Intraneural perineurioma of the mandible: case series of a rare entity

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Perineuriomas are benign peripheral nerve sheath tumors composed of perineurial cells. Functionally, the perineurium is the outer sheath around peripheral nerve fascicles, and it modulates external stretching forces, regulates endoneurial pressure, and acts as the blood−nerve barrier.[1] Unlike Schwann cells and fibroblasts, perineurial cells synthesize basement membrane proteins, such as laminin and type IV collagen, and express epithelial membrane antigen.[2]

Although benign peripheral nerve sheath tumors most commonly arise from Schwann cells, they may be composed of any cell type that forms the nerve sheath. Rarely, perineurial cells proliferate forming benign neoplasms called *perineuriomas*, which are clinically and histopathologically divided into 2 main types: extraneural and intraneural.[3] Extraneural (soft tissue) perineuriomas most often present as a subcutaneous nodule involving the limbs or trunk of middle-aged adults.[3,4] In contrast, intraneural perineuriomas typically arise within a peripheral nerve trunk in the upper limbs of young individuals. Involved nerves often undergo fusiform expansion, resulting clinically in sensory and motor deficits; however, patients may be asymptomatic when smaller peripheral nerves are involved.[5,6]

Perineuriomas rarely involve the oral region, with the literature containing only 4 previously reported cases of intraneural perineurioma arising within the mandible. We report 2 new cases presenting with clinical and histopathologic findings compatible with intraneural perineurioma of the mandible. Additionally, we review the literature and discuss histopathologic challenges associated with the diagnosis of this unusual benign neoplasm.

CASE 1

A 71-year-old male complaining of right-sided facial paresthesia presented with a well-defined, corticated, unilocular, radiolucent lesion measuring approximately 3 cm and involving the posterior right mandible (Figure 1). An incisional biopsy was performed, and the specimen was submitted for microscopic evaluation. The histologic sections revealed a relatively well-circumscribed mass composed of short, interlacing fascicles and concentric whorls of spindle cells exhibiting fusiform-shaped nuclei and inconspicuous cytoplasmic outlines (Figure 2). Immunohistochemical studies revealed strong and diffuse reactivity of concentric lesional cells with antibodies directed against epithelial membrane antigen (EMA), consistent with a perineurial origin (Figure 3). S-100 immunoreactivity highlighted central nerve axons and Schwann cells, but not the concentric lesional cells (Figure 4). As extracranial meningioma was considered in the differential diagnosis, expression of somatostatin receptor 2 (SSTR2) was evaluated; the result was negative for extracranial meningioma. These light microscopic and immunohistochemical findings supported the diagnosis of intraneural perineurioma. This patient was lost to follow-up after the diagnosis.

CASE 2

A 51-year-old male presented with an asymptomatic, well-defined, unilocular radiolucency with focally sclerotic borders involving the left body of mandible, as noted on routine dental radiography (Figure 5). Incisional biopsy revealed spindle cell proliferation arranged in variably sized whorls with concentric layers, forming a characteristic "pseudo−onion bulb" pattern (Figure 6). Immunohistochemical studies showed diffuse positivity of the concentric whorls of spindle cells to antibodies directed against EMA (Figure 7). Immunoreactivity for antibodies directed against S-100 was limited to the central portion of the whorled structures, confirming the presence of residual

Statement of Clinical Relevance

Our collaborative case series contributes 2 additional cases of intraneural perineurioma arising within the mandible, reviews the clinicopathologic features of all 6 reported cases in the literature, and discusses the histopathologic challenges associated with this rare spindle cell neoplasm.

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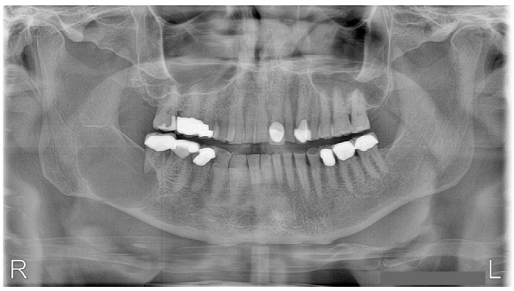

Fig. 1. Large, corticated, unilocular radiolucent lesion involving the right posterior mandible.

