Intraoral Pseudo-Onion Bulb Intraneural Proliferations in a Patient with Hemimandibular Hyperplasia: A Case Report and Review of the Literature

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Abstract This report and review of the literature describes a case of benign intraoral lesions of perineurial origin in a patient with symptomatic hemimandibular hyperplasia causing partial denture soreness. Perineuriomas are a benign peripheral nerve sheath tumor composed of perineurial cells. Intraoral perineuriomas are an extremely rare entity. Two main types of perineuriomas have been described: intraneural and extraneural perineuriomas. A third, similar entity, called an intraneural pseudoperineuriomatous proliferation, has recently been proposed in the literature as a separate and distinctive diagnosis. This report describes the histologic and clinical presentation of intraneural pseudoperineuriomatous proliferations in a patient with hemimandibular hyperplasia.

Keywords Oral pathology · Intraneural pseudoperineuriomatous proliferation · Perineurioma ·

Hemimandibular hyperplasia · Fluorescence in situ hybridization · Immunohistochemistry

Introduction

Perineuriomas are benign neoplasms composed solely of perineurial cells [1]. There are two major types of perineuriomas: the more common extraneural or soft tissue type that is generally not associated with a major nerve and the intraneural type [1, 2]. The intraneural type is a rare neoplasm that most commonly arises in a nerve of the extremities in younger individuals [1–4]. It characteristically causes progressive loss of motor function [4]. However, intraneural perineuriomas have been shown to arise in small, unnamed nerves in the oral cavity [2, 3, 5, 6].

Histologically, intraneural perineuriomas show concentric cell layers of bland, spindle-shaped perineurial cells arranged in a pseudo-onion bulb pattern around the remaining nerve axon [1, 2, 4]. Immunohistochemically, perineuriomas are classically epithelial membrane antigen (EMA) positive and S-100 negative [1–4]. While EMA is very useful in the diagnosis of perineuriomas, it is not without drawbacks. Due to the extremely thin and widely separated cytoplasmic processes of perineurial cells, EMA positivity in some perineuriomas may be difficult to demonstrate, and EMA-negative perineuriomas have been reported in the literature [5, 8]. Therefore, three other useful but nonspecific stains cited in the literature that can aid in diagnosis are Glut-1, claudin-1, and collagen type-IV [1, 2, 4, 7]. Perineuriomas are ultrastructurally and immunohistochemically similar to normal perineurial cells, but are clonal, frequently reported to demonstrate a deletion of the region of chromosome 22 where the tumor suppressor gene *NF2* resides [1, 2, 5, 7–10].

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While intraoral perineuriomas do occur, it is now suggested that not all perineurial lesions are neoplastic. Koutlas and Scheithauer [11] had proposed the term “intra-neural pseudoperineuriomatous proliferation” to describe a reactive process mimicking a perineurioma. It is seen most commonly in women, and up to 80 % of cases involve the tongue [11]. The lower lip is the second most frequent site. The preference for frequently traumatized sites such as the tongue and lower lip supports a traumatic rather than neoplastic etiology [11]. To date, chromosome 22 deletion status in these lesions has not been assessed.

Hemimandibular hyperplasia is a rare disorder that involves the three-dimensional volumetric enlargement of one half of the mandible [12–16]. Affected individuals have facial asymmetry due to abnormal growth of the involved condyle, condylar neck, ramus, and mandibular body up to and ending at the symphysis [12]. We report the first case of multiple pseudo-onion bulb intra-neural proliferations in the oral cavity of a patient with hemimandibular hyperplasia with a confirmed lack of deletion of the portion of chromosome 22 that has been implicated in true neoplastic perineuriomas.

Case Report

A 52-year-old African American man was referred to the Department of Oral and Maxillofacial Surgery for evaluation of a significant facial deformity (Fig. 1). The patient's chief complaint was increasing discomfort with an ill-fitting removable partial denture and slight functional issues. He had a distant history of jaw surgery as a child to address

Fig. 1 The patient presented with striking facial asymmetry resulting from right hemimandibular hyperplasia

jaw asymmetry, but no additional information could be obtained. The patient reported that the condition had recently worsened. The clinical exam revealed a severe facial deformity with his chin skewed left with right fullness. On opening and closing, grating sounds of the right joint were noted, and the patient reported the sensation of an enlarged right condyle. Intraorally, the patient had a prognathic and asymmetric mandible. The intraoral soft tissue examination was significant for multiple fibrotic, warty lesions over the right tongue and anterior mandibular alveolus (Fig. 2a, b). No other soft tissue lesions or abnormalities were noted.

