ORIGINAL ARTICLE

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# Clinical importance of celiac disease in patients with recurrent aphthous stomatitis

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***Background/aims:*** *Recurrent aphthous stomatitis is a common disease of the oral mucosa that is characterized by recurrent, painful ulcers of unknown etiology. The association between celiac disease and recurrent aphthous stomatitis has been evaluated in several studies, but variable results have been reported. The purpose of this study was to determine the prevalence of celiac disease in patients with recurrent aphthous stomatitis.* ***Methods:*** *The study group consisted of 82 patients, all of whom had a history of recurrent aphthous stomatitis. The control group included 82 patients who did not have aphthous stomatitis. Patients were screened for IgA anti-endomysial antibodies, IgG anti-endomysial antibodies, IgA anti-gliadin antibodies, and IgG anti-gliadin antibodies. Patients with positive serology underwent endoscopic biopsies of the duodenal mucosa. Patients in both groups were also questioned regarding gastrointestinal symptoms.* ***Results:*** *One patient (1.2%) out of 82 in the study group was diagnosed with celiac disease by biopsy. Gastroesophageal reflux disease symptoms, heartburn and regurgitation were determined to be of higher incidence in the study group ($p<0.001$ and $p<0.001$, respectively). None of the 82 patients in the control group were diagnosed as having celiac disease.* ***Conclusion:*** *It is concluded that there is no apparent etiological link between recurrent aphthous stomatitis and celiac disease and that screening recurrent aphthous stomatitis patients for celiac disease has little clinical value. Additionally, regurgitation of gastric acid to the oral cavity may precipitate the formation of aphthous stomatitis.*

**Key words:** Recurrent aphthous stomatitis, celiac disease, anti-gliadin antibody, anti-endomysial antibody, gastroesophageal reflux disease

## Rekürrent aftöz stomatitli hastalarda çölyak hastalığının klinik önemi

***Amaç:*** *Rekürren aftöz stomatit, oral mukozanın nedeni bilinmeyen, tekrarlayan ağrılı ülserleri ile seyreden, sık görülen bir hastalığıdır. Çölyak hastalığı ve rekürren aftöz stomatit arasındaki ilişki birkaç çalışmada değerlendirilmiş ancak farklı sonuçlar bildirilmiştir. Bu çalışmanın amacı rekürren aftöz stomatit'li hastalarda çölyak hastalığı sıklığını saptamaktır.* ***Yöntem:*** *Çalışma grubu rekürren aftöz stomatit öyküsü olan 82 hastadan, kontrol grubu ise rekürren aftöz stomatit öyküsü olmayan 82 hastadan oluşturuldu. Tüm olgularda IgA anti-endomisyum antikoru, IgG anti-endomisyum antikoru, IgA anti-gliadin antikoru ve IgG anti-gliadin antikoru bakıldı. Serolojisi pozitif olan olgulara endoskopi yapılarak duodenum biyopsileri alındı. Ayrıca her iki gruptaki olgular gastrointestinal semptomlar açısından sorgulandı.* ***Bulgular:*** *Çalışma grubundaki 82 hastanın birinde (%1.2) biyopsi ile çölyak hastalığı tanısı kondu. Göğüs arkasında yanma ve regürjitasyon gibi gastroözofageal semptomlar kontrol grubunda daha sık idi ($p<0.001$, and $p<0.001$, sırasıyla). Kontrol grubundaki 82 hastanın hiçbirinde çölyak hastalığı saptanmadı.* ***Sonuç:*** *Rekürren aftöz stomatit ve çölyak hastalığı arasında belirgin etyolojik bağlantı saptanmamış olup, rekürren aftöz stomatit'li hastaların çölyak hastalığı açısından taranmasının klinik değeri düşüktür. Ek olarak, oral kavite içine mide asidi regürjitasyonu, aftöz stomatit oluşumunu kolaylaştırıyor olabilir.*

**Anahtar kelimeler:** Rükürran aftöz stomatit, çölyak hastalığı, anti-gliadin antikoru, anti-endomisyum antikoru, gastroözofageal reflü hastalığı

## INTRODUCTION

Recurrent aphthous stomatitis (RAS) is one of the most common mucosal diseases in humans. It is characterized by recurrent and painful ulcerations of the oral mucous membranes. Its prevalence in the general population is estimated to vary from 5% to 66%, with a mean of 20% (1,2). The disease

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occurs in men and women of all ages. The etiology of RAS is unknown, although some factors, such as infectious agents, stress, trauma, hormonal changes, nutritional deficiencies, food allergy, and systemic diseases, have been proposed (1,2).