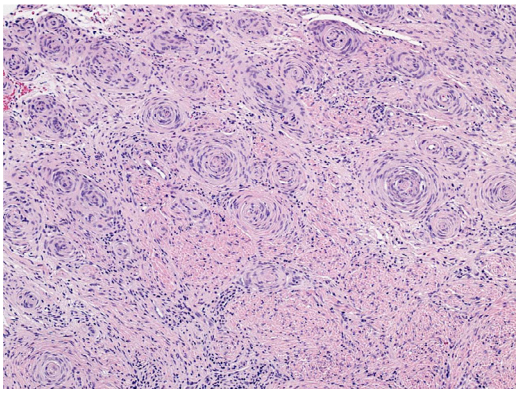

Fig. 2. Proliferation of spindle-shaped cells arranged in concentric whorls (hematoxylin and eosin, x10).

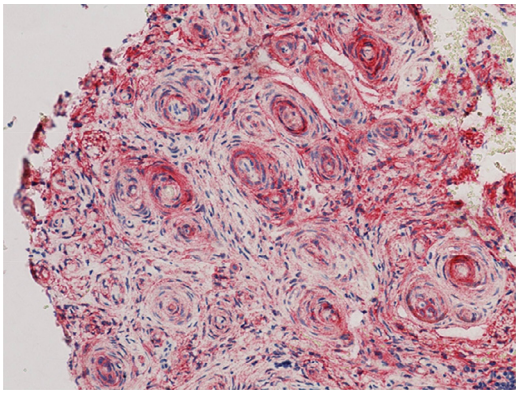

Fig. 3. Concentric spindle-shaped cells show diffuse, strong positivity for epithelial membrane antigen (x20).

nerve axons in these locations (Figure 8). A diagnosis of intraneural perineurioma was rendered and surgical enucleation of the tumor was performed. The patient was subsequently lost to follow-up.

DISCUSSION

In 1978, Lazarus and Trombetta suggested an additional category for peripheral nerve sheath tumors called "perineurioma."[7] Historically, perineuriomas were thought to represent a localized variant of generalized hypertrophic mononeuropathies, such as Charcot-Marie-Tooth disease or Dejerine-Sottas disease.[8] In these conditions, however, associated neural tumors are composed of concentric whorls of Schwann cells.[8] Thus, the nomenclature "perineurioma" replaced "localized hypertrophic mononeuropathy" once

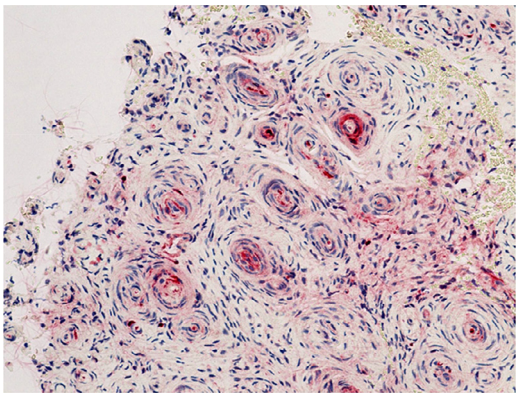

Fig. 4. S100 highlighting central nerve axons and Schwann cells, with lack of staining among concentric lesional cells (x20).

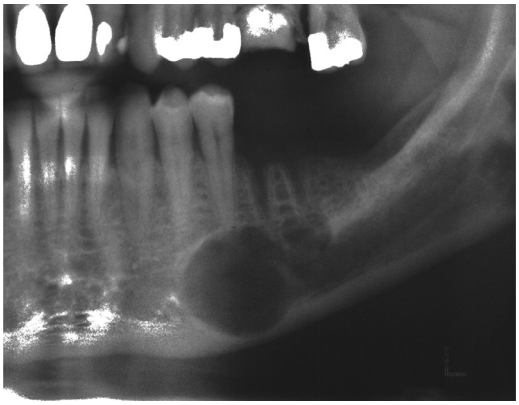

Fig. 5. Cropped panorex showing a well-defined, unilocular radiolucency of the left mandible.

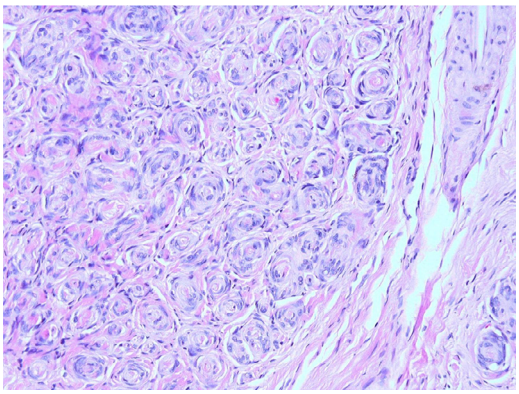

Fig. 6. Spindle cell proliferation arranged in concentric whorls forming characteristic "pseudo−onion bulb" structures (hematoxylin and eosin, x20).

