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ORIGINAL ARTICLE

Study of the correlation between the extent and clinical severity, and the histopathological characteristics of geographic tongue

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ABSTRACT

Background: Geographic tongue is an oral lesion with an unknown etiology. Recently, the Geographic Tongue Area and Severity Index (GTASI) has been proposed to assess the area and severity of geographic tongue, aiming to measure the clinical severity of the condition. However, this index does not account for the histopathology, which vary based on the clinical stage of the lesion and the biopsy area. The present study aimed to evaluate the correlation between GTASI score and its histopathological features.

Materials and methods: This cross-sectional observational study included 40 participants diagnosed with GT confirmed both clinically and histopathologically.

Results: Considering GT severity, a vast majority 60% of cases were classified as mild, with females' predominance in both mild and severe categories. The average age of participants was 56 years for mild and severe cases and 47 years for moderate ones. The prevalent histopathological features of geographic tongue included parakeratosis, acanthosis, spongiosis, basal layer hyperplasia, mono- and polymorphonuclear exocytosis, suprapapillary hypotrophy, claviform epithelial ridges, fusion of epithelial ridges, conjunctival papillary edema, and chronic subepithelial infiltration, with no significant differences taking into consideration clinical severity level. Papillary vascular ectasia, Munro microabscesses, Kogoj pustules, and dense connective tissue were more prevalent in with more severe cases of GT. Mild inflammatory infiltrate intensity was predominant in persons with mild GT, while moderate infiltrate intensity was found predominantly in moderate cases of GT.

Conclusions: The clinical severity level of GT closely corresponds with its histopathological characteristics.

Keywords: benign migratory glossitis; histopathology; geographic tongue; severity of Illness index

INTRODUCTION

Geographic tongue is an oral lesion of unknown origin, immunologically mediated, and characterized by chronic inflammation [14]. It typically involves phases of exacerbation and remission [18, 22, 23]. During the exacerbation phase, the central erythematous region reflects the atrophy of filiform papillae, while the white border consists of regenerated filiform papillae, keratin, and neutrophils [11, 12, 15, 22, 24]. To facilitate treatment and evaluate tongue lesion severity, Picciani et al. [23] developed the Geographic Tongue Area and Severity Index (GTASI), primarily based on clinical characteristics and lesion extent [23]. However, this parameter does not involve the histopathological features of geographic tongue, which can vary based on the clinical stage of the oral lesion and can be associated with clinical severity of GT [23].

Based on microscopic examination, GT is characterized by mixed and rather non-specific features such as parakeratosis, the absence of the granular layer, epithelial atrophy, acanthosis, and suprapapillary hypotrophy, defining the red portion of the lesion [19, 22, 25]. In some cases, contributing to the white portion of the lesion, there is pronounced neutrophil exocytosis, forming small clusters called Kogoj spongiotic pustules in the upper spinous layer, and Munro microabscesses in the corneal layer [19, 22, 25]. There is a subepithelial

inflammatory infiltrate, predominantly composed of T lymphocytes, macrophages, and neutrophils [19, 22, 25].

The assessment of association between histopathological findings of GT and its clinical status characterized by GTASI may deliver additional, important information unifying the primary classification of GT. Such analyses could contribute to an enhanced understanding of the etiopathogenesis of geographic tongue, its relationship with symptom severity, and clarification on whether there is a correlation between oral lesion severity and the histopathological characteristics of the lesions. Therefore, the primary aim of this study was to evaluate the potential correlation between the extent and clinical severity of GT and its histopathological characteristics.

MATERIALS AND METHODS

An observational cross-sectional study with a retrospective sample was conducted, comprising 40 participants diagnosed with clinical and histopathological evidence of geographic tongue, with an absence of candidiasis according to cytological examination. The study received approval from the Research Ethics Committee of University Hospital at the Federal Fluminense University, CAAE: 79887617.9.0000.5243.

Demographic and clinical data were collected through information from the medical records. The essential data included gender, age, and any previous occurrence of oral lesions. Clinical photographs of the GT, taken at the time of lesion biopsy, were assessed by two experienced dental practitioners (TNAD and BLSP) for calculating the GTASI,[4] resulting in calculation of severity scores: mild (< 7); moderate (7–12), and severe (≥1 2).

