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Evaluation of peripheral nerve fibers and mast cells in burning mouth syndrome

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Abstract: Emerging evidence has revealed a cross-talk in the etiopathogenesis of burning mouth syndrome (BMS) related to peripheral nerve fibers (NF) and neuropeptides secreted by mast cells. Here, we investigated the S-100$^+$ density and PGP 9.5$^+$ integrity of peripheral NF and the tryptase$^+$ mast cell density in the oral mucosa of BMS patients and healthy individuals. A total of 23 oral mucosa specimens (12 BMS and 11 controls) were evaluated. The clinical diagnosis of BMS was based on a careful examination, excluding other local and systemic causes. Samples were taken from an incisional biopsy of the tongue mucosa of individuals with symptomatic BMS, while the margins of the non-neoplastic tongue biopsy served as controls of healthy individuals. Immunohistochemistry was performed to determine the density/mm^2 of S-100$^+$, PGP 9.5$^+$ peripheral NF, and tryptase$^+$ mast cells. Similar densities of S-100$^+$, PGP 9.5$^+$ peripheral NF, and tryptase$^+$ mast cells were found in cases of BMS, with a median value of 3.70, 0.70, and 29.24/mm^2, respectively, and in the control group, with a median value of 2.60, 0.80, and 26.01/mm^2, respectively ($p > 0.05$). Moreover, the relationship between S100$^+$ and PGP 9.5$^+$ peripheral NF was the same in both groups ($p = 0.70$). This study demonstrated that there were no alterations in the density and integrity of peripheral NF in the tongue of symptomatic BMS patients. However, the sensitization of peripheral NF in this disease may not depend on mast cell density.

Keywords: Biopsy; Burning Mouth Syndrome; Mast Cells; S100 Proteins; Tongue.

Introduction

Burning mouth syndrome (BMS) is a chronic condition clinically characterized by an intraoral burning sensation commonly associated with the absence of clinical or laboratory findings.[1] This disease has a prevalence of 1.7% worldwide and of 7.7% among clinical patients.[2] BMS occurs more frequently in postmenopausal women, mainly affecting the dorsum and lateral borders of the tongue, lips, and hard/soft palate.[1,2] A myriad of pharmacological therapeutic options for BMS have been reported, including trazodone, melatonin, alpha-lipoic acid, clonazepam, and herbal compounds.[3] It is a disease of uncertain

etiopathogenesis that may impact the quality of life of affected individuals and, in extreme cases, lead to self-mutilation.[4,5]

Previous studies have invested in possible mechanisms of BMS.[6-9] In particular, changes in the density and integrity of peripheral nerve fibers (NF)[6,7] and in the salivary concentration of neuropeptides produced by these fibers and mast cells.[10] Compelling evidence reveals that an unknown early factor induces peripheral NF to produce and release a large amount of nerve growth factor (NGF) and this chemical mediator, along with other neuropeptides, appears to induce hypersensitivity in peripheral NF from the oral mucosa.[11] In addition, these neuropeptides could stimulate mast cells to secrete proteases and other chemical mediators, thus maintaining neurogenic inflammation.[11]

The neuropathic basis of BMS is usually accompanied by complaints of changes in taste, pain intensity, or other sensory perceptions.[12] Studies have investigated the etiopathogenesis and diagnosis of BMS[6-8,13] and characterized the condition as a small-fiber sensory neuropathy.[6,7,11] Along this line, it has been reported that the secretion of neuropeptides and other products of mast cell degranulation, such as tryptase, is involved in the etiopathogenesis of various neuropathic disorders.[13,14] Furthermore, a high concentration of salivary tryptase has been identified in individuals with BMS, suggesting the participation of mast cells in the symptoms of this disease.[11]

Neuronal proteins such as the gene product of protein 9.5 (PGP 9.5) and S-100 have been used to evaluate nerve structures in neuropathies.[6,13,15-18] The hypothesis is that the early loss or non-expression of PGP 9.5 seems to be associated with axonal degeneration processes,[15,17] as expected in neuropathies. PGP 9.5, a ubiquitin carboxydrolase, is expressed in axons and has been used to investigate neurodegenerative diseases.[16] In addition, PGP 9.5 has been used as a marker of epithelial NF in patients with BMS.[6,13] S-100 is used to identify fragmented and intact nerve structures, in addition to being expressed by Schwann cells. It has also been used to analyze the general NF density in leprosy cases.[16,18]

