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The prevalence of celiac disease in patients with geographic tongue

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BACKGROUND: Geographic tongue (GT) is a benign inflammatory condition usually involving the dorsal surface and lateral borders of the tongue. Numerous etiological factors of GT have been suggested, including immunological factors; genetic; atopic or allergic predisposition; emotional stress; and hormonal disturbances. GT may also coexist as one of the possible manifestations of celiac disease (CD). Therefore, the aim of this study was to investigate the prevalence of CD, positive serologic tests for CD screening, and HLA-DQ presence in patients with GT.

METHODS: Tissue transglutaminase antibodies (anti-tTG), antibodies against gliadin (AGA), and human leukocyte antigen (HLA) typing were assessed for 60 GT patients and 60 healthy control subjects. The duodenal biopsy was performed in patients with positive serologic tests.

RESULTS: We found that 9 (15%) GT patients were positive for IgA tTG, and in those patients histological changes consistent with CD were confirmed by duodenal biopsy. Only two of them reported the presence of gastrointestinal symptoms. There were statistically significant differences between the GT patients and control group for immunoglobulin (Ig) A tTG ($P = 0.03$), IgG tTG ($P = 0.04$), IgA AGA ($P = 0.04$), and IgG AGA ($P = 0.02$).

CONCLUSION: The results of our study demonstrated the increased prevalence of CD in patients with GT. Therefore, the clinical oral examination should be considered a diagnostic tool, especially in atypical or silent forms of CD, since it may contribute to provide an early diagnosis.

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Keywords: antibodies to gliadin; celiac disease; duodenal biopsy; geographic tongue; tissue transglutaminase antibodies

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Introduction

Geographic tongue (GT), also known as benign migratory glossitis, is an inflammatory condition that usually involves the dorsal surface and lateral borders of the tongue. Atrophy of the filiform papillae leaves an erythematous area with a white, yellow or gray elevated peripheral zone, and irregular jagged pattern of the tongue (1). Histological observations of the oral mucosa affected by GT revealed non-specific inflammation (2). Geographic tongue may be asymptomatic, but sometimes a burning sensation is reported after consuming spicy and/or salty foods, as well as alcoholic drinks. Discomfort may be treated with mouth rinse containing antiseptic and anesthetic agents and topical corticosteroids. The condition may spontaneously exhibit periods of remission and exacerbation (3).

The etiology and pathogenesis of GT are still unknown. Numerous etiological factors have been suggested in the literature, including immunological factors, genetic, atopic or allergic predisposition, emotional stress, and hormonal disturbances. GT may coexist with disorders such as fissured tongue, psoriasis, diabetes mellitus, gastrointestinal diseases, and Down syndrome (4).

The oral cavity is one of the areas of celiac disease (CD) manifestation. The most common and well-documented oral manifestations of CD are recurrent aphthous stomatitis (RAS) and dental enamel defects (5, 6).

Celiac disease is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals, carrying the human leukocyte antigen (HLA) DQ2 or HLA-DQ8 (7). It has a prevalence of about 1–2% in European countries (8). The clinical presentation usually involves a wide spectrum of symptoms, such as malabsorption and malnutrition, diarrhea, anorexia, constipation, vomiting, and abdominal distension. Complications associated with untreated CD include osteoporosis, obstetric complications, neurologic disorders, and enteropathy-associated T-cell lymphoma or adenocarcinoma of the jejunum (9). However, most patients manifest atypical CD, with few or no gastrointestinal symptoms, and predominant extraintestinal features. Therefore, a large number of patients remain undiagnosed (10).

A diagnosis of CD is initially determined by serologic tests and is confirmed by duodenal biopsy. Most guidelines support screening based on tissue transglutaminase (tTG) immunoglobulin (Ig) A, or tTG IgG in patients with IgA deficiency because of their high sensitivity and specificity. According to the National Institute for Health and Clinical Excellence (NICE) guidelines, a combination of anti-endomysial antibodies (EMA) and tTG tests have sensitivity and specificity similar to the individual test strategies. Anti-tTG has been found to be superior to the anti-gliadin antibodies (AGA) test, with the sensitivity and specificity greater than 95% when combined. Currently, more patients with non-gastrointestinal manifestations are being diagnosed with the help of improvements in screening serology tests for CD (11). Additionally, more than 95% of patients with CD have the DQ2 or DQ8 marker, compared to about 40% of the general population. Since the development of CD strongly depends on several HLA risk haplotypes, HLA typing has almost 100% sensitivity in detecting at-risk individuals, while also excluding those who are very low risk (12).