Celiac disease (CD), also known as celiac sprue, is an immune-mediated enteropathy induced by dietary gluten that affects genetically predisposed individuals. While it was previously considered to be a childhood disease, recent reports suggest an increased incidence among adults (3). CD may be observed in both sexes, but a female-to-male predominance of 7:1 has been noted in most studies (4). Prevalence rates of 1:120 to 1:300 have been reported in Western Europe (5-7). Recent epidemiological data have shown a prevalence of CD approaching 1% in the general population (8). CD has been classified into four phenotypes: classic, atypical, silent, and latent forms. "Classic disease" describes patients with the features of intestinal malabsorption, including diarrhea, weight loss and abdominal bloating. "Atypical disease" is characterized by few or no gastrointestinal symptoms but comes to medical attention for other reasons such as anemia, osteoporosis or infertility. "Silent disease" refers to asymptomatic patients who have villous atrophy on biopsy. These patients do not manifest any gastrointestinal symptoms or atypical features of the disease. "Latent disease" represents patients with a previous diagnosis of CD that responded to a gluten-free diet and who retain a normal mucosal histology. It can also represent patients with currently normal intestinal mucosa on a gluten-containing diet who will subsequently develop CD (9). The diagnosis of CD is based on positive serologic antibodies (antigliadin, antiendomysial and tissue transglutaminase), characteristic small intestinal mucosal abnormalities on histological examination, and clinical, serological and histological remission on a strict gluten-free diet (10). Although gastrointestinal findings are the most prominent and well-known presentations of CD, approximately 50% of patients with CD present no gastrointestinal symptoms when they are initially diagnosed. Currently, some authors consider various types of oral cavity pathologies to be clinical manifestations of CD, like dental enamel defects, soft tissue lesions and RAS (3,6,11-18). In dermatology, although dermatitis herpetiformis is an autoimmune blistering disease that appears as a cutaneous manifestation of gluten intolerance (12), the association between CD and RAS has been long suspected and has been evaluated in several studies, but conflicting results have been reported.

In the present study, we aimed to determine the relationship between RAS and CD/gastrointestinal symptoms using serologic and histopathological tests.

## MATERIALS AND METHODS

This was a prospective, controlled study. The study protocol was carried out in accordance with good clinical practices and the Declaration of Helsinki, as agreed to in 1975 and revised in 1983. All patients signed approved informed consent forms before enrollment in the study.

### Study Population

Eighty-two patients consecutively referred to the Haydarpasa Numune Education and Research Hospital Dermatology Outpatient Clinic for the management of RAS between March 2007 and March 2009 were recruited into the RAS group. Additionally, a total of 82 consecutive outpatients who were scheduled for elective esophagogastroduodenoscopy (EGD) to investigate their dyspeptic complaints and who had no history of aphthous stomatitis or any other skin manifestation compatible with CD were recruited into the control group.

Patients who met any of the following criteria were excluded: (1) age younger than 18 years; (2) presence of Behçet's or inflammatory bowel diseases; (3) presence of clinically significant associated conditions such as hepatic, cardiorespiratory or renal disease, neoplastic diseases, or coagulopathy; or (4) pregnancy or breast-feeding.

### Study Design

The diagnosis of RAS was performed by one dermatologist according to the history and physical examination based on accepted criteria. It was divided based on the clinical features of RAS: major ((larger than 1 cm and deeper than minor RAS and healing within 10 to 30 days), minor (less than 1 cm in diameter and healing within 4 to 14 days) and herpetiform aphthae (grouped aphthae, 1 to 2 mm in size and painful). All of the patients were asked to complete a questionnaire regarding their gastrointestinal symptoms.

