Subgemmal Neurogenous Plaque: A Clinical and Pathologic Review With Comparison to Common Head and Neck Neural Tumors

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Hussein Alnajar[1], Thomas R O'Toole[2], Diana Murro Lin[3], Samer Al-Khudari[4] and Paolo Gattuso[1]

[1]Department of Pathology, Rush University Medical Center, Chicago, IL, USA. [2]Department of Otolaryngology – Head and Neck Surgery, University of Kansas Medical Center, Kansas City, KS, USA. [3]Department of Pathology, University of Illinois at Chicago, Chicago, IL, USA. [4]Department of Otorhinolaryngology, Head and Neck Surgery, Rush University Medical Center, Chicago, IL, USA.

ABSTRACT

OBJECTIVE: In humans, subgemmal neurogenous plaques (SNPs) are normally found associated with taste buds. On histology, SNP may be mistaken for a neural neoplasm. The objective of this study was to correctly differentiate SNP among head and neck neural lesions and provide clinical and pathologic information that may assist in avoiding misdiagnosis. To our knowledge, this is the first study to provide an estimate of the degree of overdiagnoses of mucosal lesions in the head and neck mucosal area.

STUDY DESIGN: Retrospective pathology and chart review.

METHODS: All cases of head and neck mucosal neural lesions only in the mucosa of the oral cavity, oropharynx, or larynx from the pathology archives of a single urban tertiary care center between 3/2000 and 6/2017 were obtained. The pathologic and clinical data were reviewed.

RESULTS: Twenty-six cases were identified: 9 neuromas, 9 neurofibromas, 2 ganglioneuromas and 6 cases of hyperplastic subepithelial nerve bundles. The mean greatest dimension of SNPs was 2.0 mm (range 1-3 mm) and most were subjacent to taste buds (13 cases). The 20 cases of SNP involved 15 women and 5 men. Their median age was 60 years (range 30-85 years). Clinical data were available in 19 cases. The most common presenting complaint was of a painless lesion (8 patients).

CONCLUSIONS: This review confirmed the rarity of true neural neoplasms in the head and neck mucosa and estimates the risk of their over diagnosis given the possible diagnostic confusion with SNP.

KEYWORDS: subgemmal neurogenous plaque, hyperplastic subepithelial nerve plexus, taste buds

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CORRESPONDING AUTHOR: Hussein Alnajar, Department of Pathology, Rush University Medical Center, 1750 W. Harrison Street, Suite 570 Jelke, Chicago, IL 60612, USA.
Email: hussein_h_alnajar@rush.edu

Introduction

Neural neoplasms of the head and neck mucosa are not common. One study reviewed 303 neural tumors and found out that 45% cases were in the head and neck with only 10% of total in the oral cavity and submaxillary glands.[1] Some neural neoplasms such as neurofibroma and ganglioneuroma are associated with genetic disorders such as neurofibromatosis and multiple endocrine neoplasia type IIb (MEN IIb), respectively.

Taste buds are present in the circumvallate, fungiform, and foliate papillae and in a lesser number in the dorsal and lateral aspect of the tongue. Taste receptors can also be found in the soft palate, upper esophagus, the cheek, and epiglottis.[2] Taste buds are innervated by fibers originating from the glossopharyngeal and chorda tympani nerves.[3] Subgemmal neurogenous plaque is a well-described structure associated with taste buds and is occasionally detected in human tongue biopsies.[4,5] These subgemmal structures were described first by McDaniel[4] as aggregates of nerve plexus and ganglion cells in a neurofibroma-like proliferation. He suggested using the term *hyperplastic subepithelial nerve plexus*; however, the term subgemmal neurogenous plaque (SNP) was used after as it incorporates both the characteristic location and tissue of origin without implying the presence of a pathologic process.

The proposed function of the nerve fibers in SNP is for gustatory and somatosensory perception.[3] This neural complex is often multifocal and typically exhibits ganglion cells. The overlying epithelium demonstrates normal taste buds. To date, SNPs are generally considered to have no significant clinical consequences, and in most cases, this structure is identified as an incidental finding on a tongue biopsy[4] with a few reports of symptomatic cases.[6]

This study provides a review of all head and neck mucosal lesions evaluated by a single tertiary care medical center pathology department over a 17-year time span to present the clinical and pathologic findings associated with SNPs and identify the

real incidence and nature of true mucosal neural neoplasms. To our knowledge, this is the first study to provide an estimate of the degree of overdiagnoses of neural lesions in the head and neck mucosal area.