According to some authors, GT is one of the possible oral manifestations of CD (13–15), although there are no available data on the prevalence of CD in patients with GT. Therefore, the aim of this study was to investigate the prevalence of CD, positive serologic tests for CD screening, and HLA-DQ presence in patients with GT. We hypothesize that patients with GT will have a higher prevalence of CD compared to healthy control subjects.

Materials and methods

Patients

This study was approved by the Ethics Committee of the University of Split School of Medicine and was undertaken in agreement with the principles of the Declaration of Helsinki. All study participants provided written informed consent.

Sixty patients with a clinical diagnosis of GT from the dental clinic at the University of Split School of Medicine were prospectively enrolled to the study between September 2011 and September 2015. All patients underwent extensive interview and clinical examinations by the same oral medicine specialist. Inclusion criteria were the age of 18 or older and the oral lesions consistent with GT. The clinical diagnosis of GT was determined by the presence of one or more erythematous patches with a raised white or yellow serpiginous border at the dorsal surface or lateral borders of the tongue (2) (Fig. 1). During the anamnesis patients were asked about their smoking status, the existence of psoriasis, diabetes mellitus, gastrointestinal disorders, or other autoimmune diseases. They were also asked about the existence of gastrointestinal symptoms, such as vomiting, diarrhea, obstipation, abdominal pain, and distension or weight loss. None of the patients had been previously diagnosed with CD. Exclusion criteria were previously diagnosed gastrointestinal diseases, oral lesions other than GT and the use of drugs that could manifest side effects on the oral mucosa. Patients unable to understand the purpose of the study were also excluded.

The subjects for the control group were also recruited from the dental clinic at the University of Split School of Medicine from a pool of healthy subjects whose clinical examinations showed no signs of any oral lesions. They were matched with the patients with GT for sex and age.

Laboratory analysis

Fasting blood samples were obtained from the antecubital vein in the early morning (7 a.m.– 8 a.m.) for each study participant. Three different blood assessments were performed: full blood count and iron status, serologic tests for CD screening, and HLA typing. All test samples were analyzed in the same laboratory by the same experienced biochemist following standard protocols.

Full blood count and iron status, and red blood cell included hemoglobin (Hgb), hematocrit (hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), serum iron, total iron-binding capacity (TIBC), unsaturated iron-binding capacity (UIBC), and serum ferritin were assessed in the Department for Clinical Laboratory Diagnostics, University Hospital Center of Split, to identify patients with anemia.

Serologic tests for CD screening were performed at the Department for Clinical Laboratory Diagnostics, University Hospital Center of Split. IgA and IgG AGA, as well as IgA and IgG tTG, were measured in all sera using the Theradiag FIDIS™ Celiac DPG kit, Marne La Vallee, France (for the simultaneous detection of human IgA or IgG isotype antibodies directed against tissue transglutaminase and gliadin). The manufacturer-proposed cut-off value was 20 AU/ml for both anti-tTG and AGA. Anti-tTG and AGA were interpreted as negative, borderline or positive if the values were <15, 15–20, and >20 respectively. The Microlymphocytotoxicity test was performed as the standard serological HLA typing method at the laboratory for HLA typing, University Hospital Center of Split. All assessments were performed for the subjects in both the GT and control groups.

Diagnosis of CD

Patients positive for one or both antibodies were informed of their results and advised to visit a gastroenterologist at the

Figure 1 Clinical outlook of GT.

