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Subgemmal neurogenous plaques of the tongue: a systematic autopsy study

JOSÉ-FERNANDO VAL-BERNAL[1)], MARÍA-FRANCISCA GARIJO[2)], NATALIA FONTANIL[3)]

[1)]*Pathology Unit, Department of Medical and Surgical Sciences, University of Cantabria–IDIVAL, Santander, Spain*

[2)]*Royal Academy of Medicine of Cantabria, Santander, Spain*

[3)]*Service of Anatomical Pathology, Marqués de Valdecilla University Hospital and IDIVAL Research Institute, Santander, Spain*

Abstract

Subgemmal neurogenous plaque (SNP) is a subepithelial nerve plexus associated with taste buds, occasionally observed in tongue biopsies. There is no evaluation of the prevalence of this structure in the general population. We present a systematic study of samples obtained at random from the dorsal portion of the oral tongue in 205 consecutive complete autopsies. Each sample was about 15 mm long and 10 mm thick. Four hundred fifty-eight samples were routinely obtained and an average of 2.23±0.88 samples per case (range 1–7) was collected. The total number of SNPs observed was 556, with a mean of 2.71±2.68 per case (range 0–16). This means that for every 15 linear mm of the oral tongue, approximately 2.7 SNPs can be present. SNPs display several ages, and they do not show sex differences. The mean size of these structures was 2.1±0.94 mm (range 0.6–3.6 mm). SNP is characterized by its unique neural, zonal pattern with a superficial neurofibroma-like area and a deeper neuroma-like area. Special features of the SNPs include the presence of taste buds (49.1%), ganglion cells (26.3%), dilated thin-walled vessels (11.3%), salivary gland excretory ducts emptying on the surface of the papillae (6.1%), moderate-severe inflammatory infiltrate (6.8%), presence of lymphoid tissue in the vicinity (7.0%), and hyperplasia of the epithelial cover with pseudoepitheliomatous appearance (7.0%). The differential diagnoses include schwannoma, neurofibroma, ganglioneuroma, traumatic neuroma, mucosal neuroma, and squamous cell carcinoma. SNPs are small, normal structures that may undergo hyperplasia and are usually seen incidentally.

Keywords: hyperplastic subepithelial nerve plexus, subgemmal neurogenous plaque, pseudoepitheliomatous hyperplasia, tongue, oral cavity.

Introduction

Lingual subgemmal (subepithelial) neurogenous plaques (SNPs) are biphasic neural structures juxtaposed to taste buds. They have been described in the circumvallate, fungiform, and foliate papillae. These structures were originally described as tortuous neural proliferation with mature ganglion cells associated with taste buds in the human tongue by McDaniel in 1999 [1]. Triantafyllou & Coulter (2004) [2] described a zonal pattern of plaque organization. The superficial zone contiguous with the covering epithelium of the papilla shows elongated spindle and wavy cells intermingled with variable amounts of collagen. The deeper zone is made up of nerve bundles encased by thin perineurium with the occasional presence of mature ganglion cells. SNPs have typically been reported in the posterolateral borders of the tongue in the fungiform, foliate, and circumvallate papillae as incidental microscopic findings [3–10]. These neural structures are considered, with few exceptions, to have no significant clinical consequences. Thus, the main problem with SNPs is their overdiagnosis as neural neoplasms [2]. However, SNPs are occasionally associated with focal burning sensations, pain, or discomfort as the main symptoms [3, 4].

The experience of this microscopic neural structure is mostly limited to case reports or small series of studies in lingual samples adjacent to neoplasms or other unrelated processes.

An additional problem arose with the description of lingual pseudoepitheliomatous (pseudocarcinomatous) hyperplasia (PEH) associated with SNP [11]. Some authors considered that the epithelial proliferation associated with the plaque was neural in character and suggested the term 'neuroepithelial structure' (NES) to designate it. In these cases, the presence of epithelial nests closely associated with the SNP was considered reminiscent of the juxtaoral organ of Chievitz (JOOC) [12–15]. Those authors postulated that the epithelial nests were remnants of embryological structures involved in tongue formation. However, NESs are epithelial in nature and cannot be defined as neuroepithelial. Thus, NES is a misnomer because of its pure epithelial phenotype [16]. Furthermore, JOOC is a normal anatomical structure localized within the soft tissues of the retromolar trigone that presumably serves as a mechanosensory unrelated to the tongue [17–20].

There is no evaluation of the prevalence of SNPs in the general population. A systematic study of SNPs in normal tongues of the general population is necessary to evaluate their frequency, their morphological variation, and their associations to complete the knowledge of these structures. Thus, some authors have commented that autopsy studies of normal tongues could be helpful [4].

Aim

This study aims to contribute to the knowledge of the SNP and to present a systematic study of this structure in tongues obtained routinely at complete, consecutive autopsies, especially in adults without clinical lesions in the oral cavity, with no visible alterations in the tongue during the autopsy, or absence of associated lesions in the histopathological (HP) study.

Patients, Materials and Methods

Routine samples of the dorsal portion of the oral tongue were taken at random from 205 consecutive complete autopsies in which the tongue was removed. This retrospective study includes the autopsies performed from January 2006 to July 2010. The selected autopsies met the following three criteria: (*i*) the patients did not present clinical lesions in the oral cavity; (*ii*) no visible alterations in the tongue were observed during the autopsy; and (*iii*) there was an absence of associated lesions in the HP study. The samples comprised most of the thickness of the tongue, from the mucosa to the deep muscle layer. The total number of samples was 458. The number of samples per case ranged from 1 to 7, with a mean ± standard deviation 2.23±0.88. Each sample was about 15 mm long and 10 mm thick.