Material and Methods

Following Institutional Review Board (IRB) approval with waiver of consent, we searched our surgical pathology database for cases that had received a pathologic diagnosis of a peripheral neural tumor including neurofibroma, neuroma, traumatic neuroma, ganglioneuroma, and solitary circumscribed neuroma only in the mucosa of the oral cavity, oropharynx, or larynx between March 2000 and June 2017. Corresponding hematoxylin and eosin (H&E) slides were blinded and reviewed by an experienced pathologist (PG) who is familiar with the microscopic features of SNP. Cases that showed a biphasic pattern with a superficial unencapsulated well-circumscribed neural plexus subjacent to the surface epithelium, and a deeper portion formed by small nerve fascicles were diagnosed as SNPs. Immunohistochemistry was not used for review. Agreement between the initial diagnosis and reclassification was assessed. The electronic medical record was also reviewed to determine pertinent historical clinical findings and to examine what interventions the patients received following diagnosis. The agreement rate was defined as the concordance of an originally rendered diagnosis with the review diagnosis. The clinicopathological features of the case are summarized in Tables 1 and 2.

Results

We identified 26 cases of neural lesions in the mucosa of the oral cavity, oropharynx, or larynx in our database. Of these cases, biopsies had been obtained from the following locations: oral tongue (14 cases), oropharynx (7 cases base of tongue, 1 case of tonsillar fossa and pillar), and palate and lip (2 cases each).

Of the 26 cases identified, the most common initial diagnoses were neuroma (9 cases), neurofibroma (9 cases), proliferation of peripheral nerve or subepithelial nerve bundle (6 cases), and ganglioneuroma (2 cases). Reexamination of the cases confirmed the diagnosis of neuroma in 3 of 9 cases and neurofibroma in 3 of 9 cases. The rest of these cases were reclassified as SNP (20 cases total). The diagnosis of a head and neck mucosal neural neoplasm was confirmed in 6 of 20 or 30% of cases initially classified as a neural neoplasm.

SNPs were found in biopsies from 15 women and 5 men with a median age of 60 years (range 30-85 years). The locations of theses SNP were as follows: 10 cases oral tongue (50%), 8 cases base of tongue (40%), 1 case each glottis and tonsillar fossa (5%). The mean greatest dimension of SNPs was 2.0 mm (1-3 mm in diameter). In most of the cases, taste buds were identified in the slides (13 cases). Taste buds (Figure 1) are quite prominent ovoid lightly stained bodies, which extend perpendicularly from the basement membrane and communicate with the surface through a small opening (gustatory pores).

Clinical data were available for 19 of the SNP cases in the electronic medical record. Most patients were symptomatic with 7 patients presented with sore throat or a tender lesion, 5 had a painless lesion, while 6 patients presented with different unrelated complains including weight loss (2), otalgia, globus sensation dysphonia, dysphagia, choking, tonsilloliths, or altered sensation. One patient was entirely asymptomatic. Two cases were identified on biopsies obtained in searching for an unknown primary squamous cell carcinoma. The clinicopathological features of the patients are summarized in Table 1.

Two patients had an incidentally diagnosed neural lesion found on a biopsy that also contained a squamous cell carcinoma, and seven patients underwent biopsies during ongoing surveillance for head and neck cancer. Of these 7 patients, two patients had persistent pain or tenderness after their biopsy and would go on to have subsequent biopsy that confirmed recurrent squamous cell carcinoma after their initial biopsy demonstrated a benign mucosal neural neoplasm (2 neuromas).

In our study, three cases were confirmed to be traumatic neuroma with a recent history (6-8 months) of a prior head and neck procedure. The 3 neurofibromas were superficially located well-circumscribed non-encapsulated and no other neural lesions were identified in these patients. Two cases were called initially as ganglioneuroma were found to be SNPs with ganglion cells. The clinicopathological features of the confirmed mucosal neural neoplasms are summarized in Table 2.

Discussion

After McDaniel[4] described the subgemmal structure, he called subepithelial nerve plexus in 12 tongue biopsies; a few recent reports started recognizing SNPs as a unique structure in tongue biopsies. Studies describing SNPs microscopically and clinically are scarce.

SNPs are quite small. In this study, the average size was only 2 mm and they were found to be symptomatic in some cases or can be incidentally seen on biopsies taken for other different reason, making the recognition of these normal anatomical structures on these biopsies important. SNPs appear to be more common than previously considered as these are normal structures in the tongue associated with taste buds.[7] SNP is characterized by its unique biphasic pattern with superficial neurofibroma-like area and deeper neuroma-like areas, which helps differentiate it from other neural lesion that can be found in the head and neck such as ganglioneuroma, neurofibroma, traumatic neuroma, and mucosal neuroma.