BMS is a globally burdensome oral condition that affects middle-aged or older individuals with a complex clinical diagnosis, and the available information about its etiopathogenesis is uncertain and controversial.[19] Although BMS is considered a small-fiber neuropathy, understanding of the disease mechanisms is still sparse. Also, considering the importance of PGP 9.5, S-100 protein and mast cells in neuropathies, and the hypothesis that these proteins and cells are distributed differently in BMS patients compared to healthy controls, we investigated the density and integrity of peripheral NF and mast cell density in tongue mucosa specimens from individuals with a clinical diagnosis of symptomatic BMS and healthy controls.

Methodology

Study design and sample

This study was approved by the Ethics Committee at the Federal University of Goiás (UFG), Goiânia, Brazil (Approval No. #053/2011-00). Oral mucosa samples were collected for convenience from the anterior region of the tongue of symptomatic BMS patients (n = 12) and constituted the investigation group. The control group comprised fragments of the tongue mucosa (n = 11) of the safety margin of specimens obtained from an excisional biopsy of non-neoplastic tongue lesions from patients without a complaint of BMS. Samples were paired by sex and mean age of BMS individuals and were selected from the archives of the Laboratory of Oral and Maxillofacial Pathology of UFG.

BMS diagnosis

Individuals with a clinical diagnosis of BMS from the Oral Medicine Service of the School of Dentistry at UFG were selected. All patients had burning tongue, with or without xerostomia and dysgeusia, clinically normal dorsum of the tongue and symptoms for at least four months,[20,21] as summarized in Figure 1. Diabetes, use of angiotensin-converting enzyme inhibitors, Sjögren's syndrome, oral lichen planus, oral lichenoid lesions, allergies, migratory erythema, oral candidiasis, and other known causes of polyneuropathies were exclusion

criteria. Oral infection by candida was ruled out by microbiological culture.

Blood exams were also requested and included complete blood count, fasting blood glucose, iron, ferritin, vitamin B12, folate, zinc, T3, T4, and TSH. All values of BMS patients were within normal limits. The burning intensity was assessed using a Visual Analogue Scale (VAS) ranging from 0 (no burning)