Overall, the right half of the mandible appeared enlarged relative to the left on the panoramic radiograph, and the right mandibular canal also appeared enlarged relative to the left mandibular canal (Fig. 3). A fine-cut computed tomography (CT) scan showed that the condyle appeared hypertrophic, enlarged, irregular, and calcific with areas of exophytic bony proliferation—thus providing an explanation for his functional issues (Fig. 4a, b). Bowing, elongation, and fullness were seen in the right mandibular body consistent with hyperplasia; and, in addition to the right condyle, exophytic areas of cortical bone proliferation were noted at the right anterior mandible and ramus of the mandible (Fig. 5).

An incisional biopsy of the right tongue lesions was performed. Histopathologic examination revealed focal areas of a concentric, pseudo-onion bulb pattern of spindle-shaped perineurial cells around residual nerve fibers in a hyperplastic collagenous stroma (Fig. 6). Immunohistochemically, the specimen was positive for epithelial membrane antigen (EMA), which highlighted the concentric arrangement of the perineurial cells in the pseudo-onion bulbs (Fig. 7). The S-100 did highlight residual Schwann cells, but tumoral cells were negative for S-100 (Fig. 8). The final diagnosis rendered at that time—prior to the characterization of intra-neural pseudoperineuriomatous proliferations—was benign neural lesions consistent with intra-neural perineuriomas.

After the initial diagnosis of the incisional biopsy, dual-color *NF2* FISH analysis was performed using a *NF2*/CEN22q FISH Probe (Abnova, Taoyuan City, Taiwan) labeled with Texas Red and FITC respectively as previously described, and this showed no evidence of clonal deletion (Fig. 9) [17].

Following definitive diagnosis of the soft tissue lesions, the patient was scheduled for orthognathic surgery and a total joint replacement of the right temporomandibular joint. A noncontrast maxillofacial CT was used to fabricate the new right TMJ. The result of surgery was a positive overbite and overjet of the anterior maxilla with an appropriately positioned alloplastic joint. The patient had an uncomplicated postoperative course (Fig. 10a).

Fig. 2 Multiple fibrotic, warty lesions are seen over the right tongue (a) and right anterior mandibular alveolus (b)

Fig. 3 Panoramic radiograph showing the enlarged right mandible distal to the symphysis, along with the enlarged right mandibular canal and right condyle

The patient recently returned for excisional biopsy of the mandibular alveolar ridge lesions, extraction of the lower mandibular teeth, and placement of dental implants (Fig. 10b). Histopathologic examination revealed prominent collagenous hyperplasia with focal areas of pseudo-onion bulb proliferations. While the number of pseudo-

onion bulb proliferations was less than what was seen in the previous tongue biopsy, they both shared a strikingly similar morphologic appearance. The final diagnosis rendered for the mandibular alveolar ridge lesions was intraneural pseudoperineuriomatous proliferation, the newly described entity.

Discussion

In their case series, Koutlas and Scheithauer [11] found 37 examples of intraneural pseudoperineuriomatous proliferations, and all of the lesions reported were solitary lesions. Clinically, these lesions appear nodular or polypoid—similar to fibrous hyperplasia [11]. The lesions in our case were fibrotic and had a polypoid, warty appearance. The histologic criteria that Koutlas and Scheithauer [11] used to make the diagnosis included pseudo-onion bulbs that were characterized by a concentric arrangement of one or rarely two spindle cells with indistinct cytoplasmic borders

Fig. 4 Axial CT, bone window (a) and coronal CT, bone window (b) showing the markedly enlarged right mandibular condyle

Fig. 5 3D CT reconstruction showing the enlarged right mandible with areas of bony proliferation

Fig. 6 Islands of pseudo-onion bulbs seen in a collagenous stroma (H&E $\times 10$)

around a residual nerve fiber, varying degrees of intrafascicular collagen deposition, usually a discontinuity or absence of the perineurial sheath, and varying degrees of stromal fibrous hyperplasia. Immunohistochemically, the lesions stain the same as true intraneural perineuriomas with EMA highlighting the perineurial cells of the pseudo-onion bulb—one to two layers for this entity—and S-100 highlighting the residual Schwann cells. For true intraneural perineuriomas, the typical appearance of the concentric proliferations is whorls of five to six layers of the neoplastic, bland-looking spindle cells [1, 2, 4, 18, 19]. The authors cite nine cases in the literature that were previously

Fig. 7 EMA highlights the concentric layers of proliferating perineurium ($\times 20$)

Fig. 8 S-100 highlights the residual Schwann cells but is negative in tumoral cells ($\times 20$)

diagnosed as true intraneural perineuriomas [11]. Of these, they feel that four better fit the histologic criteria of intraneural pseudoperineuriomatous proliferations [11].