Department of Internal Medicine, University Hospital Center of Split. They underwent clinical examination with endoscopy and duodenal biopsy. The biopsy specimens were immediately conserved in a 10% formalin solution at the Department of Clinical Pathology, University Hospital Center of Split. Samples were stained with haematoxylin-eosin for microscopic examination of the duodenal mucosa and evaluated according to the modified Marsh–Oberhuber classification by the same pathologist who was blind to the clinical diagnosis and serological testing results of the patients. Diagnosis of CD was based on positive Marsh–Oberhuber scores and positive serologic tests for CD screening.

Statistical analysis

Statistical analyses were performed using the statistical software Statistica 12.0 (StatSoft Inc., Tulsa, USA). Continuous data were presented as means ± standard deviation, whereas categorical variables were presented as whole numbers and percentages. The Mann–Whitney *U* test and *t*-test for independent samples were used for the analyses of differences between the GT and the control groups. Multiple regression analysis and general regression model (GRM) from the linear/nonlinear modeling method were used to assess the influence of the predictor variable on the dependent variables, i.e., diagnosis and iron-deficiency anemia). The results of the GRM were expressed in the form of Pareto charts of the *t* values. $P < 0.05$ was considered statistically significant.

Results

Patient baseline characteristics

The experimental group consisted of 60 patients diagnosed with GT while the control group consisted of 60 healthy subjects without any oral lesions. Baseline characteristics of subjects included in the study are presented in Table 1. There were statistically significant differences between the GT group and the control group in the presence of gastrointestinal symptoms (4/60, 6.7% vs. 0/60, 0%, $P = 0.04$), other autoimmune diseases (4/60, 6.7% vs. 0/60, 0%, $P = 0.04$), the presence of iron-deficiency anemia (11/60, 18.3% vs. 0/60, 0%, $P < 0.001$), and a positive Marsh-Oberhuber score (9/60, 15% vs. 0/60, 0%, $P = 0.03$). There were no statistically significant differences in the incidence of positive HLA DQ2 and/or DQ8 between both groups (Table 1). Nine (15%) patients with GT had a confirmed celiac disease diagnosis, while no controls were confirmed to have CD. Individual characteristics of GT patients with CD are presented in Table 2.

Concentrations of the selected antibodies were significantly higher in the GT group than in the control group as follows: IgA tTG 47.55 ± 53.20 AU/ml vs. 17.25 ± 2.26 AU/ml, ($P = 0.03$), IgG tTG 26.32 ± 53.20 AU/ml vs. 12.90 ± 13.55 AU/ml, ($P = 0.04$), IgA AGA 33.23 ± 101.57 AU/ml vs. 7.67 ± 8.27 AU/ml, ($P = 0.04$), and IgG AGA 29.70 ± 69.62 AU/ml vs. 8.62 ± 7.89 AU/ml, ($P = 0.02$).

Differences in incidence of positive antibodies concentrations between the GT and the control group are presented in Table 3.

Table 1 Baseline characteristics of patients with geographic tongue and control subjects

Variable	*GT group* N = *60*	*Control group* N = *60*	P
Gender			
F	45 (75)	39 (65)	0.23
M	15 (15)	21 (35)	
Smoking habit			
No	44 (73.3)	44 (73.3)	1.00
Yes	16 (26.7)	16 (26.7)	
Gastrointestinal symptoms			
No	56 (93.3)	60 (100)	0.04*
Yes	4 (6.7)	0 (0)	
Other autoimmune diseases			
No	56 (3.3)	60 (100)	0.04*
Yes	4 (6.7)	0 (0)	
HLA DQ2			
No	47 78.3)	43 (71.7)	0.40
Yes	13 (21.7)	17 (28.3)	
HLA DQ8			
No	53 (88.3)	52 (86.7)	0.78
Yes	7 (11.7)	8 (13.3)	
HLA DQ			
No	41 (68.3)	38 (63.3)	0.56
Yes	19 (31.7)	22 (36.7)	
Gastroenterology examination			
No	42 (70)	52 (86.7)	0.03*
Yes	18 (30)	8 (13.3)	
Duodenal biopsy			
No	45 (75)	55 (91.7)	0.01*
Yes	15 (25)	5 (8.3)	
Marsh-Oberhuber score			
0	6 (40)	5 (100)	0.03*
1	2 (13.3)	0 (0)	
2	4 (26.7)	0 (0)	
3A	1 (6.7)	0 (0)	
3C	2 (13.3)	0 (0)	
Iron-deficiency anemia			
No	49 (81.7)	60 (100)	<0.001**
Yes	11 (18.3)	0 (0)	