Traumatic neuroma is a reactive but non-neoplastic proliferation of a nerve occurring in response to injury or surgery.[8,9] In the oral cavity, the injury may occur from a surgical procedure such as a tooth extraction, from a local anesthetic injection, or from trauma,[1] which results in transection injury of a sensory nerve resulting in inflammation and scarring in the area of injury. As the proximal nerve segment proliferates in an attempt to regenerate into the distal segment, it becomes entangled and trapped in the developing scar, producing a

Table 1. Summary of the clinical and pathologic features of identified subgemmal neurogenous plaques.

CASE NO.	SEX	AGE	SITE	FOLLOW-UP (MONTHS)	GANGLION CELLS PRESENT	TASTE BUDS PRESENT	CHRONIC INFLAMMATION	CLINICAL PRESENTATION
1	F	63	Oral tongue	1	No	Yes	No	No clinical data available
2	F	35	Base of tongue	4	Yes	No	Yes	Found during cancer surveillance, patient had tenderness to palpation at the right base of tongue, pain persisted after biopsy and recurrence eventually discovered
3	M	50	Base of tongue	62	No	Yes	Yes	Non-painful tongue lesion that fluctuated in appearance for 2 years
4	F	62	Oral tongue	62	No	Yes	Yes	Burning pain of the left tongue worsening over 2 years
5	F	38	Oral tongue	16	Yes	No	No	6 mm tender oral tongue lesion found on dental examination in this patient with h/o oral cavity cancer, eventually patient was re-biopsied and found to have invasive SCC in the setting of CIS
6	F	46	Oral tongue	50	No	No	Yes	Non-painful lateral tongue lesion for 1 week
7	F	53	Glottis	22	No	Yes	Yes	Dysphonia and globus sensation
8	M	41	Oral tongue	1	Yes	Yes	Yes	Non-painful, persistent right lateral tongue fluctuating in size for 6 months
9	F	74	Base of tongue	18	Yes	Yes	Yes	Asymptomatic, persistent PET scan uptake on post-treatment scan following treatment for H&N SCC
10	M	66	Oral tongue	20	No	Yes	Yes	Unknown primary H&N cancer biopsied in attempt to find the primary
11	F	76	Tonsillar fossa	12	No	No	No	Ear pain in the setting of Cis of the oropharynx found on excision specimen
12	M	85	Base of tongue	12	Yes	No	No	Dysphagia and weight loss in the setting of suspected oropharynx cancer
13	F	69	Base of tongue	11	Yes	Yes	Yes	Right-sided otalgia and right base of tongue lesion on examination
14	F	57	Base of tongue	8	No	Yes	No	Left throat discomfort for 2 months of fluctuating intensity
15	F	43	Base of tongue	8	Yes	No	No	Intermittent throat pain, tonsilloliths, choking, weight loss
16	F	56	Oral tongue	9	No	Yes	Yes	Non-painful tongue lesion
17	M	73	Base of tongue	5	No	No	No	Left-sided odynophagia and neck pain in a patient with h/o left-sided oropharynx cancer
18	F	66	Oral tongue	1	Yes	Yes	Yes	Altered sensation of lateral tongue (numb and gritty)
19	F	30	Oral tongue	2	Yes	Yes	Yes	Sore on tongue for 1 week
20	F	62	Oral tongue	1	Yes	Yes	No	Left-sided tongue pain for 3 weeks and change in tongue texture

Abbreviations: SCC, squamous cell carcinoma; CIS, Carcinoma in situ; PET, positron emission tomography; H&N, Head and neck.

disorganized composite mass of fibrous tissue, Schwann cells, and axons. Clinically, it presents as a firm tender or painful nodule.[1] Histologically, it consists of numerous haphazard nerve fibers of varying sizes, axons, and Schwann cells embedded in scar tissue.[1,10] Traumatic neuromas are sometimes confused with SNP. However, the intraoral location, the identification of all elements of the nerve fascicles, and the presence of a scar related to a prior procedure plus the lack of the

Table 2. Summary of the clinical features of the confirmed mucosal neural neoplasms of the head and neck mucosa.