The tissue had been routinely processed and stained with Hematoxylin–Eosin (HE). For this study, all paraffin-embedded blocks were sectioned and immunohistochemically stained for S100 protein. In eight selected blocks, the following immunostainings were performed: neurofilament (NF) protein, cluster of differentiation 34 (CD34), epithelial membrane antigen (EMA), and cytokeratin 7 (CK7). Immunohistochemical (IHC) staining was accomplished using the EnVision FLEX+ Visualization System (Dako, Agilent Technologies, SL, Las Rozas, Madrid, Spain). The IHC reaction was carried out using appropriate tissue controls for the antibodies utilized. Automatic staining was performed on a Dako Omnis stainer (Agilent Technologies, SL). Antibodies used in this study are detailed in Table 1.

Table 1 – ***IHC antibodies used in this study***

Antibody	Source	Clone	Dilution	Retrieval solution pH (Dako)
S100 protein	Abcam	Ab55787	1:100	High
CD34	Dako	QBEnd 10	FLEX RTU	High
NF protein	Dako	2F11	FLEX RTU	Low
EMA	Dako	E29/EP1	FLEX RTU	High
CK7	Dako	OVLT12/30	FLEX RTU	High

Abcam, Cambridge, UK; CD34: Cluster of differentiation 34; CK7: Cytokeratin 7; Dako (Agilent Technologies, SL, Las Rozas, Madrid, Spain); EMA: Epithelial membrane antigen; IHC: Immunohistochemical; NF: Neurofilament; RTU: Ready-to-use.

In 25 consecutive cases, the greatest dimension of the SNP outline was measured using a microscope Vernier scale [21].

The different variables in the study are included in Table 2. Demographic data were collected from the autopsy records. All histological parameters were evaluated by a single pathologist (JFVB). The data were analyzed by descriptive statistics using the Microsoft Excel spreadsheet. A Student's *t*-test was used to compare the means of the two groups (male and female).

Table 2 – ***Incidence of the different variables in the study population***

No. of tongues examined	205		
Mean age [years]	65±15.77	Range 0.25–92	
Sex	141 (68.8%) males	64 (31.2%) females	M:F ratio, 2.2:1
No. of samples	458	Mean 2.23±0.88 per case	Range 1–7
No. of SNPs	556	Mean 2.71±2.68	Range 0–16
No. of samples with SNPs	412 (90%)		
No. of samples without SNPs	46 (10%)		
No. of SNPs in each male	362/141	2.6	
No. of SNPs in each female	194/64	3.0	
No. of SNPs in each male sample	362/319	1.1	
No. of SNPs in each female sample	194/139	1.4	
Mean age [years] of patients with at least one SNP	64.6±15.9	Range 0.25–92	
Presence of taste buds	273 (49.1%)		
Presence of ganglion cells	146 (26.3%)		
Presence of vascular ectasia	63 (11.3%)		
Excretory ducts emptying into the surface of the papilla	34 (6.1%)		
Moderate-severe inflammatory infiltrate	38 (6.8%)		
Lymphoid tissue in the vicinity of SNP	39 (7.0%)		
PEH	39 (7.0%)		
Main greatest dimension [mm] of the SNP	2.1±0.94	Range 0.6–3.6	

F: Female; M: Male; PEH: Pseudoepitheliomatous hyperplasia; SNP: Subgemmal (subepithelial) neurogenous plaque.

Results

The mean age of the autopsied patients was 59±15.77 years, with a range of three months to 92 years. Men accounted for 141 (68.8%) cases and women for 64 (31.2%). The male-to-female ratio was 2.2:1.

In 205 autopsies, 458 samples were routinely taken from the dorsal surface of the oral tongue. Forty-six (10%) samples did not contain SNPs, and 412 (90%) samples had at least one SNP. The total number of SNPs observed was 556, with a mean of 2.71±2.68 per case (range 0–16). A total of 362 SNPs were observed in 141 men, so each man showed a mean of 2.6 SNPs. One hundred ninety-four SNPs were observed in 64 women, so each woman showed a mean of 3.0 SNPs. Three hundred nineteen male samples showed 362 SNPs, so each male sample had an average of 1.1 SNPs. One hundred thirty-nine female samples showed 194 SNPs, so each female sample had an average of 1.4 SNPs. The difference between men and women was not statistically significant (Student's *t*-test, *t*-value 0.90964, *p*-value 0.207233, not significant at $p<0.05$). Patients with at least one SNP had a mean age of 64.6±15.9 years (range 0.25–92 years). Our results indicate that for every 15 linear mm of the oral tongue, approximately 2.7 SNPs can be observed.

Histopathologically, SNPs were present in the fungiform, foliate, and circumvallate papillae of the tongue. The

SNPs were usually contiguous to the covering squamous epithelium, which often contained taste buds (Figure 1A). The cellularity of the plaque contrasted with that of the stroma of the papilla at low magnification. However, the cell density of the plaque was variable. Taste buds were seen in 273 (49.1%) SNPs. They were decorated with S100 protein (Figure 1B) and CK7. SNPs displayed a biphasic pattern made up of a superficial non-encapsulated, circumscribed neural plexus, rectangular or ovoid in shape, and a deeper portion composed of small nerve fascicles mostly vertically oriented in a parallel manner (Figure 2). These fascicles were intermingled with a variable number of ganglion cells surrounded by a layer of small supportive cells, also known as satellite cells (Figure 3). Ganglion cells were observed in 146 (26.3%) SNPs. The superficial component made up the bulk of the plaque and consisted of elongated, wavy, ill-perceived delimited cells with tapered, spindle-shaped nuclei and inconspicuous nucleoli showing a predominant vertical arrangement (Figure 4); an organization predominantly parallel to the surface (Figure 5); or patternless layout. The elongated cells were organized as tangled individual elements (Figure 6) or as twisted and intertwined cords (Figure 7). Most cells were S100 positive and recognizable as Schwann cells. The cells were interspersed with variable amounts of collagen. NF protein staining revealed that axons formed composites with the Schwann cells (Figure 8). The ratio of Schwann cells to axons was approximately equal. CD34 immunostaining revealed the presence of endoneurial fibroblasts in the nerve bundles of the deep zone (Figure 9). These cells were scarce in the intermediate zone and absent on the surface of the plaque.