The histopathological examination involved material obtained from an incisional biopsy of the tongue lesion using a 5 mm punch, aiming to evaluate the essential histopathological features of geographic tongue, such as parakeratosis, acanthosis, suprapapillary hypotrophy, papillary vascular ectasia, papillary edema, spongiosis, claviform epithelial ridges, basal layer hyperplasia, fusion of epithelial ridges, exocytosis of polymorphonuclear and/or mononuclear cells, Munro microabscess, and Kogoj pustules. The inflammatory infiltrate was categorized as acute when it predominantly consisted of polymorphonuclear cells, chronic when primarily mononuclear, and mixed when both cell types were present in roughly equal proportions.

Before categorizing the inflammatory infiltrate, specific criteria were established as follows: first, the scanned sections from each participant were evaluated, and the section showing the most intense inflammatory infiltrate was selected. Subsequently, using the

ImageScope program (Leica Biosystem, Olympia, WA, USA) at a 40× magnification, the area with the highest cell density was captured. A grid was then employed for manual cell counting, resulting in a total of 360 cells. Therefore, the total cell count was divided into three: mild infiltrate (up to 120 cells), moderate infiltrate (120 cells to 240 cells), and intense infiltrate (above 240 cells). Subsequently, eight subepithelial areas were identified and selected non-equidistantly and at random using a 1 cm diameter circle at 2× magnification. They contained an adequate number of cells for analysis and were intended to cover different regions of the biopsy fragment with a predominant presence of mono- and polymorphonuclear inflammatory cells, thereby minimizing interference from other cell types (Fig. 1A). Furthermore, each selected area was individually magnified to 40×, and an image was captured from the central region of the circle using the “Snapshot” tool (Fig. 1B). The captured images were saved in TIFF format and stored in the image database prepared for this study.

To count the cells in each area, the captured and saved images were opened using the NIH ImageJ software, converted to 8-bit and grayscale for further analysis and cell counting. The results were presented as the arithmetic mean of the number of cells found in each participant. Inflammatory intensity was considered mild when the average count was up to 120 cells, moderate when the count ranged from 120 to 240 cells, and intense when the count exceeded 240 cells.

Finally, the classification of connective tissue into either loose or dense was conducted. Loose connective tissue was characterized by a high quantity of fibroblasts and a lower amount of collagen fibers, resulting in a pale pink appearance. In contrast, dense connective tissue was classified if there was a higher number and thick collagen fibers.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 22.0. Fisher’s exact test was utilized to evaluate differences among two or more categorical variables. For data that did not follow a normal distribution, group comparisons were made using the Mann–Whitney test. Spearman correlation was applied to assess the strength of relationships between variables. The predetermined level of statistical significance for all analyses was set at 5% ($p < 0.05$).

RESULTS

Based on GTASI, participants were categorized as follows: 24 (60%) were classified as mild, 9 (22%) as moderate, and 7 (18%) as severe (Fig. 2). Females were the majority, comprising 57.5% of the sample, with a higher male frequency in the moderate group,

accounting for 71.5%. The age of the participants ranged from 18 to 85 years, with an average of 56 years for the mild and severe categories and 47 years for the moderate category (Tab. 1). Other oral alterations, distinct from geographic tongue, were observed in all moderate and severe cases (Tab. 2). No statistically significant differences were found between the groups (Tab. 1).

The histopathological assessment revealed parakeratosis, acanthosis, spongiosis, basal layer hyperplasia, and mononuclear exocytosis in all cases. Polymorphonuclear exocytosis, fusion of epithelial ridges, conjunctival papillary edema, and chronic inflammatory infiltrate were consistently found in all moderate and severe cases. However, suprapapillary hypotrophy and claviform epithelial ridges were predominantly observed in the mild category (Tab. 3, Fig. 3). On the other hand, Munro microabscess, Kogoj pustule, and papillary vascular ectasia was prevalent in the moderate and severe categories, showing a significant difference compared to the mild category.

