



# Histomorphometric characterization of subgemmal neurogenous plaques

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**Objectives.** The aim of this study was to characterize the histomorphometric features of subgemmal neurogenous plaques (SNPs) to better understand their relationship to surrounding microanatomy included in the tissue biopsy samples of the tongue.

**Study Design.** A 12-year retrospective study on the files of 3 oral pathology centers yielded 28 SNPs. Hematoxylin and eosin–stained sections were used for histologic analysis, and immunohistochemical staining for S100 protein was performed to better characterize the neural structures. Slides were scanned and histomorphometric analysis carried out using ImageScope software.

**Results.** Twenty-one women (75%) and 6 men (21.4%) comprised the sample (mean age 46.4 and 49 years, respectively). Twenty cases (71.4%) were juxtaposed to the tongue epithelium and 16 cases (57.1%) were associated with lymphoid tissue. The mean area of the SNPs was 0.160 mm<sup>2</sup>, and the mean distance to the overlying epithelium was 0.312 mm.

**Conclusions.** SNPs are normal neural structures located on the posterior border of the tongue that represent a non-neoplastic regional anatomic variation. In some cases, signs or symptoms may be present, and further investigation should be performed. Pathologists should be aware of this entity to avoid confusion with neural lesions. (Oral Surg Oral Med Oral Pathol Oral Radiol 2017;123:477-481)

Subgemmal neurogenous plaques (SNPs) are neural structures found in the posterolateral region of the tongue, that were originally described by McDaniel<sup>1</sup> as nerve fascicles and aggregates of ganglion cells juxtaposed to taste buds. Associated clinical symptoms and signals, such as burning sensation, erythema, ulcers, white patches, and hyperplastic nodule, are uncommon.<sup>2,3</sup> Because the clinical and histopathologic features of SNPs can vary from patient to patient, their structure may represent a diagnostic challenge for clinicians and pathologists,<sup>2</sup> occasionally leading to misdiagnosis.<sup>3,4</sup>

Only 2 other previous small case series describe the morphologic features of SNPs. McDaniel<sup>1</sup> performed a histomorphologic study on 12 SNPs and described the relationship between SNPs and taste buds, the diameter

of SNPs, and the mean number of ganglion cells. The author concluded that these neural structures represented a variation in regional anatomy. More recently, Triantafyllou and Coulter<sup>4</sup> reviewed 16 SNPs through histopathology and immunohistochemistry and described the cellular components of SNPs as well as their morphologic organization. Both groups concluded that pathologists should be aware of the variable morphologic features of SNPs to avoid confusion with other neural lesions, such as neurofibromas or traumatic neuromas, and thus misdiagnosis.

The aim of this multicenter collaborative study was to characterize the histomorphometric and immunohistochemical features of SNPs to better understand their relationship with surrounding morphologic structures of the tongue.

This work was supported by grants from the State of São Paulo Funding Agency (FAPESP).

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Received for publication Jul 15, 2016; returned for revision Oct 28, 2016; accepted for publication Dec 30, 2016.

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2212-4403/\$ - see front matter

<http://dx.doi.org/10.1016/j.oooo.2016.12.014>

## Statement of Clinical Relevance

Subgemmal neurogenous plaques are considered normal findings representing a non-neoplastic regional anatomic variation. In some cases, signs or symptoms might be present, and further investigation should be performed. Pathologists should be aware of this entity to avoid confusing it with other lesions.

## MATERIAL AND METHODS

The study was approved by the Ethics Committee for Human Studies, Piracicaba Dental School, Brazil (protocol number: 132/2014).

### Patients and clinicopathologic findings

A 12-year retrospective review (January 2002 to December 2013) of the files of the oral pathology departments at the University of Campinas (Piracicaba Dental School, Piracicaba, Brazil), the Federal University of Rio Grande do Sul (Porto Alegre, Brazil), and the Federal University of Pará (Belém, Brazil) was performed, and 28 SNP cases were retrieved.

Demographic data (age and gender), location of the lesion, and original clinical and histologic diagnoses were collected from the biopsy requisitions and laboratories reports.