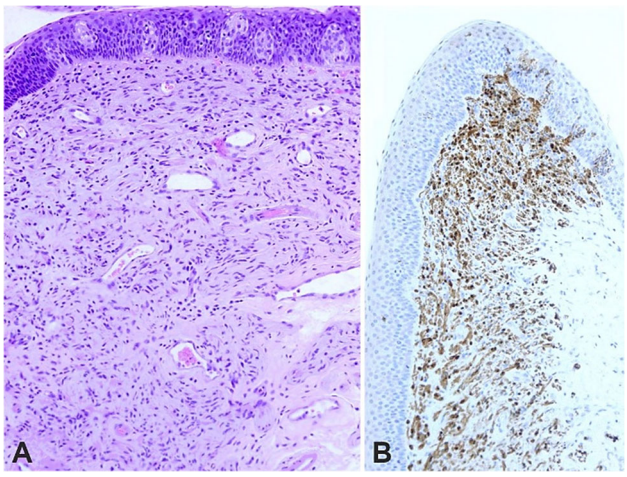


Figure 1 – ***Taste buds in the SNPs: (A) Taste buds are visible in a plaque covering the epithelium; (B) Continuity of the SNP with the taste buds can be seen. HE staining: (A) ×200. S100 protein immunostaining: (B) ×100. HE: Hematoxylin–Eosin; SNP: Subgemmal neurogenous plaque.***

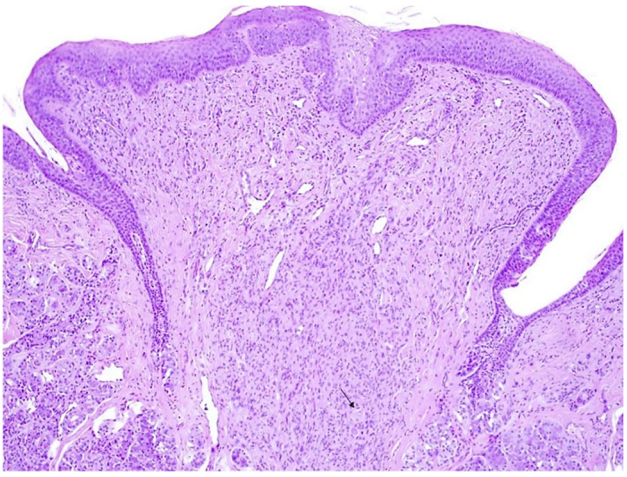


Figure 2 – ***Complete SNP showing a biphasic pattern. The arrow points to a ganglion cell. HE staining, ×100.***

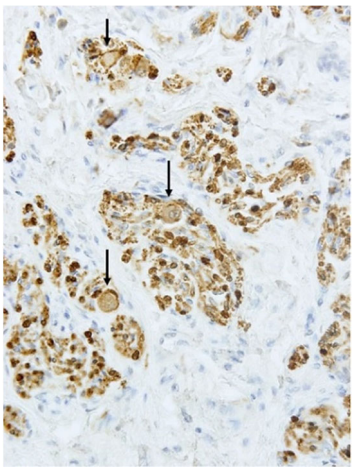


Figure 3 – ***The base of the plaque is composed of small nerve fascicles intermingled with ganglion cells (arrows). S100 immunostaining, ×200.***

Additionally, the encompassed thin-walled vessels occasionally appeared dilated (Figure 10). This vascular ectasia was present in 63 (11.3%) SNPs. The nerve fascicles of the deeper zone showed a thin perineurium that was positive for EMA (Figure 11). Occasional cases presented with prominent hyperplasia of the nerve fascicles at the bottom of the plaque (Figure 12). In the intermediate zone, expanded nerve fascicles with loose endoneurium could be seen. All cases contained minor salivary glands in the vicinity of the plaque, whose ducts emptied into the bottom of the furrows or moats (Figure 2). However, some excretory ducts emptied into the tip of the plaque (34 cases, 6.1%) and occasionally showed squamous metaplasia (Figure 13). A slight amount of subepithelial lymphoplasmacytic infiltrate was present in all cases. However, lymphoplasmacytic inflammation was moderate to severe in 38 (6.8%) SNPs. On the other hand, scattered mast cells were frequently present. The presence of lymphoid tissue in the immediate vicinity of the plaques was observed in 39 (7.0%) SNPs (Figure 14). Very occasionally small lymphoepithelial cysts were associated with the plaques. Some plaques encompassed the excretory ducts of the minor salivary glands.

In a substantial number of cases, two (Figure 15A) and up to four contiguous plaques were observed to be isolated by the separating groove of the papillae. Typically, each circumvallate papilla might contain one to two plaques. Two symmetrically placed SNPs were also present on opposite sides of a circumvallate papilla with the appearance of a mirror image (Figure 15B).

In 39 (7.0%) cases, exuberant epithelial hyperplasia of the overlying squamous epithelium of the plaque was noted (Figure 16). This epithelium showed downward irregular projections that extended into the *lamina propria*

in intimal association with the neural components of the SNP (Figure 17). Due to the incidence of the sections, some projections appeared as discrete epithelial nests with a pseudoinfiltrative appearance. Nests were of two types, intermingled. Most consisted of squamous epithelium with acidophilic cells, sometimes keratinized, often surrounded by basal cells (Figure 18A). From time to time, the squamous nests showed clear cells with well-defined limits (Figure 18B). The second type consisted of predominant basal cells (Figure 19). No significant atypia or irregular mitoses in the acanthotic epithelial covering of the plaque or the pseudoinvasive nests were observed. The florid epithelial proliferation was considered to be PEH.