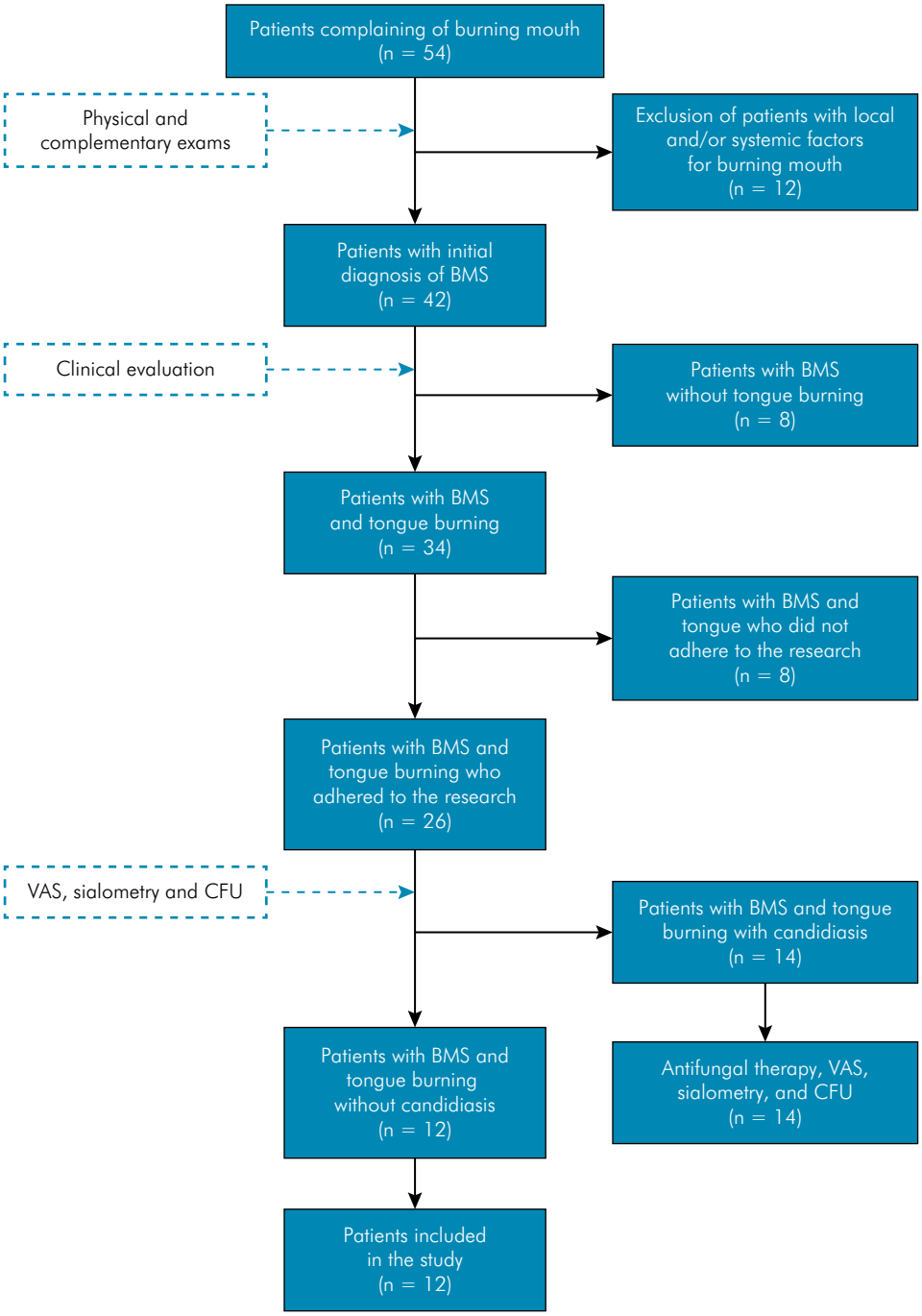

Figure 1. Stages of clinical diagnosis of burning mouth syndrome (BMS) (sampling). CFU: colony-forming unit; VAS: visual analogue scale.

to 10 (unbearable burning). Incisional biopsies of patients with BMS were performed by the same operator (L.A.C.). Symptomatic sites in the anterior region of the tongue were selected and a sample was taken from each patient, fixed in 10% neutral buffered formalin, and paraffin-embedded.

Histology and immunohistochemical assessments

Five-µm-thick sections were stained with hematoxylin and eosin (H&E). H&E slides were evaluated qualitatively and the following parameters were analyzed: integrity of the epithelium, keratinization and its thickness, inflammatory infiltrate, collagenization, density (NF/mm^2), and integrity of peripheral NF. An integration reticle (4740680000000-Netzmikrometer ×12.5, Carl Zeiss, Göttingen, Niedersachsen, Germany) connected to a light microscope (AxioScope; Carl Zeiss) was used to observe 20 alternating fields at ×40 magnification. Keratin thickness was measured using a millimeter ruler connected to a light microscope at ×20 magnification. In addition to a microbiological culture, Periodic acid-Schiff and Grocott-Gomori histochemical staining were performed to rule out the possibility of fungal hyphae in the samples evaluated.

For immunohistochemical staining, 3-µm-thick sections mounted on polarized slides (StarFrost®, Waldemar Knittel Glasbearbeitungs GmbH, Germany) were used for the polymer-based detection method. The sections were immersed in citrate buffer (Sigma-Aldrich), pH 6.0, and heated to 95ºC for 25 minutes for antigenic recovery of the S-100 and PGP 9.5 proteins. No antigenic recovery was performed for the tryptase protein. Next, the sections were incubated with their respective primary antibodies previously submitted to the standardization stage for 12 hours at 4ºC. Table 1 shows the antibodies used and their specifications. The sections were incubated with the Starr Trek Universal HRP Detection System Kit (Biocare Medical, Pacheco, USA). The reaction was developed using 3.3'-diaminobenzidine (DAB) in a chromogenic solution. S-100$^+$ and PGP 9.5$^+$ peripheral NF and tryptase$^+$ mast cells were considered as an internal positive control, while negative controls consisted of replacement of the primary antibody with 1% bovine serum albumin in the buffer solution. S-100$^+$ and PGP 9.5$^+$ peripheral NF and tryptase$^+$ mast cells were evaluated semi-quantitatively (density/mm^2) on the entire slide.[22] All sections were evaluated by two examiners (D.A.C.A. and A.C.B.) in a blinded fashion and disagreements were resolved by consensus. The ratio between S-100$^+$ and PGP 9.5$^+$ NF needed to obtain the density of degenerate NF was also determined. The same quantification process as described for H&E-stained slides was used for NF immunostaining.