### Histomorphometric study

After specimen selection, new 5- $\mu$ m-thick sections were obtained and subsequently stained with hematoxylin and eosin (H&E).

For quantitative analysis and distribution of the nerve plexus and ganglion cells, H&E slides and immunohistochemical slides (1 slide per case) were scanned using an Aperio ScanScope CS scanner (Aperio Technologies Inc., Vista, CA). The mean distance between SNPs and the overlying epithelium was assessed by drawing a straight line from the periphery of the SNP to the basal membrane of the epithelium (most inferior point of the closest epithelial ridge). The relationship between SNPs and lymphoid tissue was assessed by drawing a line from the periphery of the SNP to the periphery of lymphoid tissue. Lymphoid tissue was characterized by aggregates of lymphocytes in the lamina propria, with or without reactive germinal centers. When the SNP was in close contact with the epithelium or lymphoid tissues, it was considered to be juxtaposed to these structures. The mean area of the SNPs was calculated by drawing a line that surrounded the nerve fibers of the SNPs. All these analyses were done by using the Aperio ImageScope software (Aperio Technologies Inc., Vista, CA).

### Immunohistochemistry

Immunohistochemical analyses were performed on 3- $\mu$ m-thick sections, which were dewaxed with xylene and hydrated in an ethanol series. Antigen retrieval was carried out using a citrate buffer, and endogenous peroxidase activity was blocked with 10% hydrogen peroxide. After washing in phosphate-buffered saline (pH 7.4), slides were incubated overnight with the primary monoclonal antibody anti-S100, diluted

**Table I.** Clinical and histopathologic diagnoses

	Diagnoses	
	Clinical	Histopathologic
SNP	2 (7.1%)	3 (10.7%)
Papillitis	4 (14.3%)	1 (3.6%)
SCC	3 (10.7%)	3 (10.7%)
Lichen planus	1 (3.6%)	1 (3.6%)
Traumatic lesion	1 (3.6%)	—
Hyperkeratosis	—	2 (7.1%)
Leukoplakia	1 (3.6%)	—
Erythroplakia	1 (3.6%)	—
Lingual tonsil	—	2 (7.1%)
Lymphoid hyperplasia	—	4 (14.3%)
Lymphoepithelial cyst	—	2 (7.1%)
Descriptive	—	8 (28.7%)
NA	15 (53.5%)	2 (7.1%)

NA, Not available; SCC, squamous cell carcinoma.

1:10000 (Dako Corp., Carpinteria, CA). All slides were subsequently exposed to the avidin–biotin complex and horseradish peroxidase reagents (LSAB Kit – DakoCytomation, Dako, Glostrup, Denmark) and diaminobenzidin tetrahydrochloride (DAB, Sigma, St. Louis, MO), and subsequently counterstained with Carazzi hematoxylin. Negative control was obtained by omitting the primary antibody, and tonsil tissue was used as positive control.

## RESULTS

### Clinical findings

Of the 28 cases included in the study, 21 (75%) were women and 6 (21.4%) were men; in 1 case (3.6%), information about gender was not available. Age at diagnosis ranged from 13 to 77 years (mean age 49 years for males and 46.4 years for females; overall mean age 45.3 years).

Clinically, only 2 cases (7.1%) were initially suspected to be SNPs. The most frequent clinical diagnosis was lingual papillitis (4 cases [14.3%]), followed by oral squamous cell carcinoma (SCC; 3 cases [10.7%]).

### Histologic findings

Histologically, 3 cases (10.7%) were initially diagnosed as SNPs with the presence of no other lesion, 4 cases (14.3%) were diagnosed as lymphoid hyperplasia, 3 cases (10.7%) represented SCCs with SNP adjacent to the tumor cells, 2 cases (7.1%) were diagnosed as hyperkeratosis, 2 cases (7.1%) as lingual tonsil, 2 cases (7.1%) as lymphoepithelial cysts, 1 case (3.6%) as papillitis, and 1 case (3.6%) as lichen planus. Of the remaining 10 cases, 8 (28.7%) received a descriptive diagnosis, and in 2 cases (7.1%), the microscopic diagnosis was unavailable (Table I).