All of the patients eligible for the study underwent EGD with conscious sedation. Prior to EGD, fasting venous plasma samples were taken from all patients for antibodies to gliadin IgA and IgG and

to endomysium IgA and IgG. Serum IgA levels were also measured to rule out IgA deficiency. IgA and IgG antibodies to gliadin were assessed by ELISA (Euroimmun, Lubeck, Germany), and IgA and IgG antibodies to endomysium were assessed by an indirect immunofluorescence method (Euroimmun, Lubeck, Germany). To ensure consistency of the evaluation, all of the EGD examinations were performed by the same attending endoscopist using the Pentax EG-2970K videogastroscope (Asahi Optical, Tokyo, Japan). From all of the patients, a total of four biopsy specimens were taken from the distal part of the duodenum, and the biopsy specimens were fixed in a 10% formalin solution. All of the preparations were stained with hematoxylin-eosin for microscopic examination of the duodenal mucosa and were evaluated according to the Marsh classification by a single experienced pathologist, who was blinded to the results of the serologic tests that assessed CD status. Following these tests, cases with at least one positive serologic test with abnormal duodenal biopsy compatible with CD were defined as CD.

### Statistical Analysis

Statistical calculations were performed using SPSS (Statistical Package for the Social Sciences) version 11.5 statistical software (SPSS Inc., Chicago, IL, USA). The chi-square and Fisher's exact chi-square tests were used for comparison of the qualitative data. The results were evaluated at a 95% confidence interval and at a significance level of $p<0.05$.

## RESULTS

Clinical features of RAS were detected as minor in 44 (53.7%), major in 31 (37.8%) and herpetiform in 7 (8.5%) in the buccal mucosa, labial mucosa and tongue. The RAS and control groups included 82 patients each, and there were no statistically significant differences between the groups with respect to age and gender ($p=0.66$, $p=1.00$, respectively). Pathologic examination of the duodenal biopsies revealed CD (Marsh IIIC) in only one patient in the RAS group, whereas none of the patients in the control group was positive for CD (Table 1).

The following gastrointestinal symptoms were evaluated in the two groups: epigastric pain, chronic diarrhea, steatorrhea, abdominal distension/bloating, regurgitation, and weight loss. Reflux-like symptoms such as regurgitation and retrosternal heartburn were significantly higher in the RAS group ($p<0.001$ and $p<0.001$, respectively) (Table 2).

**Table 1.** Demographic data and positive serologic test results (results given as number and percentage of patients)

| | RAS group (*n = 82*) | Placebo group (*n = 82*) | *p-value* |
|---|---|---|---|
| Age (y), (mean±SD) | 34.3±12.8 | 35.3±14.8 | 0.66 |
| Gender [number (%)] | | | |
| Male | 30 (36.5) | 30 (36.5) | 1.000 |
| Female | 52 (63.5) | 52 (63.5) | |
| Race (%) | | | |
| White | 100 | 100 | 1.000 |
| Positive serologic test results [number (%)] | | | |
| Gliadin IgA antibody | 2 (2.4) | 1 (1.2) | 0.56 |
| Gliadin IgG antibody | 3 (3.6) | 1 (1.2) | 0.311 |

RAS: Recurrent aphthous stomatitis

**Table 2.** Gastrointestinal symptoms for RAS and control patients (parametric test: chi-square test/Fisher's exact chi-square test) (results given as number and percentage of patients)

| **GIS symptoms [number (%)]** | **RAS group** (*n = 82*) | **Placebo group** (*n = 82*) | *p-value* |
|---|---|---|---|
| Epigastric pain | 12 (14.6) | 6 (7.3) | p=0.13 |
| Abdominal distension/bloating | 22 (26.8) | 16 (19.5) | p=0.26 |
| Heartburn | 66 (80.5) | 14 (17.1) | **p<0.001** |
| Regurgitation | 66 (80.5) | 15 (18.3) | **p<0.001** |
| Steatorrhea | 7 (8.5) | 4 (4.9) | p=0.34 |
| Diarrhea in childhood | 3 (3.7) | 3 (3.7) | p=1.00 |
| Weight loss | 10 (12.2) | 8 (9.8) | p=0.61 |

RAS: Recurrent aphthous stomatitis

## DISCUSSION

Recurrent aphthous stomatitis (RAS) is characterized by painful ulcers that recur at intervals of a few days to up to 2–3 months. The peak of onset is during childhood, and it decreases in severity and frequency with age (1). Despite detailed study, the etiology of RAS is still unknown, but many predisposing factors, including trauma, stress, smoking cessation, hormonal imbalance, and food hypersensitivity, have been proposed (1,2). There is also strong evidence from histopathological studies that T-cell-mediated immune responses are associated with RAS (1,2).