Data analysis

Data were analyzed using the GraphPad Prism software version 7.00 (Graph-Pad software, La Jolla, USA). The nonparametric Mann-Whitney test was used for the comparative analysis of the density of NF and mast cells. For all analyses, the level of significance was set at < 0.05.

Results

All patients with BMS (n = 12) were women (100%), with a mean age of 67 (± 6.1) years (range: 58 to 74 years) and had burning of moderate intensity (mean: 6.8 ± 1.0, VAS) in the dorsum and lateral border of the tongue. The mean duration of symptoms was 45 (±12) months (range: 12 to 60 months). The patients did not report loss of taste, thermal sensation, or other sensory

Table 1. Antibodies used for immunohistochemical analysis.

Antibodies	Clone	Sources	Nature of antibodies	Dilution
PGP 9.5	Z5116	Dako, USA	Monoclonal (human)	0,25
S-100	N1573	Dako, USA	Monoclonal (human)	0,736111111
Tryptase	M7052	Dako, Denmark	Monoclonal (human)	1,430555556

changes in the mouth. Dry mouth was reported by nine patients (75%) and 11 (91.6%) were taking clonazepam as burning mouth treatment (Table 2). The control group (n = 11) had a predominance of females (72.7%) with a mean age of 62 (± 7.3) years (range: 51 to 73 years).

Analysis of H&E-stained slides from the two groups revealed similar integrity of the epithelial lining, keratin layer thickness, and collagenization (Figures 2A-F). NF were present in the lamina propria of all BMS patients and controls, with a similar morphology (Figures 2C and 2F). All samples from the BMS group showed basophilic structures on the epithelial surface suggestive of biofilm (Figure 2B). Thus, because of the possible presence of biofilm in all BMS samples and the report of dry mouth as a secondary complaint by most of these BMS patients, the presence of fungi in the histological sections was investigated. However, Periodic acid-Schiff and Grocott-Gomori staining were negative for the presence of fungi. This analysis was not foreseen in the methodology since a subclinical infection by *Candida* spp. determined by microbiological evaluation was an exclusion criterion for the BMS group.

All BMS samples exhibited structures with the morphology of S-100$^+$ and PGP 9.5$^+$ peripheral NF in the lamina propria, with a nuclear and cytoplasmic brownish and homogeneous staining pattern. Quantitative analysis demonstrated that the BMS group had S-100$^+$ and PGP 9.5$^+$ peripheral NF densities (medians: 3.7 and 0.7/mm^2, respectively) similar to the control group (medians: 2.6 and 0.8/mm^2, respectively) ($p > 0.05$). In addition, the relationship between S-100$^+$ and PGP 9.5$^+$ peripheral NF in BMS and controls was the same ($p = 0.70$). Brown-colored, tryptase$^+$ mast cells were identified in the submucosa close to blood vessels in all BMS samples (median: 29.2/mm^2), with a density similar to that of the control group (median: 26.0 mast cells/mm^2) ($p = 0.64$) (Table 3; Figure 3).

Discussion

The main findings of the present study were similar density and integrity of S-100$^+$ and PGP 9.5$^+$ peripheral NF and tryptase$^+$ mast cells of BMS and control tongue mucosa samples. These results suggest that the integrity and density of peripheral NF on tongue mucosa do not change in individuals with BMS and, possibly, the sensitization of these

Table 2. Clinical and demographic characteristics of patients with burning mouth syndrome (n = 12) and healthy patients (n = 11).