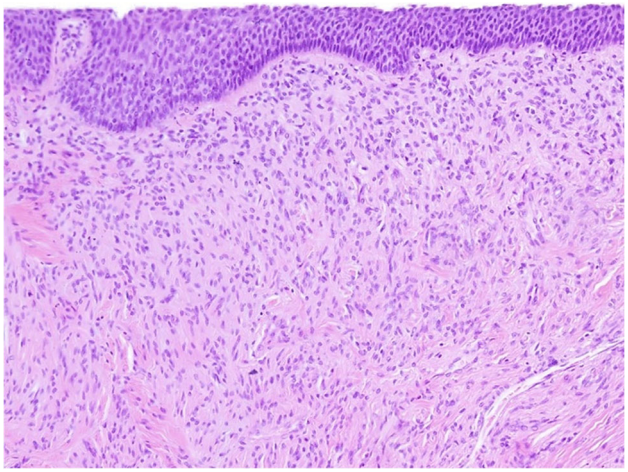


Figure 4 – ***Superficial component of a cellular SNP showing elongated, wavy cells in a predominant vertical arrangement. HE staining, ×200.***

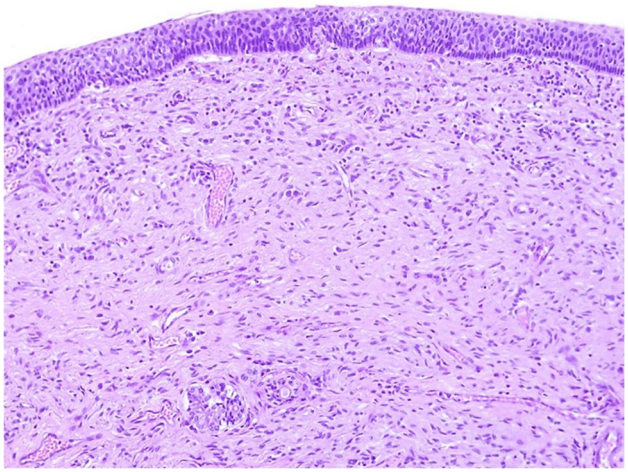


Figure 5 – ***Superficial component of the SNP with individual, elongated, wavy cells parallel to the surface. HE staining, ×200.***

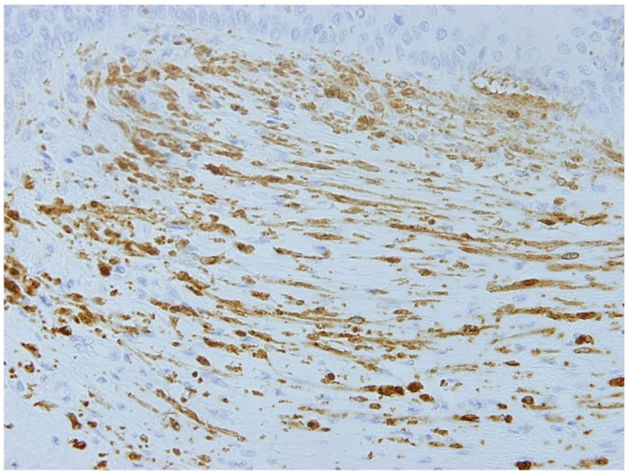


Figure 6 – ***Elongated cells recognizable as Schwann cells organized as individualized elements parallel to the surface. S100 protein immunostaining, ×400.***

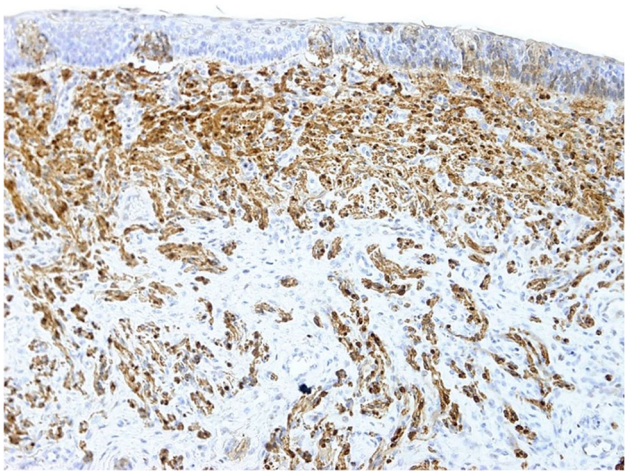


Figure 7 – ***Schwann cells form twisted and intertwined cords. S100 protein immunostaining, ×200.***

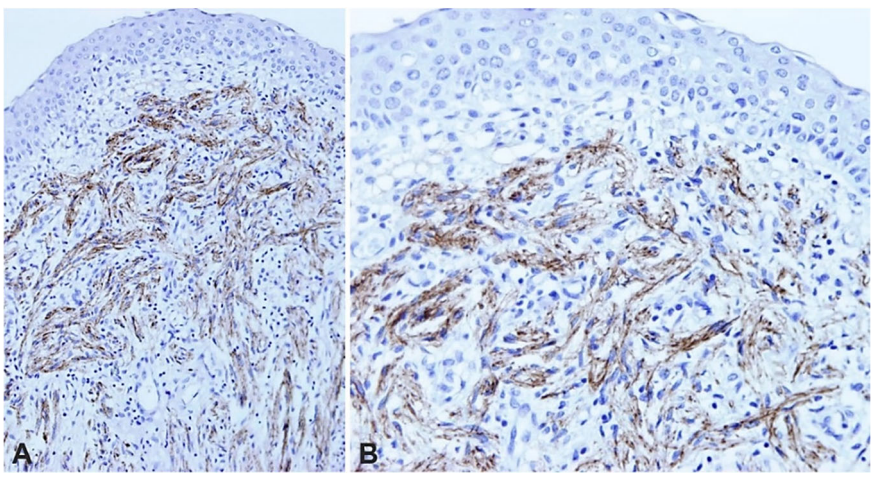


Figure 8 – ***(A) Axons are combined with the Schwann cells. (B) The Schwann cell/axon ratio is about the same. NF protein immunostaining: (A) ×200; (B) ×400. NF: Neurofilament.***