Data are presented as *N* (%).
GT, geographic tongue; HLA, human leukocyte antigen.
Marsh-Oberhuber score (according to the modified Marsh-Oberhuber classification), 0: normal mucosa; 1: elevated intraepithelial lymphocyte (IEL) count (>30 IEL/100 enterocytes); 2: elevated IEL, crypt hyperplasia, and normal villous structure; 3A: mild villous flattening (partial villous atrophy), elevated IEL, and crypt hyperplasia; 3B: marked villous flattening (subtotal villous atrophy), elevated IEL, and crypt hyperplasia; 3C: flat mucosa (total villous atrophy), elevated IEL, and crypt hyperplasia.
*$P < 0.05$, significant difference between control and GT group.
**$P < 0.001$

Predictors of the geographic tongue diagnosis

Correlations between the presence/absence of GT (diagnosis) and selected predictor variables are presented in Fig. 2. According to the multiple regression analysis, high degree of the statistically significant correlations between presence/absence of geographic tongue (diagnosis) and selected predictor variables were obtained (R = 0.82; $P = 0.02$). The concentrations of tTG and AGA antibodies in patients with confirmed CD increased almost linearly with the increasing Marsh-Oberhuber score.

Correlations of iron-deficiency anemia, geographic tongue and celiac disease

Across the GT group, 11 patients (18%) presented with iron-deficiency anemia. Among those 11 patients, CD was

Table 2 Individual characteristics of patients with geographic tongue and celiac disease

Patient	*Age (years)*	*Gender*	*IgA tTG titer (AU/ml)*[a]	*Gastrointestinal symptoms*	*HLA DQ*	*Marsh-Oberhuber score*	*IEL count*	*Iron-deficiency anemia*
1	47	F	186	Weight loss	DQ2	3C	50	Yes
2	46	F	48	None	DQ8	2	79	No
3	59	F	166	Abdominal distension	DQ2	3A	49	Yes
4	27	F	32	None	DQ2	1	37	No
5	58	M	62	None	DQ2	1	31	No
6	71	F	41	None	DQ8	2	52	No
7	66	F	22	None	DQ2	2	71	No
8	42	F	331	None	DQ2	3C	67	Yes
9	39	F	58	None	DQ8	2	56	No

IgA tTG, immunoglobulin A tissue transglutaminase antibodies; HLA, human leukocyte antigen; IEL count, number of intraepithelial lymphocytes per 100 enterocytes.
[a]Reference range is 20 AU/ml or less.

Table 3 Differences in incidence of positive antibodies concentrations between patients with geographic tongue and control subjects

Variable	*GT group* N = *60*	*Control group* N = *60*
IgA tTG	9 (15)	0 (0)
IgG tTG	15 (25)	9 (15)
IgA AGA	13 (21.7)	3 (5)
IgG AGA	14 (23.3)	2 (3.3)

Data are presented as *N* (%).
IgA tTG, tissue transglutaminase immunoglobulin A antibodies; IgG tTG, tissue transglutaminase immunoglobulin G antibodies; IgA AGA, immunoglobulin A antibodies against gliadin; IgG AGA, immunoglobulin G antibodies against gliadin; GT, geographic tongue.

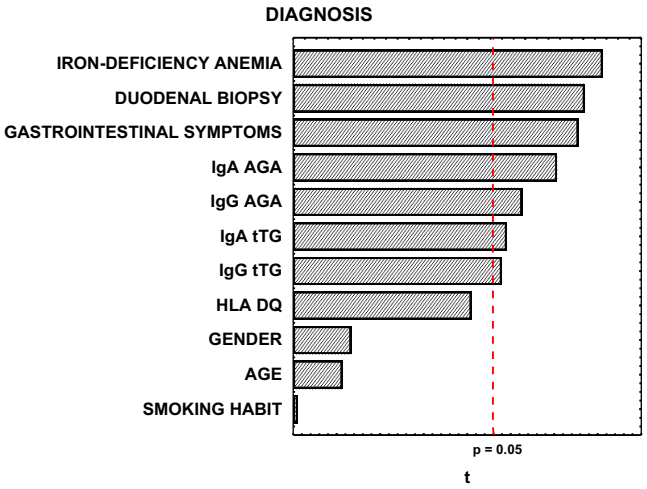

Figure 2 Pareto charts of various predictor variables on the presence of the GT (diagnosis).