Variables	Burning mouth syndrome	Healthy patients
	n (%)	n (%)
Age (years)		
< 67	5 (41.6)	7 (63.6)
≥ 67	7 (58.4)	4 (36.4)
Sex		
Male	0 (0)	2 (27.3)
Female	12 (100)	9 (72.7)
Ethnicity		
Caucasian	9 (75)	0 (0)
Not Caucasian	3 (25)	11 (100)
Alcoholism		
Yes	0 (0)	-
No	12 (100)	-
Smoking		
Yes	2 (16.7)	-
No	10 (83.3)	-
Burning		
Dorsal surface and other sites	12 (100)	-
Xerostomia		
Yes	9 (75)	-
No	3 (25)	-
Burning duration (years)		
< 3.75	4 (33.4)	-
≥ 3.75	8 (66.6)	-
Burning type		
Continuous (daytime)	3 (25)	-
Intense (nighttime)	5 (41.6)	-
Sporadic	4 (33.4)	-
Pharmacological treatment		
Yes	11 (91.6)	-
No	1 (8.4)	-
VAS (median)		
< 6.8	4 (33.3)	-
≥ 6.8	8 (66.7)	-

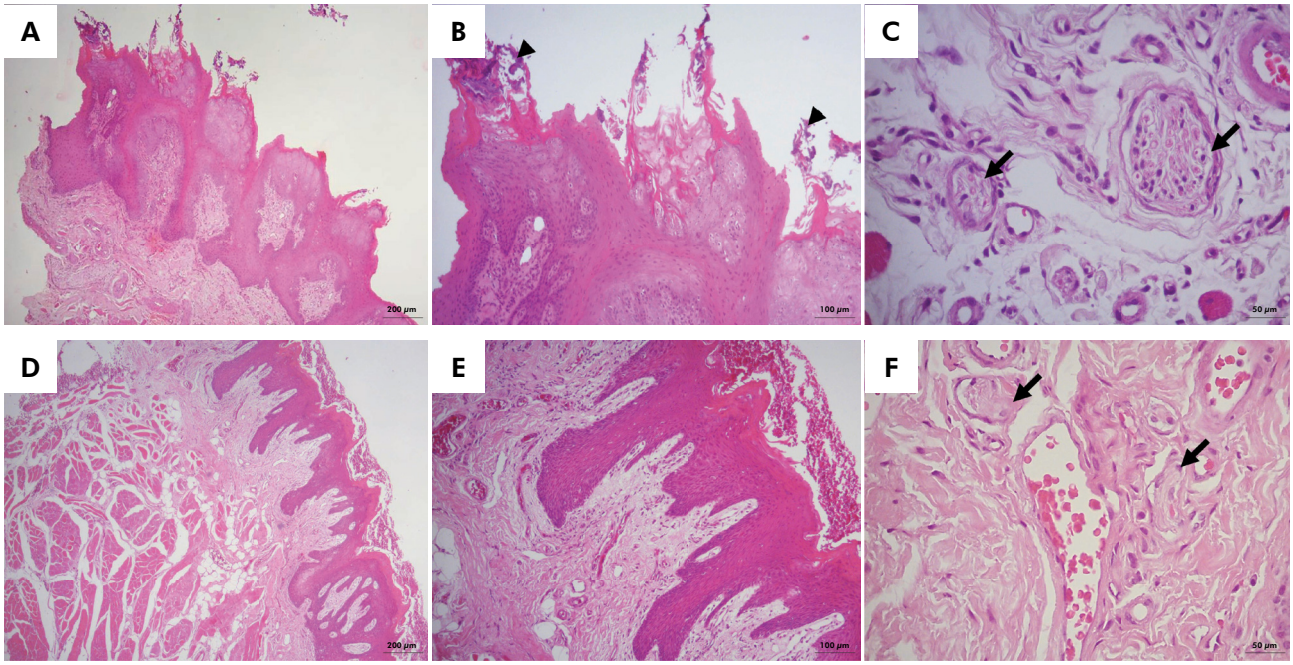

Figure 2. Histology of the tongue mucosa in burning mouth syndrome (A-C) and control (D-F) samples. Peripheral nerve fibers (C and F, arrows) and basophilic structures (B, arrowhead) suggestive of a biofilm on the epithelial surface of burning mouth syndrome specimens. Hematoxylin and eosin, ×10 (A and D), ×20 (B and E) and ×40 (C and F).

Table 3. S-100$^+$, PGP 9.5$^+$, hematoxylin and eosin (H&E) peripheral neural fibers (NF) and tryptase$^+$ mast cells from patients with burning mouth syndrome (BMS) and controls.