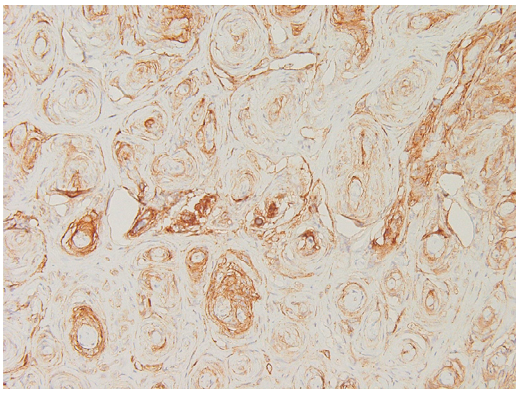

Fig. 7. Diffuse expression of epithelial membrane antigen within the concentric layers of spindle cells (x20).

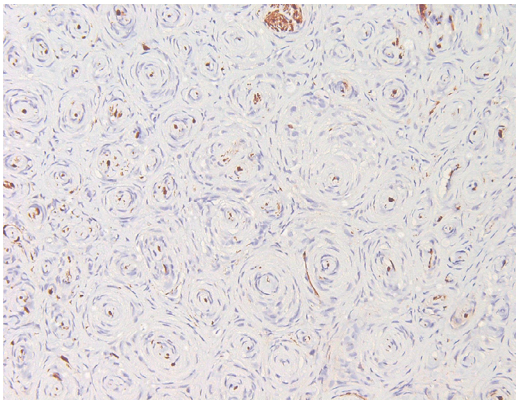

Fig. 8. S-100 protein expression of Schwann cells localized to the central portion of the "pseudo−onion bulb" structures (x20).

electron microscopy demonstrated the distinction between perineurial and Schwann cells.[8] Perineuriomas were also initially considered to represent reactive proliferations secondary to extensive nerve injury, similar to the "onion bulb" formations that have been noted in association with traumatic neuromas.[9] Fluorescent in situ hybridization studies, however, have more recently identified recurrent deletions on chromosome 22, supporting the neoplastic nature of this process.[3,10] These findings were confirmed in subsequent studies, which also discovered that extraneural and intraneural perineuriomas may exhibit different genetic profiles.[4,11]

Perineuriomas rarely involve the oral cavity. To our knowledge, 22 cases of extraneural perineurioma arising in the oral region have been reported in the English language literature.[12] Despite being described as the "soft tissue" variant, extaneural perineurioma occurs most commonly in the mandible.[2,13,14] In contrast, intraneural perineuriomas of the oral cavity show a predilection for the tongue.[12] Including our current series, a total of 19 cases of oral intraneural perineurioma have been reported in the English language literature, including 6 cases arising within the mandible (Table I).[10,12,15,16] Upon review of these cases, the mean age at diagnosis among patients with intraneural perineurioma of the mandible is 51 years (range 16−71 years) with a 4:2 male predilection. Radiographically, all cases presented with unilocular radiolucency. Bony expansion was observed in 2 cases; however paresthesia was only reported in association with a single, nonexpansile lesion.

Histopathologic features of intraneural perineurioma consist of a proliferation of spindle-shaped cells characteristically arranged in concentric whorls, described as a "pseudo−onion bulb" pattern (see Figures. 2 and 6). Historically, the term "onion bulb" has been used to describe the whorled morphology of generalized hypertrophic neuropathy. Thus, the term "pseudo−onion

Table I. Clinical data of intraneural perineuriomas of the mandible reported in the literature.

	Ethunandan et al.[16]	*Huguet et al.*[10]	*Vencio et al.*[25]	*Solomon et al.*[26]	*Ko et al. Case 1*	*Ko et al. Case 2*
Clinical						
Age/Gender	48/male	64/male	59/female	16/female	71/male	51/male
Radiograph	Fusiform, well-defined	Unilocular, well-defined	Unilocular, well-defined	Unilocular, well-defined	Unilocular, well-defined	Unilocular, well-defined
Symptoms	Paresthesia	Not reported	Not reported	Asymptomatic	Paresthesia	None
Bone expansion	−	+	−	+	Not reported	Not reported
Treatment	Surgery	Surgery	Surgery	Surgery	Biopsy	Biopsy
Associated nerve	IAN	IAN	IAN	IAN	IAN	IAN
Recurrence/follow-up	None after 2 years	Not reported	Not reported	None after 8 months	Lost to follow-up	Lost to follow-up
Histopathology						
"Pseudo−onion bulb" morphology	+	+	+	+	+	+
Immunohistochemistry						
EMA	+	+	+	+	+	+
S100	−	−	−	−	−	−