confirmed in three of them (27.3%) by duodenal biopsy with the highest Marsh-Oberhuber score (one of them 3A and 2 of them 3C). Additionally, they were positive to HLA DQ2 marker, while two of three patients also developed gastrointestinal symptoms. Considering all 11 patients with iron-deficiency anemia, all of them were female, with a mean age of 45 ± 12.02 years. Among them, four (36.4%) were active smokers and three (27.3%) suffered from other autoimmune diseases, i.e., systemic lupus erythematosus, vitiligo and Raynaud syndrome.

Histologic findings in patients with positive duodenal biopsy for CD (Marsh-Oberhuber score 1, 3A and 3C) are shown in Fig. 3.

Discussion

The results of our study showed that celiac disease was prevalent among 15% of patients with geographic tongue, as confirmed by a duodenal biopsy. In addition, the GT group had significantly higher blood concentrations of immunoglobulin antibodies (IgA tTG, IgG tTG, IgA AGA, and IgG AGA), known as valuable screening serologic predictors for CD with the specificity and sensitivity greater than 95% (10, 11). There was also a higher incidence of increased concentrations (>20 AU/ml) of the selected antibodies in the GT group compared to the control subjects. There was no statistically significant difference in incidence of the human leukocyte antigens DQ2 or DQ8 obtained by HLA-typing between the GT patients and control subjects.

Oral manifestations of CD previously described in the literature may affect developing dentition and oral mucosa (13–17). Recently, many studies confirmed a higher frequency of dental enamel defects in patients with CD (16, 17). The association between oral mucosa abnormalities and CD was proposed by Ferguson et al. (18), who found that 24% of patients with RAS showed histological evidence of CD confirmed by jejunal biopsy. On the contrary, Pastore et al. (14) emphasized conflicting data on the association between CD and RAS. Additional oral signs associated with CD mentioned in the literature include angular cheilitis, glossitis and oral lichen planus (OLP) (19, 20). As can be seen, among many oral manifestations of CD, evidence between the association of GT and CD is lacking in the literature. Therefore, to the authors' best knowledge, this is the first prospective study confirming GT as a possible oral manifestation of CD.

In our study, nine (15%) GT patients were positive for IgA tTG, and duodenal biopsy confirmed histological changes consistent with CD in all of them. All other patients from the GT and the control group were negative

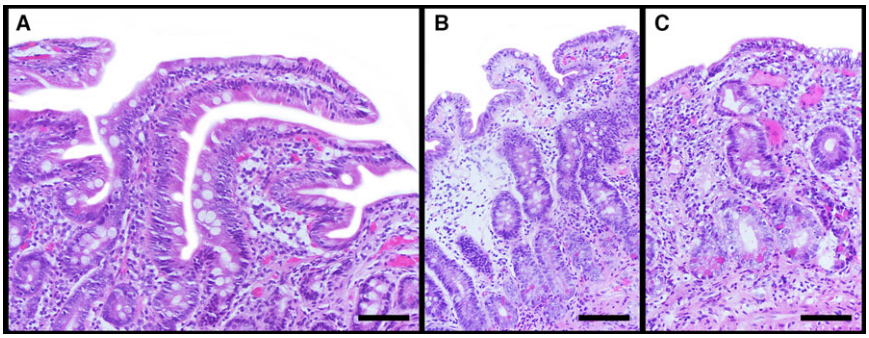

Figure 3 Positive duodenal biopsy of patients with GT.(A) Marsh-Oberhuber score 1. HE staining (magnification: × 100; scale bar: 10 μm); (B) Marsh-Oberhuber score 3A. HE staining (magnification: × 40; scale bar: 25 μm); (C) Marsh-Oberhuber score 3C. HE staining (magnification: × 40; scale bar: 25 μm).

for IgA tTG, which confirmed the general agreement that the best strategy for serological screening for CD is the detection of IgA tTG (21).