Variables	BMS		Control		p-value*
	Median	Minimum-maximum	Median	Minimum-maximum	
S-100$^+$ (NF/mm^2)	3.7	0-22.3	2.6	0-10.0	0.66
PGP 9.5$^+$ (NF/mm^2)	0.7	0-7.3	0.8	0-5.2	0.72
Ratio (NF S-100$^+$/NF PGP 9.5$^+$)	0.4	0-12.4	0.4	0-15.7	0.70
H&E (NF/mm^2)	1.1	0-9.7	2.1	0-10.4	0.35
Triptase$^+$ mast cells (cells/mm^2)	29.2	5.2-95.5	26.0	1.7-87.4	0.64

*Mann-Whitney test, $p < 0.05$.

nerve structures does not depend on the density of mast cells.

The literature on this subject is heterogeneous and diverse. There are studies with similar findings as the present one, *i.e.*, similar density of peripheral NF in the lamina propria of the tongue mucosa of individuals with BMS and controls.[7] Others have shown increased NF density (Nav1.7$^+$ sodium channels; P2X3$^+$)[23] and some have observed lower epithelial NF density (PGP 9.5$^+$) in tongue samples from BMS patients,[6,13] suggesting that the disease is a trigeminal neuropathy.[6] However, the quantitative analysis of NF performed by Lauria et al.[6] and Penza et al.[13] was restricted to intraepithelial ramifications. Because of the lack of studies investigating the neuropathic etiopathology of BMS, in particular using the S-100 protein, we also searched for parameters in studies on NF changes in other neuropathies, such as leprosy.[16,18] The S-100 protein has been suggested to be a superior strategy for the simultaneous identification of intact and fragmented nerve structures than H&E.[18] Furthermore, in leprosy