Considering the intensity of the inflammatory infiltrate, the mild inflammatory infiltrate was more common in cases of mild severity, while the moderate inflammatory infiltrate was prevalent in moderate cases of GT (Tab. 3). Notably, no cases exhibited an intense inflammatory infiltrate. Concerning the connective tissue, dense connective tissue was the prevailing type across all severity categories of geographic tongue (Tab. 3).

When analyzing the inflammatory intensity and the numerical values of the GTASI, a tendency of mild association was observed, presenting a weak correlation coefficient at 0.099 ($p = 0.543$; Fig. 4). Nonetheless, when considering only two groups, mild and non-mild (moderate and severe), based on the clinical severity of the GTASI and correlating it with the average numerical value of inflammatory cells for each case, the association became more evident ($p = 0.078$, Figure 4). Furthermore, the average inflammatory cell count showed a significant association ($p = 0.015$), with the GTASI scores (Fig. 4).

DISCUSSION

The association between clinical features of GT evaluated using GTASI and its histopathological characteristics has not been studied sufficiently. Few recent studies with a numerically significant sample size were found in the literature [7, 23]. Santos et al. [7] utilized the GTASI to monitor a case of geographic tongue associated with fissured tongue in a hospitalized patient due to health issues caused by COVID-19 [7]. In our group, most cases

of GT were classified as mild, while in the above report, the initial assessment presented as severe,
which decreased to moderate after ten days of hospital discharge, while no specific treatment was applied; however, an alleviation of the clinical severity of GT along with the improvement in the patient's systemic condition was observed [7]. This phenomenon suggests that overall systemic inflammatory condition can be related to the severity of GT.

Regarding the demographic and clinical profile of the sample, although GT has been reported equally in both genders, some studies demonstrate a higher incidence in females [1, 6, 14, 20, 21, 23, 24, 26]. In this context, the results of our study also incline a slight predilection in females. Although males predominated in the moderate category of GT, there was no statistical difference between the groups ($p < 0.05$). GT is frequently reported in population below the age of 30 [6, 14, 27]. Contrarily, the participants' average age was higher in this study, reflecting the wide age range of the individuals evaluated, ranging from 74 to 85 years. Furthermore, most participants could not recall the age at which the tongue lesions first appeared, suggesting that despite being evaluated at an older age, the initial lesions likely occurred at a younger age.

On through intraoral examination, other lesions distinct from geographic tongue were observed in 85% patients, with fissured tongue being most prevalent in all groups as the association between GT and fissured tongue has been frequently reported in the literature [1, 5, 10, 13, 17, 20, 27]. Thus, our study not only reinforces this clinical association but suggests in pioneer way that, that the presence of fissured tongue may be closely related to an increase in the clinical severity of GT.

In the histopathological evaluation, parakeratosis, polymorphonuclear neutrophils forming microabscesses (Munro’s microabscess), occasional presence of small spongiotic pustules (Kogoj pustule), acanthosis, spongiosis, regular increase in the spinous layer with thickening of the lower portion, conjunctival papillary edema, suprapapillary hypotrophy, fusion of ridges, exocytosis, and acute and chronic inflammatory infiltrate in the submucosa, primarily composed of T lymphocytes, macrophages, and neutrophils, are characteristic findings in geographic tongue [9, 20, 22, 26]. It must be noted that these histopathological characteristics can vary depending on the clinical stage of the lesion and the biopsy area [7, 9, 22]. In the histopathological assessment of the 40 participants, classified according to the severity degree of GTASI, parakeratosis, acanthosis, spongiosis, basal layer hyperplasia, and mononuclear exocytosis were present in all cases. Polymorphonuclear exocytosis was observed in all cases of moderate and severe degrees and in most of the mild cases, indicating

that is a common aspect, irrespective of the clinical severity degree. Suprapapillar hypotrophy was predominant in the mild degree but was also present in most moderate and severe cases, along with claviform epithelial ridges, demonstrating that the reduction in epithelial thickness at the ends of the conjunctival papillae due to a reduction in cell numbers and the widening of epithelial cones are characteristic findings of geographic tongue and are not necessarily related to a lower clinical severity degree of the lesion. Conversely, fusion of epithelial ridges was observed in all cases of moderate and severe degrees and in most mild cases, as was conjunctival papillary edema. Arguably, since there was no statistically significant difference between the groups, these findings cannot be correlated with the increased clinical severity of the tongue lesions. Nonetheless, even though they are not directly associated with clinical severity parameters, these findings generally represent the inflammatory-mediated various, non-specific immunological disorders that constitute the pathogenesis of GT.