Some authors have reported that patients with RAS have an increased prevalence of CD and have suggested that RAS may be their presenting complaint. In 1976, Ferguson et al. (15) found that 24% of patients with RAS showed histological evidence of CD on jejunal biopsy. In another study conducted by Ferguson et al. (16), 2 (4%) of 50 RAS patients were diagnosed as having CD. Subsequently, Jokinen et al. (17) showed an association between RAS and CD (11%). De Freitas et al. (18) also revealed that up to 31% of patients with CD have aphthous stomatitis. Aydemir et al. (3) described 2 cases with coexisting RAS and CD in a group of 41 patients with RAS. Veloso et al. (19) reported villous atrophy in 4 (16%) of 25 patients with RAS. Additionally, Olszewska et al. (20) concluded that every patient with RAS should be asked specifically about gastrointestinal symptoms and screened for IgA EMA (positive in 4.7% of subjects). Tyldesley (21) reported that CD was associated with recurrent aphthae. Campisi et al.'s research (8) showed that the epidemiological association found between CD and aphthous-like ulcers suggests that recurrent aphthous-like ulcers should be considered a risk indicator for CD and that a gluten-free diet leads to ulcer amelioration (Table 3).

In contrast, Sedghizadeh et al. (7), Shakeri et al. (2.83%) (22) and Robinson et al. (23) demonstrated little or no significant etiological link between these two diseases (Table 3). Rose et al. (24) and O'Farrelly et al. (25) reported that it was unnecessary to perform jejunal biopsy in patients with RAS. In our study group, which included 82 patients, 3 (3.6%) were AGA IgG positive and 2 (2.4%) were AGA IgA positive, whereas in the control group that included the same number of patients, 1 (1.2%) was AGA IgG and AGA IgA positive. EMA IgA and IgG were only positive in 1 patient in the RAS group. In duodenal biopsies of the antibody-positive patients in both the RAS and control groups, only 1 (1.2%) patient was diagnosed as having CD in the RAS group, even though the patient was free of typical clinical symptoms of this disease. There were no statistically significant differences between the groups. Both EMA and AGA were positive in this patient. On the basis of these findings, it appears that the prevalence of CD in the RAS population does not significantly differ from that of the unaffected matched population.

We know that almost 50% of recently diagnosed celiac patients do not present with classical gastrointestinal symptoms (26). In our study, there were no statistically significant differences between the gastrointestinal symptoms of the groups, which is consistent with the literature. However, retrosternal heartburn and regurgitation were higher in the RAS group (80.5%), and the difference was statistically significant ($p<0.05$). Although

**Table 3.** Prevalence of celiac disease in patients with recurrent aphthous stomatitis

| References | No. of RAS patients | No. of RAS patients with CD | Improvement in RAS on a gluten-free diet |
|---|---|---|---|
| Aydemir et al. (3) | 41 | 2 (4.8%) | Not reported |
| Campisi et al. (8) | 269 | 61 (22.7%) | Yes |
| Ferguson et al. (15) | 33 | 8 (24%) | Yes |
| Ferguson et al. (16) | 50 | 2 (4%) | Yes |
| Jokinen et al. (17) | 82 | 4 (4.9%) | Not reported |
| De Freitas et al. (18) | 48 | 6 (31%) | Not reported |
| Veloso et al. (19) | 24 | 4 (16%) | Not reported |
| Olszewska et al. (20) | 42 | 2 (4.7%) | Yes |
| Tyldesley et al. (21) | 97 | 6 (6.2%) | Yes |
| Shakeri et al. (22) | 247 | 7 (2.83%) | Yes |
| Robinson et al. (23) | 87 | 0 | Not reported |

CD: Celiac disease. RAS: Recurrent aphthous stomatitis.

heartburn and regurgitation are symptoms of gastroesophageal reflux disease, there are no data in the literature regarding the relationship between these two disorders. Acid reflux to the oral cavity may facilitate the recurrence of aphthous stomatitis. Robinson et al. (23) reported upper gastrointestinal symptoms in 7/87 patients with RAS, but they did not perform a detailed investigation. Well-designed studies about this association are required in the future.

The present study confirms previous studies suggesting that there is little association between RAS and CD. Finally, we conclude that screening patients with RAS for CD is unlikely to be of clinical value.

***Declaration of interest:*** *We report that we have no commercial associations (e.g., equity ownership or interest, consultancy, patent and licensing agreement, or institutional and corporate associations) that might be a conflict of interest in relation to the submitted manuscript.*

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