−, negative; +, positive; *EMA,* epithelial membrane antigen; *IAN,* inferior alveolar nerve.

bulb" is used to distinguish the similar concentric whorled arrangement of perineurioma.[1] In contrast, extraneural perineuriomas show a more varied histomorphology, with variable cellularity and histologic patterns, including a whorled, lamellar, or storiform arrangement of spindle cells. A distinct variant of extraneural perineurioma is the sclerosing perineurioma. Clinically, this type tends to present as a small painless nodule affecting the fingers or hands and histologically exhibit concentric whorls of tumor cells seen within a markedly dense collagenous stroma.[17,18] Reticular perineurioma is another variant that is exceedingly rare and tends to occur in the upper distal extremities in young to middle-aged individuals. Histologically, these tumor cells form a netlike pattern in a fibromyxoid matrix.[18] Interestingly, benign peripheral nerve sheath tumors showing hybrid features of perineurioma and schwannoma or neurofibroma are also recognized.[19] These tumors are composed predominantly of Schwann cells with admixed perineurial cells forming vague whorls.[19]

The differential diagnosis for intraneural perineurioma includes a variety of spindle cell lesions that exhibit a lamellated or whorled histologic pattern. Solitary circumscribed neuromas, neurofibromas, and traumatic neuromas can all produce onion bulb−like structures. As already discussed, lesions associated with hereditary hypertrophic neuropathies of Charcot-Marie Tooth disease and Dejerine-Sottas disease closely resemble intraneural perineuriomas. Moreover, overlapping features of the whorled histologic pattern observed in meningiomas may even suggest this diagnostic consideration. Therefore, immunohistochemical studies are necessary to make a definitive diagnosis. The characteristic immunohistochemical profile of perineurioma includes diffuse expression of EMA among lesional cells, with S-100 expression limited to the central portion of cellular whorls, likely representing residual nerve axons and Schwann cells. Moreover, glucose transporter-1 is reported to be a useful supplemental immunohistochemical marker, with tumor cells showing diffuse, membranous staining of comparable intensity to EMA.[4,20] Despite overlapping morphologic features, other benign peripheral nerve sheath tumors included in the differential diagnosis are composed primarily of Schwann cells and will, thus, exhibit diffuse expression of S-100. A combination of S-100 and EMA may be observed in hybrid neural tumors. Although meningiomas exhibit diffuse positivity to EMA, S-100 expression is limited to peripheral sustentacular cells, as opposed to the central axons seen in perineuriomas. Additionally, expression of SSTR2 may help confirm a diagnosis of meningioma. Case 1 reported here was negative for SSRT2. Case 2 was not evaluated for SSRT2 expression. Atypical perineuriomas have been described for tumors that show a marked hypercellularity and mild cytologic atypia. This designation, however, has no known clinical significance and is likely akin to "degenerative" changes seen in ancient schwannomas.[21] Low-grade fibromyxoid sarcomas can mimic perineurioma, especially in limited biopsy specimens. Histologically, LGFMS is characterized by alternating zones of collagenous and myxoid stroma, collagen "rosettes," and arching vessels, features not present within perineuriomas.[21] Recently, mucin 4 immunohistochemistry has been shown to be a sensitive and specific marker for LGFMS, which is often diffusely cytoplasmic positive for LGFMS, but negative in perineurioma.[22] Malignant peripheral nerve sheath tumors rarely exhibit an immunohistochemical profile suggestive of perineurioma and have been described as "malignant peripheral nerve sheath tumors with perineurial differentiation" or as "malignant perineurioma."[1] Among the 13 reported cases of malignant perineurioma, only 1 occurred in the oral cavity.[23,24]

Currently, there are no standardized guidelines for the treatment of perineurioma; however, it is a benign neoplasm, and surgical excision appears to be curative.[7] Because of the rarity of oral perineuriomas, the rate of recurrence is difficult to ascertain; however, it is estimated that approximately 5% of oral lesions will recur, most likely as a result of incomplete excision.[1,11]

CONCLUSIONS

Intraneural perineurioma of the mandible is a rare entity that may pose a diagnostic challenge to the pathologist. Awareness of its characteristic histopathologic features and immunohistochemical profile is important to distinguish this unique neoplasm from other spindle cell lesions that may be considered in the differential diagnosis.

PRESENTATION

Both cases were presented as abstracts at the American Association of Oral and Maxillofacial Pathology (AAOMP) Meeting, Miami, FL, USA, 2019, and at the AAOMP meeting in San Francisco, CA, USA, 2008.

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