CASE NO.	SEX	AGE	SITE	DIAGNOSIS	FOLLOW-UP TIME (m:MONTHS)	HISTORY OF PREVIOUS PROCEDURE	TIME AFTER PRIOR PROCEDURE	CLINICAL PRESENTATION
1	M	65	Tongue	Neuroma	N/A	Excision	Unknown	Persistent uptake in the base of tongue on post-treatment PET scan following oropharynx cancer treatment
2	F	8	Tongue	Neuroma	157	Excision	8m	Non-painful ventral tongue lesion at site of prior excision
3	M	38	Lower lip	Neuroma	N/A	Excision	6m	Fluctuating lower lip swelling and fullness on examination noted under prior mucocele excision scar
4	F	47	Palate	Neurofibroma	187m	N/A	N/A	Lesion at the junction of the hard and soft palate on the left in a smoker
5	F	32	Tongue	Neurofibroma	1m	N/A	N/A	Persistent non-painful tongue lesion of 5-month duration
6	M	26	Palate	Neurofibroma	1m	Tooth extraction	Unknown	Persistent non-painful lesion of the palate for 1 year

Abbreviation: PET, positron emission tomography.

biphasic pattern make them distinguishable from SNP. In our study, the traumatic neuroma cases had a recent history of a prior head and neck procedure.

Solitary circumscribed neuroma (SCN), also called palisaded, encapsulated neuroma, is a common benign lesion with no association with neurofibromatosis or MEN2b syndrome. Most SCN occurs in the skin and mucosal sites of the face such as cheeks, nasolabial folds, and nose with, oral lesions being a less common site. Clinically, SCNs are small and painless. Histologically, they are sharply circumscribed dermal nodule, consist of a proliferation of Schwann cells arranged in fascicles with intervening clefting artifact between bundles and accompanied by a variable number of axons. Most lesions are not fully encapsulated and are only focally palisading.[11,12] The bundled arrangement of Schwann cells, the very thickened perineurial capsule, and the clefting artifact will not be seen in SNP cases and will help differentiating the two in cases of confusion. Although these are common when compared with traumatic neuromas, ganglioneuromas, and mucosal neuromas, no cases were found in our study.

On the other hand, mucosal neuromas of the lips and mouth are part of MEN IIb an inherited autosomal-dominant trait associated with pheochromocytoma, C-cell hyperplasia, medullary thyroid carcinoma, and parathyroid hyperplasia. Identification of these lesions and differentiating them from other neural tumors and SNPs is important, since they can be a part of this life-threatening syndrome. Histologically, they are rarely solitary and characterized by tortuous bundles of nerve with a prominent perineurium, surrounded by normal connective tissue in the submucosa of the oral cavity.[8] The frequent presence of multiple lesions in case of mucosal neuroma, lack of the biphasic pattern, the haphazard distribution, and the prominent thickening of perineurium surrounding nerve bundles facilitate differentiating mucosal neuromas from SNPs.

Neurofibroma may occur as circumscribed solitary lesions or as multiple lesions as part of the syndrome neurofibromatosis (von Recklinghausen's disease of skin). The cause of solitary neurofibroma is unknown. Neurofibromatosis, on the other hand, is inherited as an autosomal-dominant trait. It has variable expressivity and about half the cases appears after spontaneous mutation.[1] Two subsets have been defined: one associated with the NF1 gene and the other with the NF2 gene. Oral lesions are typically associated with NF1. This condition includes multiple neurofibromas, cutaneous café-au-lait macules, freckling in the axillary or inguinal regions, optic glioma, Lisch nodules, and a distinctive osseous lesion. Histologically, both lesions, unlike SNPs, lack zonal pattern and show the same microscopic features with spindle-shaped cells that have fusiform or wavy nuclei found in a delicate connective tissue matrix with no deep neuroma-like areas. Mast cells are characteristically scattered throughout the lesion. Solitary lesions are well-circumscribed while the one in neurofibromatosis shows no distinct margin between the neurofibroma and the surrounding tissue. The plexiform neurofibroma is a histologic subtype that is highly characteristic of neurofibromatosis. In this variety, a myxomatous matrix supports extensive interlacing masses of nerve tissue.

Finally, ganglioneuromas are rare benign tumors of neurogenic origin. They usually present in patients between 1 and 30 years of age with a slight female predominance. They are most commonly localized in posterior mediastinum (34%), retroperitoneum (27%), adrenal gland (19%), cervical (2%), and parapharyngeal area (1%).[8] Unusual sites include the spermatic cord, heart, bone, and intestine.[13] Ganglioneuromas most often