Papillary vascular ectasia was observed in all moderate cases, most severe cases, and in just over half of the mild cases ($p = 0.066$) of GT. This finding was directly related to the localized erythema that commonly occurs in GT [20] and, in this study, demonstrated a positive correlation with the clinical severity of the lesion. Such characteristic can be related to vascular endothelial growth factor (VEGF) and interleukin-8 released by keratinocytes, which contribute to the increased number and dilation of vessels, influencing the intense vascularization of geographic tongue [2, 8, 20] VEGF causes an increase in microvascular permeability, contributing to the arrival of inflammatory cells that release cytokines and other substances, resulting in the maintenance of the inflammatory response [2, 8, 20]. As a mitogen, it could be associated with the basal layer hyperplasia of the epithelium. Furthermore, the maintenance of the inflammatory response would lead to the exacerbation and active process of GT consequently increasing its clinical severity.

Munro’s microabscess and Kogoj pustule are described in the white margins of GT lesions [4, 20, 22]. When neutrophils are recruited by interleukin-8 synthesized by CD4 T cells and then migrate through the epithelium, forming collections in the corneal and spinous layers [19, 20, 22]. As the inflammatory activity of the white area is crucial for GT persistence, Amal Dafar et al. [4] proposed a classification for GT where lesions were simply categorized in dichotomous way into active and passive. Active forms correspond to lesions with the erythematous area surrounded by a white halo, while passive forms consist of depapillated areas with the absence of a white halo. The results of our study revealed that Munro’s microabscess and Kogoj pustule were present in all severe cases and in most moderate cases (89%), being less frequent in the mild cases (Munro’s microabscess, p =

0.072, and Kogoj pustule, p = 0.013). This finding demonstrates that the clinical severity degree reflects the intense activity of the inflammatory cells in the white halo.

Despite an intense neutrophilic activity in the white halo region, GT is deemed of chronic inflammatory nature. Consequently, there is a predominance of mononuclear cells, primarily lymphocytes, in the subepithelial inflammatory infiltrate [3, 9, 16, 20–22]. In our sample, chronic inflammatory infiltrate was present in all moderate and severe cases and in most mild cases. It was also observed that the inflammatory intensity was correlated with clinical severity of GT. Mild inflammatory intensity was predominant in the mild group of GT, with statistical significance, just as moderate inflammatory intensity was predominant in the moderate group. The group of patients with severe GT predominantly showed mild inflammatory intensity, but when examining absolute numbers, four participants were classified with mild inflammatory intensity and three as moderate. To better understand the results, a numerical value of GTASI, not the index categories alone, was analyzed in relation to inflammatory intensity. Based on this analysis, a trend between GTASI severity and inflammatory intensity was observed (p = 0.543), despite a weak correlation coefficient (0.099). Subsequently, a new analysis was conducted, taking into consideration only two GTASI severity categories, mild and non-mild (including the moderate and severe groups), and the average value of inflammatory cells for each case, making the association between increased clinical severity and inflammatory intensity more evident (p = 0.078). Finally, the GTASI value and the average number of inflammatory cells were positively correlated, (p = 0.015). As a result, it is evident that the clinical severity of the lesion seems correlated with inflammatory intensity of the lesions and some histopathological characteristics, such as papillary vascular ectasia, and the presence of Munro’s microabscess and Kogoj pustule.

Dense connective tissue (DCT) was predominant in the moderate and severe categories GT, while it was present in just over half of the mild cases. However, no studies were found demonstrating correlation between the presence of DCT with an increase in clinical severity of the lesions. Therefore, this finding, in addition to being related to the chronic nature of the lesion with periods of exacerbation and remission, tends to be associated with greater clinical severity of the lesions.