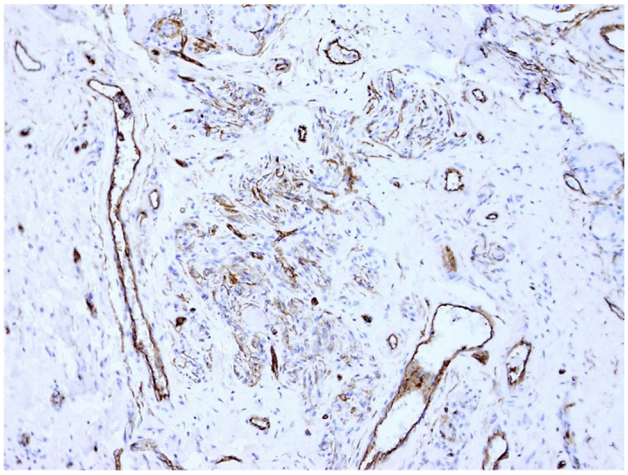


Figure 9 – ***CD34-positive endoneurial fibroblasts are shown in the nerve fascicles at the base of the plaque. Anti-CD34 antibody immunostaining, ×200. CD34: Cluster of differentiation 34.***

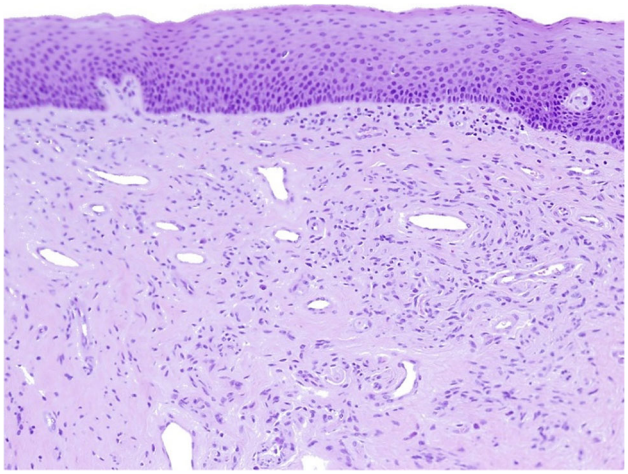


Figure 10 – ***Low cell density plaque showing vascular ectasia. HE staining, ×200.***

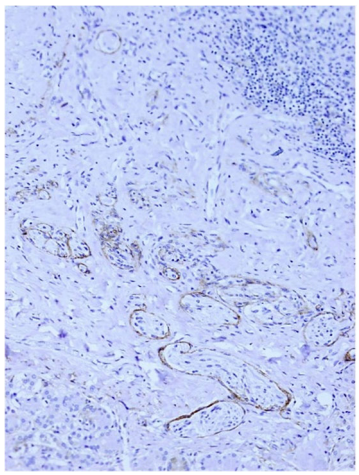


Figure 11 – ***Nerve fascicles of the deeper zone are showing a thin perineurium positive for EMA. Anti-EMA antibody immunostaining, ×200. EMA: Epithelial membrane antigen.***

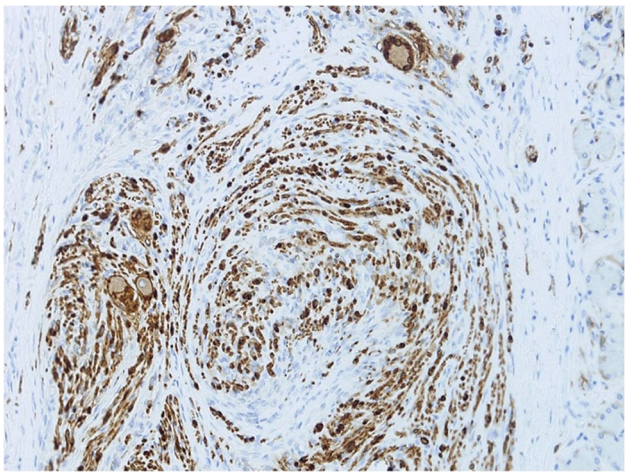


Figure 12 – ***Hyperplasia of the nerve fascicles with the presence of ganglion cells in the depth of the plaque. S100 protein immunostaining, ×200.***

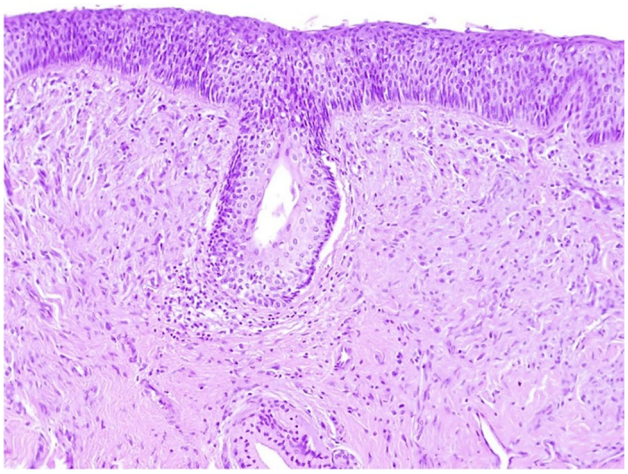


Figure 13 – ***Salivary excretory duct with squamous metaplasia emptying into the surface of the plaque. HE staining, ×200.***