As previously described in the literature, CD is closely related to the well-defined HLA pattern, which is characterized by the presence of HLA DQ2 and/or HLA DQ8 (12). Since 40% of the general population displays the same HLA pattern as CD patients, the latest diagnostic guidelines suggest that a positive HLA-typing result alone should not be used as the only diagnostic criterion for CD (22). In the present study, all GT patients with confirmed CD had positive HLA DQ2 or DQ8 (seven were positive for DQ2 and two for DQ8), although there was no significant difference in the presence of HLA DQ2 and DQ8 between the GT and the control group.

Eighteen (30%) GT patients and eight control subjects (13.3%) with positive serologic tests were advised to be examined by a gastroenterologist. Taking into account that the duodenal biopsy is still the gold standard for the diagnosis of CD in adults (23), biopsies were performed in 15 (25%) GT patients and five control subjects (8.3%). Patients who showed only slightly increased IgG antibodies did not undergo a biopsy, but were recommended for a follow-up examination after 3 months. The concentrations of tTG and AGA antibodies in patients with the confirmed CD increased almost linearly with the increasing Marsh-Oberhuber score. A gluten-free diet was recommended to all patients with confirmed CD. The limitation of this study might be the lack of evidence about the oral mucosa response to the proposed diet. Further studies are needed to establish the association between GT and CD and to monitor the oral responses of GT patients with CD to the gluten-free diet.

Previous serologic studies demonstrated that most patients with CD present with oligosymptomatic, latent, potential, and extraintestinal forms of the disease. These non-classic clinical presentations have become increasingly common and might affect about 50% of all diagnosed patients (24).

The current study shows that among four (6%) GT patients reporting gastrointestinal symptoms (two with weight loss, and two with abdominal distension), two of them had confirmed CD; the remaining seven GT patients with CD had no gastrointestinal symptoms. It is significant that adult patients often remain undiagnosed, due to the absence of symptoms or atypical clinical presentations (25). The undiagnosed CD patients remain untreated, leaving individuals exposed to the risk of long-term complications, such as infertility, osteoporosis, or cancer (26).

During the anamnesis, none of the GT patients included in our study reported the existence of psoriasis, often associated with GT (27). Four patients (6%) from the GT group had some other autoimmune diseases (systemic lupus erythematosus, vitiligo, and Raynaud syndrome).

Also, some studies (4) revealed that GT is less prevalent in active smokers. In our study, there was no significant difference in the smoking habits between the GT and the control group.

An additional symptom of CD is iron-deficiency anemia, often recorded in newly diagnosed CD patients, which sometimes persist despite initiation of a gluten-free diet (28). Iron deficiency may also lead to the oral mucosa atrophy because iron is essential for the oral epithelial cells function. In patients with symptomatic GT, nutritional deficiency should be excluded prior to the additional CD screening (29). Eleven patients (18.3%) from the GT group in our study developed iron-deficiency anemia while all the patients from the control group had normal blood count. Also, three GT patients (33%) with the confirmed CD had iron-deficiency anemia. Although GT might be a direct manifestation of iron deficiency anemia, we believe it was not the case in our study because six (67%) of our GT patients with CD did not develop iron deficiency anemia.

Still, it is not clear whether the tongue lesions are a direct manifestation of CD or the result of malabsorption on the rapidly dividing mucosal cells that are already predisposed to soreness by a pre-existing disease. Although the proximal part of the intestinal mucosa is the main site of the gut that is involved in CD, gluten-driven T cell activation may also be present in any other part of the gastrointestinal tract, including the mouth, as its initial segment (14).

In conclusion, the results of this prospective study warrants future studies to establish the clinical oral examination as a diagnostic tool, especially in atypical or silent forms of CD, since it may contribute to an early diagnosis of CD and may help to prevent its progress and complications (24, 26).

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Conflict of interest

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