CONCLUSIONS

The observed correlations suggest that the degree of clinical severity of geographic tongue is closely associated with its histopathological features, reinforcing the importance of histopathological evaluation in the diagnosis and future treatment of geographic tongue.

ARTICLE INFORMATION AND DECLARATIONS

Data availability statement

The above-mentioned work has not previously been published and that it has not been submitted to the Publishers of any other journal (with the exception of abstracts not exceeding 400 words). Data openly available in a public repository that issues datasets with DOIs.
All the co-authors named and the relevant authorities of the scientific institutions in which the work has been carried out are familiar with the contents of this work and have agreed to its publication

Ethics statement

The study received approval from the Research Ethics Committee of University Hospital at the Federal Fluminense University, CAAE: 79887617.9.0000.5243.

Author contributions

All authors have made substantial contributions to all aspects in the preparation of this manuscript: (1) the conception and design of the study, analysis, and interpretation of data, (2) the first draft and revisions with critical assessment of important intellectual content, (3) the final approved version to be submitted.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Table 1. Sample distribution according to sociodemographic and clinical profile.

Variant		**GTASI score**						**Total**		**p**
		Mild		**Moderate**		**Intense**				
		n = 24	**% = 100**	**n = 9**	**% = 100**	**n = 7**	**% = 100**	**n = 40**	**% = 100**	
Sex*	Male	9	37.5	**6**	**67**	2	28.5	17	42.5	0.228
	Female	**15**	**62.5**	3	33	**5**	**71.5**	**23**	**57.5**	
Age**	Minimum - maximum	23–85		18–74		32–80		-		0.405
	Average	56 (dp = 18)		47 (dp = 17)		56 (dp = 16)		-		
	Median	58,5		42		56		-		
	Absent	**15**	**62.**	**6**	**67**	**5**	**71.5**	**26**	**65**	

			5							
Oral	Present	**18**	**75**	**9**	**100**	**7**	**100**	**34**	**85**	0.09
alterations*	Absent	6	25	0	-	0	-	6	15	5

*Fisher's exact test; **student t-test.

Table 2. Sample distribution according to oral lesion.

Oral lesion*	**Mild**	**Moderate**	**Intense**
	n = 24	**n = 9**	**n = 7**
Fissured tongue	75%	78%	6%
Actinic cheilitis	0	11%	28.5%
Benign migratory erythema	4.5%	11%	14.5%
Oral lichen planus	0	0	14.5%
Squamous papilloma	0	11%	0

*Each participant could present more than one oral lesion

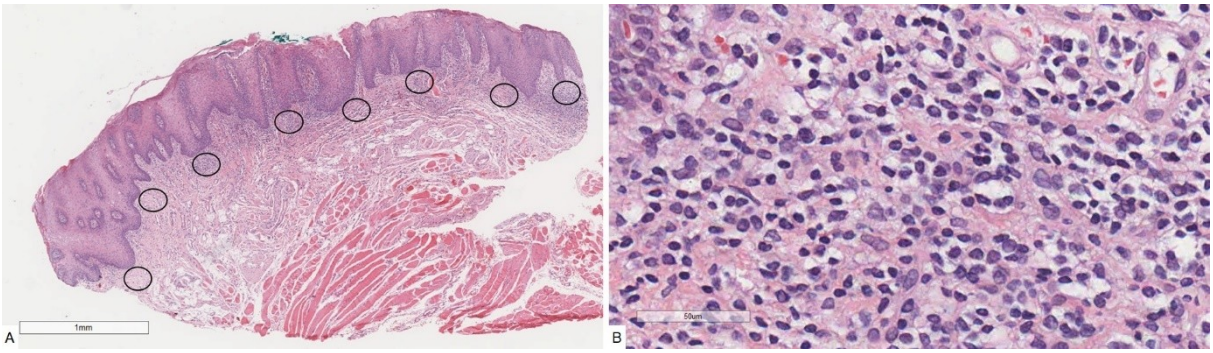


Figure 1. Photomicrographs illustrating areas selected for analysis; **A.** Selection of eight areas to analyze the intensity of the inflammatory infiltrate (2× magnification); **B.** An area selected for analysis of the intensity of the inflammatory infiltrate at 40× magnification