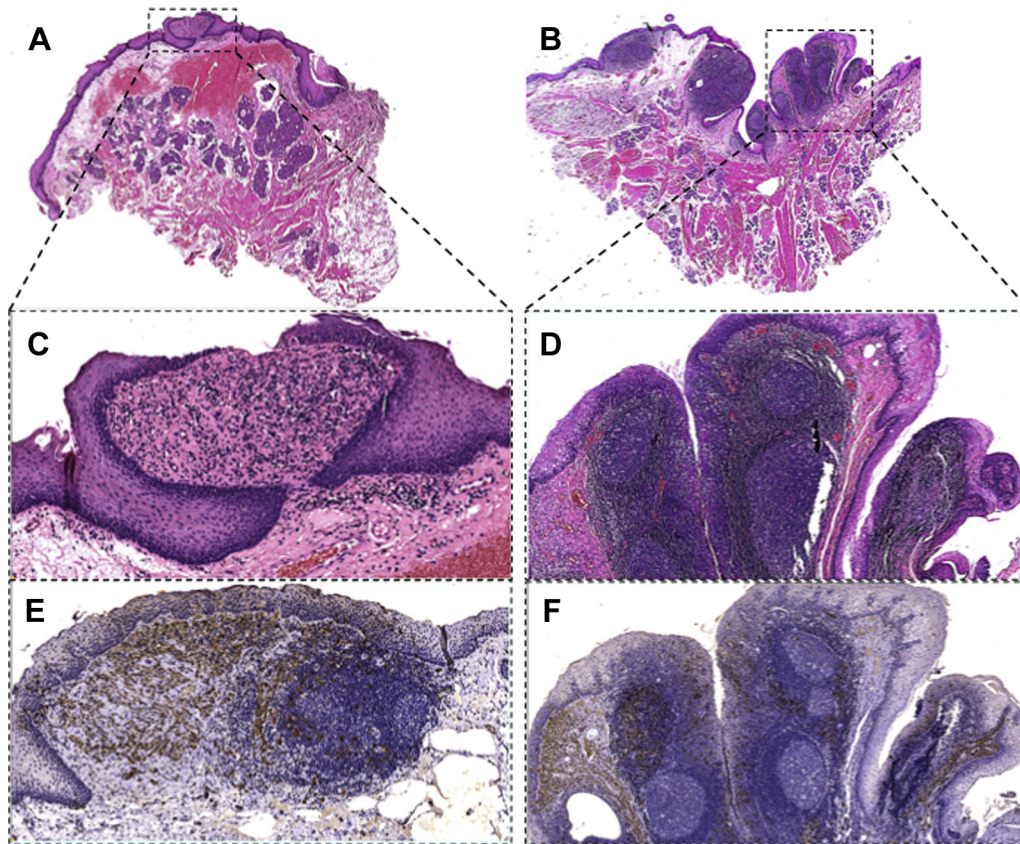


Fig. 1. **A-D**, Sublingual neurogenic plaques showing nerve fascicles and aggregates of lymphoid cells located in the lamina propria (hematoxylin and eosin [H&E], original magnification  $\times 40$  and  $\times 250$ ). A high-resolution version of the images is available as eSlides: VM03563 and VM03565. **E and F**, Immunohistochemistry showing spindle neural cells positive for S-100 (immunohistochemistry [IHC], original magnification  $\times 250$ ). A high-resolution version of the images is available as eSlides: VM03564 and VM03567.

### Histomorphometric findings

From a microscopic point of view, SNPs were composed of a superficial circumscribed neural plexus parallel to the surface of the epithelium and a deeper portion formed by small nerve fascicles located in a stroma of fibrous connective tissue. Ganglion cells were not present in the samples. Lymphoid tissue with reactive germinal centers were frequently associated with these neural structures (Figure 1A-1D and Figure 2A and 2B). The immunoprofile of SNPs was characterized by brisk positivity to S100, and all spindle neural cells were positive for S-100, revealing a cytoplasmic brownish color. Immunostained cells comprise approximately 10% of the slides showing no staining intensity variation among different cases (Figure 1E and 1F).