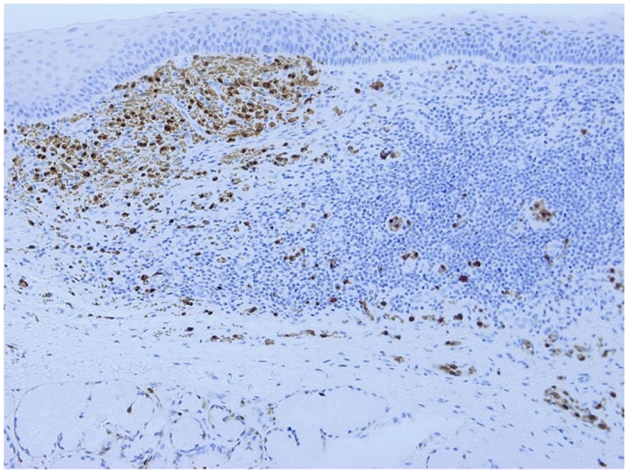


Figure 14 – ***Lymphoid tissue in the vicinity of a plaque. S100 protein immunostaining, ×200.***

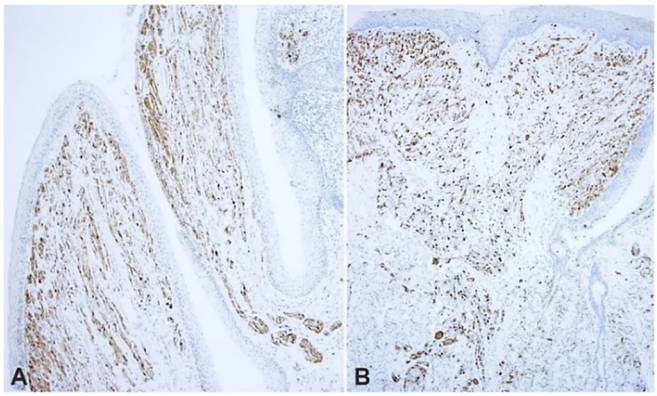


Figure 15 – ***Adjacent SNPs: (A) Two contiguous plaques are separated by the cleft of a papilla; (B) Two symmetrical mirror plaques. S100 protein immunostaining: (A and B) ×100.***

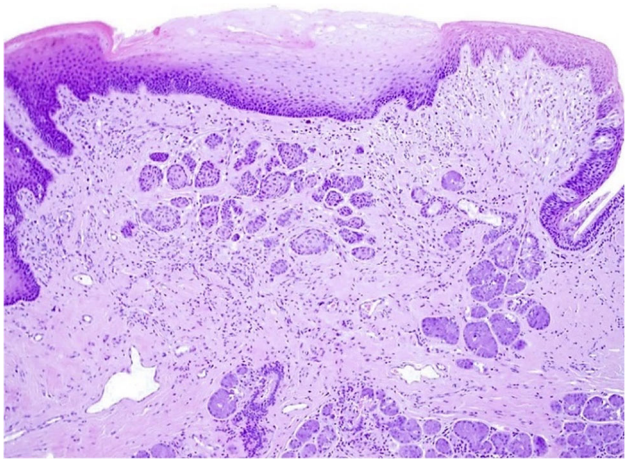


Figure 16 – ***Pseudoepitheliomatous hyperplasia in an SNP. HE staining, ×100.***

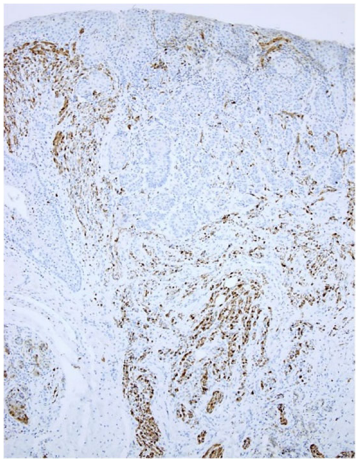
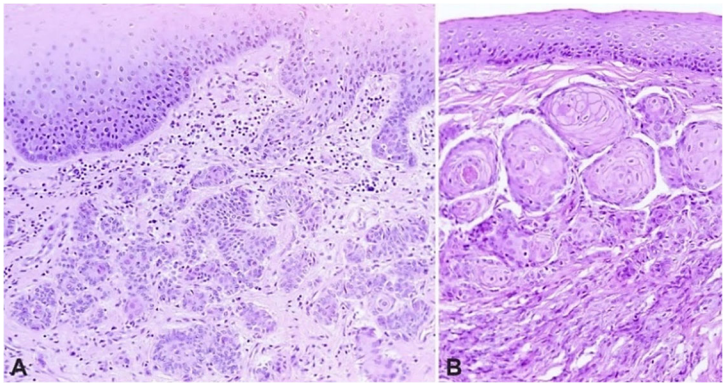


Figure 17 – ***Pseudoepitheliomatous hyperplasia associated with the neural component of the plaque. S100 protein immunostaining, ×100.***

Figure 18 – ***Pseudoepitheliomatous hyperplasia: (A) Squamous nests with acidophilic cells are often surrounded by basal cells; (B) Squamous nests are constituted by cells with well-defined limits. HE staining: (A and B) ×200.***



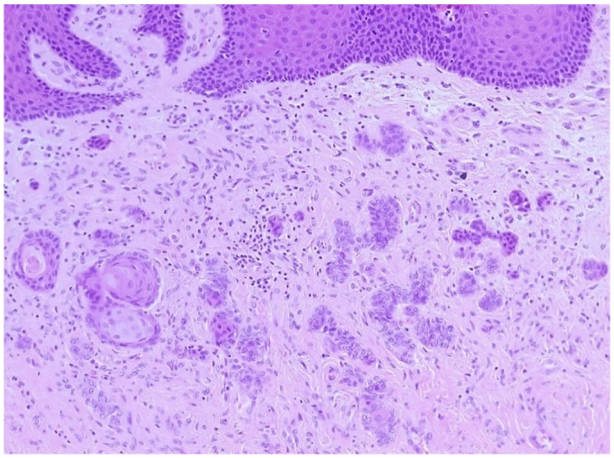


Figure 19 – ***Pseudoepitheliomatous hyperplasia with predominant basal cell nests. Some squamous nests show keratinization. HE staining, ×200.***

The mean greatest dimension of the SNP was 2.1±0.94 mm (range 0.6–3.6 mm).