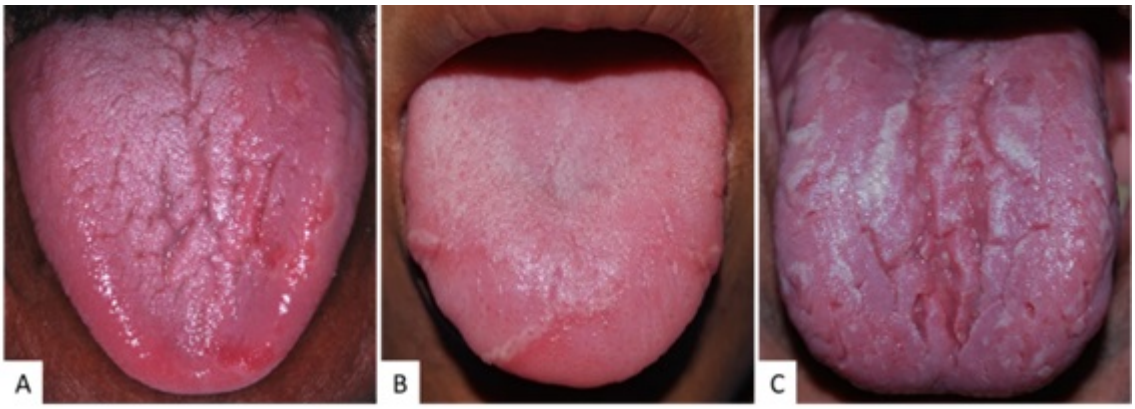


Figure 2. Classification of extension and clinical severity of geographic tongue; **A.** Mild; **B.** Moderate; **C.** Severe.