The mean area of the 28 cases of SNPs was  $0.160 \text{ mm}^2$  (range  $0.005746\text{-}0.707383 \text{ mm}^2$ ). In 20 cases (71.3%), neural structures were found juxtaposed to the oral mucosa. In the remaining 8 cases (28.7%), the mean distance between the neural structures and the epithelium was

$0.312 \text{ mm}$  (range  $0.166\text{-}0.636 \text{ mm}$ ), comprising deeper portions of the SNP. With regard to the relationship between the SNP and lymphoid tissue, 10 cases (35.8%) showed neural structures in close relationship to lymphoid tissue, in 6 cases (21.4%), the mean distance was  $0.6613 \text{ mm}$  (range  $0.0027\text{-}0.1303 \text{ mm}$ ), and in 12 cases (42.8%), lymphoid tissue was absent (Table II).

### DISCUSSION

SNPs of the tongue are recently described structures that are characterized by the presence of nerve plexus associated with taste buds in the posterolateral border of the tongue.<sup>1,5</sup> Several studies identified SNPs in biopsy specimens<sup>1,4</sup>; however, little is known about these structures.<sup>3</sup> This study attempted to better understand and characterize SNPs by using digital analyses and immunohistochemistry.

With regard to the nature of SNPs, some authors believe that they may be reactive neuronal dysplasias,<sup>4</sup> incidental findings,<sup>1</sup> or normal structures associated with taste buds.<sup>2</sup> Taking together the information

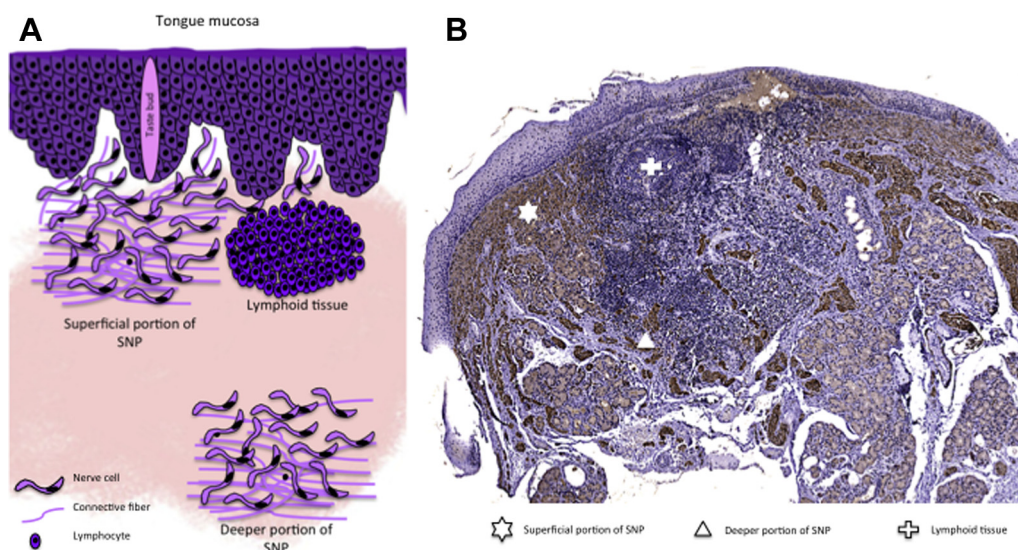


Fig. 2. **A** and **B**, A schematic diagram showing the morphology of subgemmal neurogenous plaques (SNPs). SNPs were composed of a superficial circumscribed neural plexus parallel to the surface of the epithelium and a deeper portion formed by small nerve fascicles. Lymphoid tissue was characterized by accumulations of lymphocytes in the lamina propria. A high-resolution version of the image is available as eSlide:VM03566.