The suspected etiology of the intraneural pseudoperineuriomatous proliferation is trauma [11]. One theory put forth by Koutlas and Scheithauer [11] is that these lesions can result from chronic compression resulting in nerve ischemia. Given the expansion of the patient's right mandible, his partial denture was potentially compressing the alveolar soft tissue nerve endings causing ischemia and the reactive proliferation of the perineurium seen in this case. Moreover, the patient's enlarged right mandible and functional impairment may have increased the incidence of accidental trauma to the right side of the tongue. The cause of his hemimandibular hyperplasia is unclear; but, as reported in the literature, hormonal influences, hypervascularity, infection, or trauma are factors that can contribute

Fig. 9 Dual-color fluorescence in situ hybridization probe negative for *NF2* deletion. A normal copy number shows *two red NF2* signals and *two green* chromosome 22 centromeric probes. Only individual and well-delineated cells were scored. Overlapping cells were excluded from the analysis. Hemizygous deletion in *NF2* would show *one red* and *two green* signals

to irregular growth in one of the condyles and mandible [14]. While no known syndrome has been described with such a presentation to date—another reason that a reactive etiology is favored—this certainly does not preclude this as a syndromic process.

True perineuriomas—once thought to be reactive—are now generally agreed to be neoplastic. In 1995, Emory et al. [9] demonstrated the clonal nature of the intraneural perineurioma and its association with abnormalities of chromosome 22. Giannini et al. [8] also showed a deletion of part or all of chromosome 22 in extraneural perineuriomas and supported the view that both types of perineuriomas are neoplasms of perineurial cells. The specific deletion of a portion of chromosome 22 is also noted in

benign and malignant schwannomas, neurofibromas, meningiomas, and gliomas [5]. It is thought that the tumor suppressor gene *NF2* resides in the affected region of chromosome 22 [1, 2, 5, 7]. Although mutations in the *NF2* gene have been documented in perineuriomas, this entity is thought to have no association with neurofibromatosis type 1 or 2 [2, 4, 20]. Ausmus et al. [7] reported a case of an extraneural perineurioma in a patient with neurofibromatosis type 1. It was initially believed that the patient in this case may have neurofibromatosis type 1 due to the enlarged IA canal and multiple oral lesions, but biopsy confirmed the lesions were of perineurial origin and CT analysis verified the diagnosis of hemimandibular hyperplasia. *NF2* FISH in this case demonstrated a vast majority of the sampled cells had no chromosome 22 aberrations. This lack of a characteristic clonal alteration supports the theory that the lesions in our case were reactive rather neoplastic. However, one point of note is that the sensitivity and specificity of the *NF2* FISH probe has not yet been assessed for perineuriomas; and, given that the performance characteristics are unclear, a neoplastic process cannot entirely be ruled out in this case.

While this case is unique given the association with hemimandibular hyperplasia, Siponen et al. [2] did report a similar case of multiple orofacial intraneural perineuriomas in a patient with hemifacial hyperplasia. The case from Siponen et al. [2] demonstrated more extensive soft and hard tissue involvement with enlargement of the soft tissue compartments, cerebellar hemisphere, and teeth—in addition to epidermal nevi—on the affected side. Also, in this report and in contrast to our case, these lesions were not located in trauma prone sites and did actually meet acceptance by Koutlas and Scheithauer [11] for true intraneural perineuriomas, based on histologic features. *NF2* FISH testing was not performed, but their case

Fig. 10 A lateral cephalometric radiograph showing the alloplastic TMJ (a). Cropped panoramic radiograph showing the dental implants following mandibular extractions (b)

showed a neural predominant proliferation without fibrous hyperplasia. Given the scarcity of such cases, a relationship between these two scenarios cannot be excluded and would require more cases to establish whether these are similar but distinct or on a spectrum.

Ultimately, given the clinical, histologic, and immunohistochemical findings of concentric, EMA-positive perineurial layers in the pseudo-onion bulbs surrounded by collagenous hyperplasia, and *NF2* FISH results, we now support the diagnosis of multiple benign neural lesions consistent with intraneural pseudoperineuriomatous proliferations for the original tongue biopsy. Moreover, we feel that the more recent excisional biopsy of the mandibular alveolar ridge lesions is also best classified as this entity. While this is the second case of multiple orofacial pseudo-onion bulb perineurial proliferations published in association with hemifacial enlargement, it is a unique clinical presentation associated with hemimandibular hyperplasia. Moreover, because we believe the lesions in our case to be intraneural pseudoperineuriomatous proliferations, this is the first published report of this lesion presenting on the alveolar ridge and also in a multifocal, synchronous pattern.

In summary, pseudoperineuriomatous proliferations are rare mimics of perineuriomas. Multiple intraneural pseudoperineuriomatous proliferations have not yet been reported using this nomenclature in the literature, and this entity has not yet been described on the alveolar ridge. The current case is the first case of pseudoperineuriomatous proliferations occurring in a patient with hemimandibular hyperplasia reported in the literature.

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