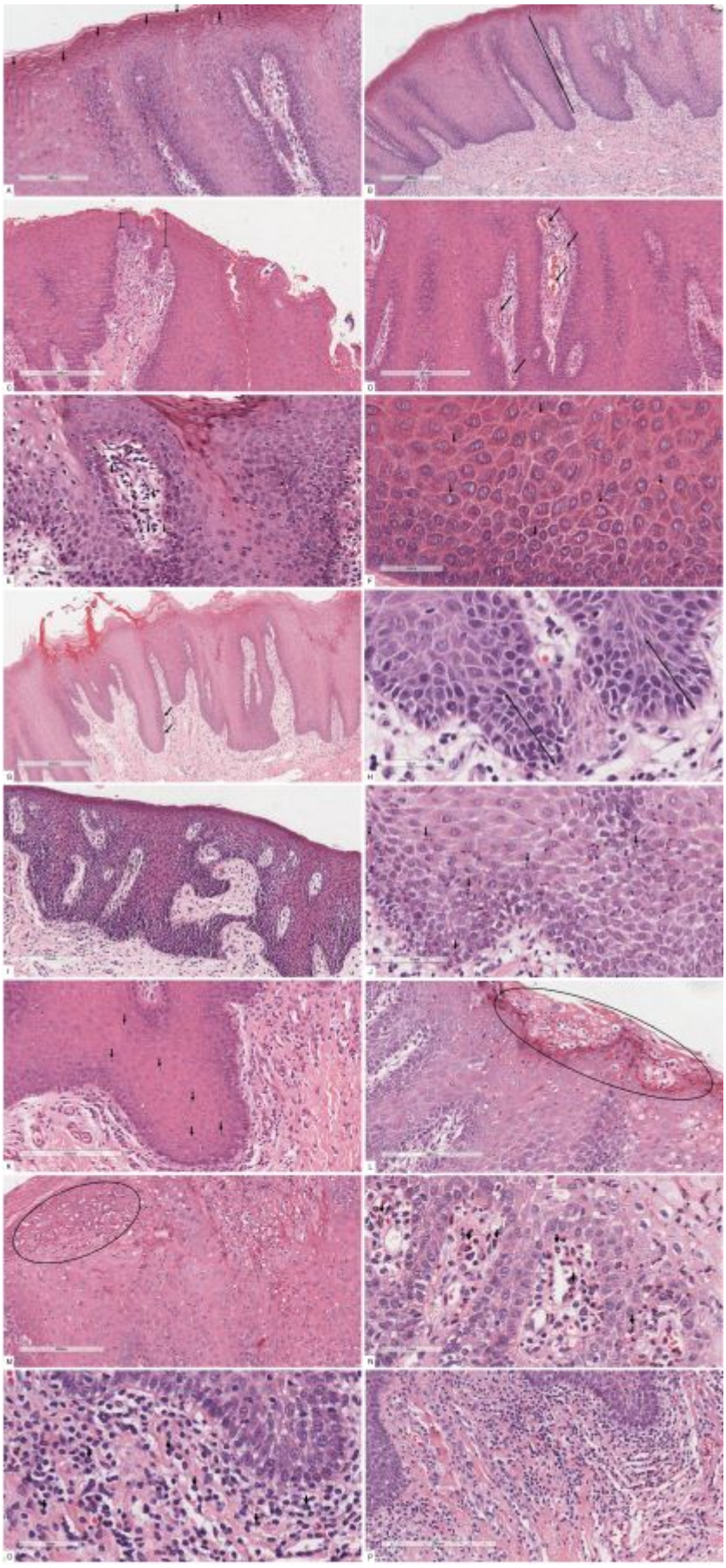
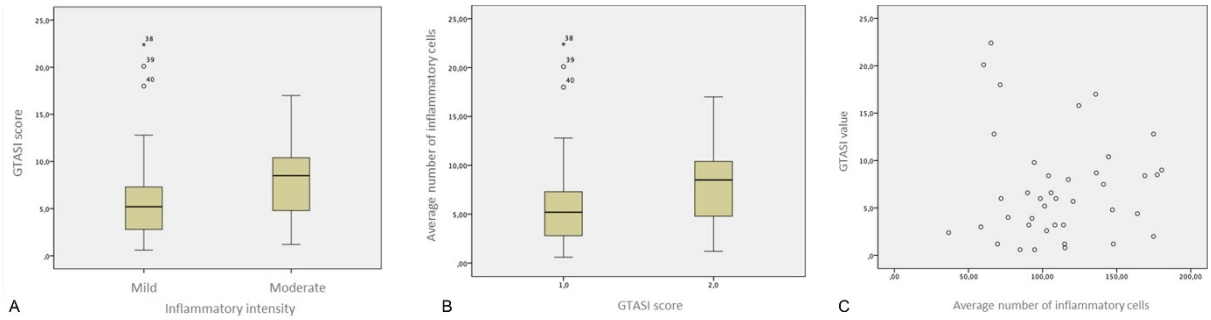


Figure 3. Histopathological features of geographic tongue; **A.** Presence of nucleated cells in the stratum corneum (black arrows); **B.** increased epithelial thickness (black line); **C.** suprapapillary hypotrophy (black line); **D.** vascular ectasia (black arrows); **E.** presence of edema of the conjunctive papillae (black arrows); **F.** Spongiosis; **G.** Clavicular epithelial ridge (black arrows); **H.** Hyperplasia of the basal layer at 40× magnification (line with black arrow); **I.** Fusion of epithelial ridges. J. Exocytosis of polymorphonuclear cells (black arrows); **K.** Exocytosis of mononuclear cells (black arrows); **L.** Munro microabscess (black circle); **M.** Kogoj pustule (black circle); N. Inflammatory infiltrate composed mainly of polymorphonuclear cells (black arrows). O. Inflammatory infiltrate composed mainly of mononuclear cells (black arrows). P. Dense connective tissue.



Statistical analyses; **A.** Correlation between inflammatory intensity and GTASI score; **B.** Correlation between the average number of inflammatory cells and the GTASI score; **C.** Association between the average number of inflammatory cells and the GTASI value.