**Table II.** Morphologic characterization of subgemmal neurogenous plaques (SNPs)

Distance from SNP to epithelium (mm)	n (%)	Distance from SNP to lymphoid tissue (mm)	n (%)
Juxtaposed	20 (71.3%)	Juxtaposed	10 (35.8%)
0.312 mm (0.166-0.636 mm)	8 (28.7%)	0.6613 mm (0.0027-0.1303 mm)	6 (21.4%)
		Absence of lymphoid tissue	12 (42.8%)

acquired from these 28 cases and from previous cases reported in the literature, we could infer that SNPs may be considered normal structures that sometimes give rise to symptoms.<sup>2,5</sup>

Although uncommon, symptoms, such as burning sensation and pain, may be associated with SNPs. Gueiros et al.<sup>2</sup> first reported the presence of clinical symptoms associated with SNPs. These authors' analyzed 7 cases of SNPs, and in 5 of them, pain and burning were present. In the current series, only 2 cases (7.1%) were diagnosed clinically as SNP on the basis of the presence of burning sensation; the remaining 26 cases (92.9%) received different clinical diagnoses, and no symptoms were reported. In the 2 cases with a clinical diagnosis of SNP, the epithelium was juxtaposed to the plaque, and the average distance to lymphoid tissue was 0.2902 mm.

Histologically, SNPs are characterized by spindle neural cells arranged parallel to the epithelium, and ganglion cells may also be found throughout the structure.<sup>4</sup> It is important to recognize SNPs to avoid confusion with other neural lesions, such as traumatic neuromas and neurofibromas, and thus misdiagnosis.<sup>2</sup> As shown in Table I, only 3 cases (10.7%) were histologically diagnosed as SNPs, and the remaining

25 cases (89.3%) were diagnosed as other lesions, and the SNPs were present in the specimen. Val-Bernal et al.<sup>3</sup> described a case of a male patient diagnosed with disseminated lung SCC and who also presented pseudoepitheliomatous hyperplasia associated with SNPs on the posterior border of the tongue. They concluded that although SNPs do not have major clinical consequences, pathologists should be aware of this lesion to avoid misdiagnosing it as carcinomatous neural invasion.

Palazzolo et al.<sup>6</sup> described the presence of structures similar to the juxtaoral organ of Chievitz (JOC) associated with SNPs. JOC is characterized by epithelial nests associated with peripheral nerves in the head and neck region.<sup>7</sup> JOC is usually located in the buccotemporal space<sup>8</sup>; however, there are cases described in other head and neck sites, such as the mandible and the maxilla.<sup>9,10</sup> Fonseca et al.<sup>11</sup> reported a case of SNP associated with epithelial nests dispersed in connective tissue, showing no signs of atypia or mitotic figures. Although these structures are considered normal residual embryologic structures, pathologists should be aware of the existence of the JOC to avoid confusing SNPs with other lesions, such as SCC. No case of JOC-associated SNP was observed in our study.

Few papers attempted to provide a morphologic description of SNPs. McDaniel was the first author to characterize this structure morphologically. He concluded that the nerve plexus and ganglion cells were associated with taste buds and the tongue epithelium.<sup>1</sup> Other reports regarding SNPs have focused on the immunoprofile of the structure.<sup>2-6</sup>

Apparently, from a microscopic point of view, SNPs are composed of a superficial circumscribed neural plexus, which is placed parallel to the surface of the epithelium. Interestingly, some cases may also present a deeper portion formed by small nerve fascicles.

Several studies used a wide range of antibodies to characterize the presence of neural filaments.<sup>2,4,5</sup> In the present study, the immunoprofile of the lesion showed spindle cells of the superficial neural component positively stained for the antibody anti-S100. Although SNPs are considered normal structures, they remain a diagnostic challenge.

Since SNP is considered a normal structure when there are no signs or symptoms associated, no treatment is required. However, if the patient complains of burning sensation or pain, an adequate investigation should be carried out aiming to establish the correct diagnosis. In such cases, treatment consists of conservative surgical removal of the symptomatic area.<sup>2</sup>

## CONCLUSIONS

SNPs represent normal structures of the microanatomy of the posterior border of the tongue. Most probably, they represent an underrecognized variant of the tongue. Pathologists should be aware of this entity to avoid misdiagnosis.

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