Table 2 summarizes the distribution and frequencies of the various variables in the current series.

Discussions

SNPs are biphasic neural structures associated with taste buds that are mostly detected incidentally in tongue biopsies [1, 2, 7, 8, 10]. Although these structures do not have significant clinical consequences, their knowledge is important to avoid diagnostic difficulties.

SNPs can be observed in individuals of a wide range of ages and do not show sex differences. Our findings indicate that for every 15 linear mm of the dorsum of the oral tongue, approximately 2.7 SNPs can be observed. The reported prevalence of SNPs that have been observed in lingual biopsies is variable between 4.0% and 1.7% [2, 4]. In our

sample of 458 specimens, we found 556 SNPs, a prevalence that is much higher than the one published. The difference seems to be due to the different sampling locations and the number of samples. As for the count of the plaques, the mirror images could correspond to a single plaque whose three-dimensional image would conform to a complete contiguous subepithelial ring [2, 11]. However, in this study, these structures were counted as two plaques.

Special features of the SNPs included the presence of taste buds, ganglion cells, dilated thin-walled vessels (vascular ectasia), salivary gland excretory ducts draining on the surface of the papillae, moderate-severe inflammatory infiltrate, presence of lymphoid tissue in the immediate vicinity, and hyperplasia of the epithelial cover with a pseudoepitheliomatous appearance.

Taste buds were observed in 49.1% of the papillae. This fact can be explained because not all papillae show taste buds. Thus, 67% of the fungiform papillae have no taste buds [22]. However, Alnajar *et al*. [9] observed the presence of taste buds in 65% of the papillae in a study of 20 SNPs. Nevertheless, it should be noted that depending on the plane of section, the taste buds may not be observable.

We observed ganglion cells in 26.3% of the SNPs. Ganglion cells were absent in a study of 28 SNPs studied [6]. Alnajar *et al*. [9] observed 65% of these cells in a study of 20 plaques. The differences in frequency can be explained because some plaques appear incomplete with the deepest part incomplete or absent, and by the great difference in the number of samples.

Dilated thin-walled vessels have rarely been described in SNPs [3]. We observed this feature in 63 (11.3%) plaques. This alteration has also been observed in a cutaneous neural lesion that shows some similarities with the SNP [23].

The excretory ducts of the minor salivary glands normally empty into the furrows or moats of the papillae. However, in 34 (6.1%) SNPs, the ducts were emptied at the papillary tip and sometimes they showed squamous metaplasia. To our knowledge, this type of ectopic drainage has not been reported in the literature. On the other hand, Soames [24] described squamous metaplasia in the superficial part of the orthotopic ducts. In a microscopic examination of 100 cadaver tongues, this author reported that "the superficial portions of the ducts frequently showed squamous metaplasia".

A mild subepithelial lymphoplasmacytic infiltrate was present in all SNPs. However, a moderate to severe inflammatory infiltrate was observed in 38 (6.8%) plaques. Alnajar *et al*. [9] reported chronic inflammation in 12 of 20 (60%) plaques. However, they did not distinguish the degree of inflammation.

In the present work, the presence of lymphoid tissue juxtaposed to the plaques occurred in 39 (7.0%) cases. In a study of 28 SNPs, Pellicioli *et al*. [6], observed aggregates of lymphoid cells in the vicinity of the plaques in 16 (57.1%) cases. The difference is probably due to the different sampling and the volume of cases studied.

The presence of nests or islands of squamous epithelium in the *lamina propria* of the tongue has been interpreted differently by various authors. Thus, Baughman [25], who conducted a cadaver study of median rhomboid glossitis in 184 tongues, ascribed the three (1.6%) epithelial nests found to squamous metaplasia of the serous von Ebner's glands. Subsequently, Soames [24] observed "frequent" squamous metaplasia of the superficial parts of the ducts of the mucous and serous glands in an investigation of 100 cadaver tongues while reviewing the region of the foramen cecum. In a study of the mucosa of 76 cadaver tongues, Delemarre & van der Waal [26] found in 11 (14.5%) of them squamous metaplasia of serous glands occurring exclusively within the circumvallate papillae. A serial section study revealed continuity with the overlying epithelium [26]. Palazzolo *et al*. [12] interpreted the epithelial nests in the SNPs as NESs based on their close association with the neural structures of the plaque. Additionally, these authors were struck by the fact that the set of epithelial nests in the SNP was similar, if not identical, to the anatomical structure of the JOOC. Other authors [13–15] adhered to this interpretation, and all of them considered that the collection of epithelial nests associated with the SNP was a persistent non-involuted JOOC of lingual location.

Our group in 2006 reported a case of prominent PEH associated with two SNPs [11]. After studying the cases of the present investigation, we suggest that the epithelial nests and islands of squamous epithelium that infiltrate the SNPs come from the surface epithelium and are induced by factors produced by the SNP. It is a process similar to that observed in granular cell tumors [27] or Spitz melanocytic nevus [28] on the tongue, melanocytic nevus [29] on the gingiva, and malignant melanoma involving the palate and the maxillary gingiva [30]. Furthermore, the superficial papular neuroma [22], a recently described skin lesion, shows similarities to the lingual SNP, such as subepithelial location, proliferation of S100-positive spindle cells, presence of nerve fibers, dilated superficial thin-walled vessels, and minimal to mild inflammation. This lesion is associated with epidermal hyperplasia. All these lesions share some similarities that suggest a possible histogenetic and pathogenetic relationship.