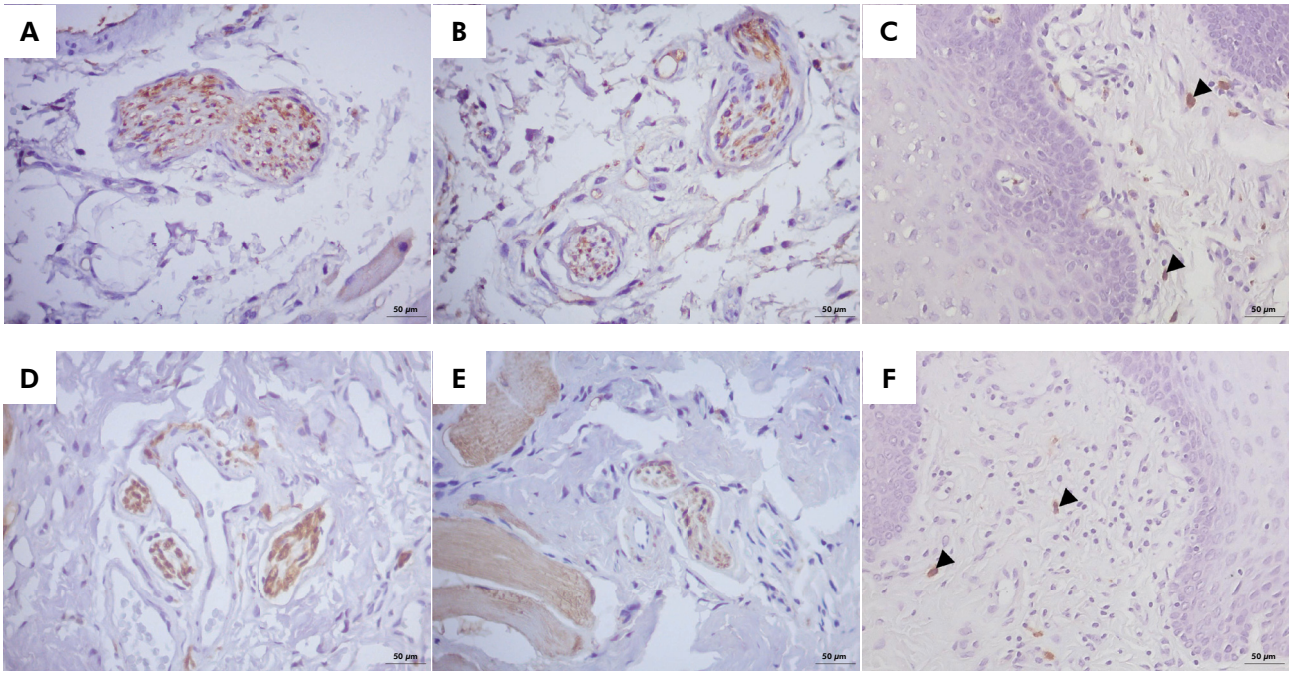

Figure 3. S-100^{+} and NF PGP 9.5^{+} peripheral neural fibers and mast cells tryptase^{+} (arrowhead) distributed in the lamina propria of tongue mucosa samples from individuals with burning mouth syndrome (A-C) and control healthy individuals (D-F). Immunohistochemistry, ×40 (A-F).

cases, there is a 90.9% and 100% reduction of S-100 and PGP 9.5 immunoexpression for NF, respectively. These investigations also suggest that PGP 9.5 would be the best neuronal marker for the differentiation of intact nervous structures.[16]

In many cases, the clinical diagnosis of BMS is not described.[8,19] The diagnosis is complex and is done by exclusion based on well-established criteria in order to ensure that the burning symptoms are not due to systemic or other local underlying conditions. In fact, a biopsy-based approach to diagnosing BMS is still debated. One study demonstrated that BMS may exhibit two distinct clinical types and that a tongue biopsy can contribute to the diagnosis.[13] In particular, cases of oral lichenoid lesions exhibiting unconventional oral symptoms unrelated to clinical features and closely resembling those found in BMS have been reported.[24]

Randomized clinical trials often underreport the inclusion and exclusion criteria of participants,[19] and thus the results of therapeutic interventions from these clinical trials must be interpreted with caution due to the heterogeneous disease definitions and the lack of standardization in diagnostic criteria. In a similar way, studies that investigate the neuropathic etiopathogenesis of the disease also require caution. In the current study, the sample was selected based on well-defined clinical criteria, but the disease could not be characterized as a neuropathy. Perhaps, nociception may involve broader anatomical aspects such as the central nervous system and not only peripheral sites. In addition, nociception is related to a number of other factors such as the secretion and action of neuropeptides.[25]

The small sample size of this study could be pointed out as a limitation, but it is important to consider the inherent difficulty in diagnosing BMS patients and obtaining a biopsy in this oral condition. Nevertheless, our results draw attention to the fact that investigation of other etiological factors of BMS is necessary for a better understanding of the disease, favoring correct diagnosis and more accurate treatment choices.

In order to investigate the concentration of neuropeptides in individuals with BMS, Borelli et al.[10]

detected high salivary tryptase concentrations and suggested the participation of mast cells in the etiopathogenesis of the disease. Some studies have demonstrated the participation of mast cells in idiopathic diseases and in some neuropathic conditions.[13,26] These loose connective tissue cells are important for the secretion of neuropeptides[11] and there is evidence for the same functional and NF interactions in the oral mucosa of humans.[27] Nonetheless, there is a lack of studies exploring the density of mast cells in the oral mucosa of symptomatic individuals with BMS. In addition, a high expression of NGF has been documented in BMS.[7] This protein can stimulate mast cells to secrete mediators such as tryptase in inflammation[11,28] and neuropathic pain.[29] Possibly, local factors may influence the intensity and maintenance of the activation and degranulation of resident mast cells, promoting the secretion of a large number of substances that contribute to BMS symptoms.

We acknowledge that this study reports results based on a limited sample. However, considering that there is no consensus on biopsy as part of the clinical management of BMS patients, the recruitment of participants is limited. The results of this study confirm that the etiology of BMS is unclear and should be formally elucidated. There was no difference in the morphology and density of peripheral NF and tryptase$^+$ mast cells between tongue samples from patients with a clinical diagnosis of BMS and controls. However, further studies should be carried out to better understand the relationship between the activation and secretion profile of these cells and the etiopathogenesis of BMS.

Conclusion

In summary, patients with BMS did not show changes in peripheral NF density and integrity or in the density of mast cells in the tongue mucosa. Possibly, other neuropathic mechanisms are associated with the etiopathogenesis of BMS, and clinical and complementary exams still seem to be the most appropriate and least invasive approach to the diagnosis of this condition.

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