafascicular collagenous component	From limited to prominent (sclerosis)	Present
Association with another pathologic process	Main lesion	Comprises usually part of another lesion (e.g. fibrous hyperplasia, fibroma)

perineurial rather than a Schwann cell response. They lack both axonal sprouting and microfascicle formation.

The distinction of IPP from neurofibroma, especially the plexiform variant, generally poses no problem. The latter diagnosis is only problematic in that an unnecessary neurofibromatosis type 1 (NF1) evaluation of the patient and family members might be undertaken. The diagnosis is easily established if the three basic immunohistochemical stains used in the study of peripheral nerve sheath tumors are applied (S-100, EMA and NFP). The simple demonstration of EMA-positivity in pseudo-onion bulbs excludes both neurofibroma and the occasional true onion bulbs sometimes encountered in neurofibromas and in peripheral nerve in the setting of NF1.

The literature contains also rare examples of what their authors referred to as plexiform perineuriomas [27–30], two of them occurring on the lips, upper and lower, respectively. These peculiar tumors are classified as subtypes of STP since they reveal histopathologic features encountered in STP. It is not clear from the provided illustrations if these tumors arose within a nerve or nerves. In our ostensible example of IP with a plexiform pattern, features of STP were also present. However, there was definitely intraneural development as proven in the early PsOb development seen in the base of the lesion. Thus, it will be of interest to investigate the presence of an intraneural component in the other published examples of plexiform perineurioma before classifying as variants of STP.

In summary, we have reported our experience with intraneural perineurial cell proliferations of the mouth, introducing the term intraneural pseudoperineuriomatous proliferation to describe a not uncommon, apparently reactive process characterized by pseudo-onion bulb formation in nerves trauma prone and occurring preferentially in young, female patients. In that they share morphologic similarities with intraneural perineurioma, general and oral pathologists should be aware of IPP in order to avoid an erroneous and possibly clinically more significant diagnosis.

As a final note, the last draft of this manuscript was corrected by Dr. Bernd Scheithauer a few months before his sudden death. This paper, a “fun” one according to

Bernd, is dedicated to the memory of this giant of pathology whose continuous smile was turning always into a full-hearted laugh whenever a “chewie” (no relation to Chewbacca, member of the wookie species) crossed the lenses of his microscope.

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