We consider the observed PEH as an epithelial induction caused by an underlying process and an expression of the pluripotentiality of the epithelium. We speculate that growth factors and interleukins produced by neural or melanocytic proliferations could provide the proliferative stimulus involved in the development of epithelial hyperplasia. Thus, Barkan & Paulino [31] reported that the production of transforming growth factor-alpha (TGF-α) by the granular cell tumor is related to the development of PEH, which is a common companion to this type of tumor. Reported factors that could be involved in PEH include epidermal growth factor (EGF), epidermal growth factor receptor (EGFR), TGF-α, fibroblastic growth factor (FGF), platelet-derived growth factor (PDGF), interleukin (IL)-1, IL-6, IL-7, IL-8, IL-10, and IL-12 [32, 33].

There are two types of PEH: (*i*) squamous cell proliferation, which may be misinterpreted as squamous cell carcinoma (SCC), and (*ii*) basal cell proliferation, which can be misinterpreted as basal cell carcinoma [34]. Both kinds of PEH can be observed in SNPs. Stages in the differentiation of PEH include: (*i*) acanthosis of the overlying epithelium, (*ii*) proliferation of rete ridges with deeper extension and irregular interpapillary projections, and (*iii*) established PEH [32].

The SNP is similar to the lesion described by Daneshvar as pharyngeal traumatic neuroma with mature ganglion cells (pharyngeal pseudoganglioneuroma) [35]. Furthermore, the illustration of one of the lesions in the Daneshvar study showed prominent hyperplasia of the overlying squamous cell epithelium [35]. The Daneshvar lesion should be considered an extra-lingual SNP.

SNP is clinically confused with foliate papillitis, lymphoepithelial cysts, inflammatory fibrous hyperplasia, candidiasis, lingual tonsillitis, and SCC [36].

The differential HP diagnoses of SNPs include schwannoma, neurofibroma, ganglioneuroma, traumatic neuroma, mucosal neuroma, and SCC.

A schwannoma is an encapsulated nerve sheath tumor composed entirely of Schwann cells. It is a biphasic lesion showing Antoni A and B patterns, and it can display palisading and Verocay bodies. Axons are absent [37].

Neurofibromas are located in the submucosal tissue and are not subepithelial. The margins are usually poorly defined. Unlike neurofibromas, SNPs show a zonal pattern. In addition, approximately an equal ratio of Schwann cells to axons occurs in the SNP. That ratio is markedly increased in neurofibroma. These features help differentiate SNPs from neurofibromas [2].

Unlike an SNP, a ganglioneuroma is an encapsulated or circumscribed lesion usually larger than 3.75 cm that commonly shows binucleate or multinucleate ganglion cells. These cells often form clusters against a neuromatous background and may show ballooning degeneration [1].

Traumatic neuromas consist of proliferated endoneurial and perineural connective tissue, Schwann cells, and regenerative axons. The last ones, at the distal end of the proximal segment, sprout by budding and evolve in all directions. The nerve fibers are organized into microfascicles of varying sizes [38].

The mucosal neuroma occurs in the setting of multiple endocrine neoplasia (MEN) type IIb. In the involved tongue, there are numerous small pinheads to a few millimeter nodules at the tip, anterior one-third, and along the lateral borders. Histopathologically, there are numerous tortuous, branched, and loosely arranged nerve bundles with a prominent perineurium. The nerves vary in size and often show endoneurial mucin [39]. Ganglion cells are usually absent. Mucosal neuromas have also been reported to be isolated [40].

As opposed to PEH, SCC shows nuclear atypia, individual necrotic keratinocytes, numerous mitotic figures, deep invasion into the connective tissue, and absence of an underlying process [33, 41]. An IHC panel consisting of p53, E-cadherin, and matrix metalloproteinase-1 (MMP-1) can help in the differential diagnosis. The malignant cells show strong positive nuclear staining for p53. PEH lesions are positive for p53, but they are stained less intensely, and the staining is predominantly localized to the basal cell layer [42]. Malignant cells and adjacent stroma are reactive to MMP-1. E-cadherin staining is reduced in invasive cell nests [33]. The specificity and sensitivity of MMP-1 for SCC are 94% and 81%, respectively [43]. However, a properly oriented HE-stained section remains the "gold standard" for diagnosis [43].

Conclusions

SNP is characterized by its unique neural biphasic pattern with a superficial neurofibroma-like area and a deeper neuroma-like area. We consider SNPs to be small, normal structures associated with taste buds that may suffer hyperplasia and are usually incidentally observed. They are more frequent than previously acknowledged. We postulate a diagnosis of PEH to explain the squamous and basal cell nests in the mucosal *lamina propria* of the tongue in intimal association with the neural components of the SNP. The so-called NESs are epithelial and not neuroepithelial in character. Oral pathologists should be aware of the features of SNP to avoid misdiagnosis and inadequate treatment.

Conflict of interests

The authors declare that they have no conflict of interests.

Compliance with ethical standards

The authors declare that the procedures followed in this research conform to the ethical standards in accordance with the *World Medical Association* and the Declaration of Helsinki. This research is exempt from approval by the Ethics Committee of our institution because it is a retrospective study.

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Corresponding author
José-Fernando Val-Bernal, Professor, MD, PhD, Pathology Unit, Department of Medical and Surgical Sciences, University of Cantabria, Avda. Cardenal Herrera Oria s/n, 39011 Santander, Spain; Phone +34 942 315098, Fax +34 942 315952, e-mail: fernando.val@unican.es

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