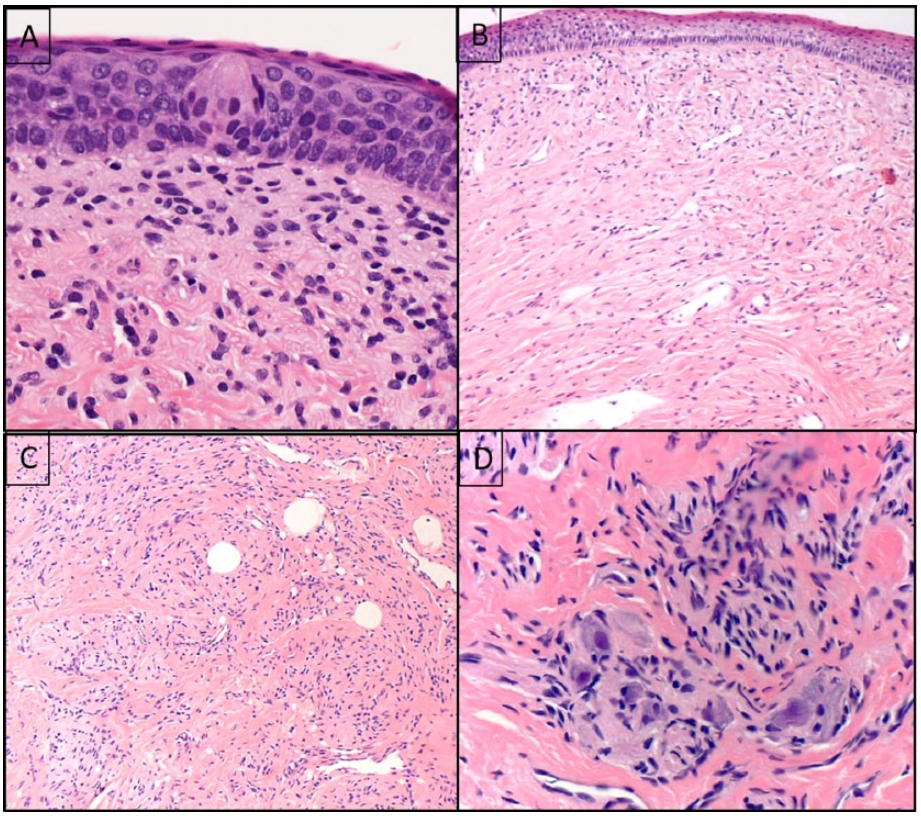

Figure 1. Subgemmal neurogenous plaques (SNPs) are associated with taste buds in majority of cases (A). Histologically, they show a biphasic pattern. The superficial zone is characterized by ovoid to spindled cells in a collagenous stroma that runs under the epithelium (neurofibroma-like pattern) (B). The deeper zone is characterized by small nerve fascicles (neuroma-like pattern). (C) Occasional ganglion cells can be seen in these lesions confusing them with ganglioneuroma (D).

are asymptomatic. Ganglioneuromas have been rarely reported in the tongue.[14,15] Clinically, cervical ganglioneuromas usually cause sign and symptoms related to compression of nerves or vessels of the neck.[13] Histologically, they are well-defined and encapsulated masses, characterized by clusters of mature ganglion cells surrounded by fascicles of Schwann-like cells with decreased number of axons. The ganglion cells are relatively mature with lack of satellite cells and Nissl bodies.[8,13] Elements of immature neurogenic tumors can be seen in about 25% of ganglioneuromas, which indicates malignant or potentially malignant behavior. It is hypothesized that neuroblastic tumors undergo a maturational process or spontaneous regression of neuroblastoma to ganglioneuroma.[8] The two cases in our study originally called ganglioneuroma were found in tongue biopsies from female patients outside of the typical age range (38 and 72 years). Review of these cases revealed that they are non-encapsulated SNPs with ganglion cells; taste buds were not seen in the overlying epithelium.

Awareness of SNPs is important, as they are unique subgemmal structures that are associated with taste buds and usually found in tongue biopsies that show distinctive biphasic pattern, with superficial neurofibroma-like plaques and deeper neuroma-like areas. Clinically, they can present as painful or painless lesions and can be discerned during surveillance for a head and neck carcinoma. Recognizing this entity by pathologist as well as clinicians as a normal anatomical structure is important to avoid overcalling them as neural neoplasms. The results of this study show that neural tumors are rare in the head and neck, particularly so when malignant. Caution should be exercised before calling ganglioneuromas, neurofibromas, mucosal neuromas, or neuromas in this anatomical region.

Author Contributions

Conceived and designed the experiments: HA, TO, DL, SA and PG. Analyzed the data: HA, TO and DL. Wrote the first draft of the manuscript: HA. Contributed to the writing of the manuscript: HA, TO and DL. Agreed with manuscript results and conclusions: HA, TO, DL, SA and PG. Jointly developed the structure and arguments for the paper: AHA, TO, DL, SA and PG. Made critical revisions and approved final version: TO, DL, SA and PG. All the authors reviewed and approved the final manuscript.

ORCID iD

Hussein Alnajar https://orcid.org/0000-0003-0046-8538

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