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Clinical and immunopathological assessment of the oral mucosa in coeliac disease: a pilot study

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Abstract

Background Coeliac disease (CD) is a lifelong immune-mediated systemic disease that develops in genetically predisposed subjects who show intolerance to gluten proteins. Intestinal wall inflammation with villi atrophy results in malabsorption of nutrients and leads to several gastrointestinal and systemic symptoms. High serum levels of anti-endomysial and anti-tissue transglutaminase autoantibodies can be revealed in patients with CD. The aim of the study was to evaluate the presence of IgA, IgG, IgM, and C3 complement deposits in the oral mucosa and its condition in CD patients.

Methods Thirty CD patients underwent complete clinical examination followed by mycologic evaluation, of whom 10 additionally had oral mucosa biopsy. Direct immunofluorescence (DIF) was performed on the oral mucosa specimens using polyclonal rabbit IgG, IgA, IgM, and C3 antibodies. The results were statistically analyzed.

Results The most common complaints included pain due to oral ulcers, xerostomia, and gingival bleeding. Frequently observed comorbidities were anemia, allergy, and thyroid disorders. Common oral mucosal findings included white-coated tongue, *linea alba*, and atrophic glossitis. Candidiasis was revealed in 13 subjects (43.3%). IgA, IgG, IgM, or C3 deposits in the oral mucosa specimens were shown in none of the patients.

Conclusions Coeliac disease may increase the frequency of white-coated tongue, *linea alba*, and atrophic glossitis and may promote the development of oral candidiasis. However, there are no evident markers in the CD patients' immunopathologic examination of the oral mucosa specimens.

Keywords Coeliac disease, Oral mucosa, Immunodiagnostics, Direct Immunofluorescence

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Background

Pathologic lesions in the oral cavity often precede systemic disease development. A correlation between dermatologic or gastrointestinal conditions and the oral cavity state has recently been of high interest [1, 2]. Clinical assessment of the oral cavity expanded by several accessory approaches may be an essential and valuable indicator in the early diagnosis of dermatological and gastrointestinal diseases.

Coeliac disease (coeliac sprue, gluten enteropathy, CD) is a lifelong immune-mediated systemic condition that develops in genetically predisposed subjects who show intolerance to wheat, rye, barley, and oat proteins, which include gliadin, secalin, hordein, and avenin [3–8]. CD can be presented with classic gastrointestinal symptoms but also as an atypical, silent, and latent form with a broad spectrum of non-gastrointestinal manifestations. Intestinal wall inflammation with villi atrophy results in malabsorption of nutrients and leads to several gastrointestinal and systemic symptoms like chronic diarrhea, steatorrhoea, abdominal distention, weight loss, severe abdominal pain, loss of appetite, and low height. Non-gastrointestinal symptoms of CD include anemia, neurologic disturbances, lactose intolerance, iritis, osteoporosis, alopecia areata, depression, fertility disorders, hyperthyroidism, and insulin-dependent diabetes [3, 9–15].

The impaired absorption of several nutrients in CD may also induce deficiency symptoms in the oral cavity. The risk of oral candidiasis and other opportunistic infections rapidly increases with the development of immunodeficiency and dryness.

The etiopathogenesis of CD is a combination of immunologic and genetic predispositions modified by environmental stimuli.

Specific T lymphocytes become provoked by gluten proteins [16]. That initiates the immunologic cascade, as stimulated T cells produce proinflammatory cytokines, leading to intestinal epithelium damage [3, 8]. High serum levels of CD-specific markers, such as antibodies against tissue transglutaminase (tTG), endomysial antibodies (EMA), antibodies against deaminated gliadin peptides (DGP), and deaminated gliadin analogous fragments (GAF) can be detected in patients with coeliac disease, and thus are a reliable diagnostic tool for CD [16–18].

The exact mode of inheritance of coeliac disease has not been established so far. The genetic predisposition was confirmed in family studies, which show that 5–20% of first-degree relatives of probands are similarly affected [19, 20]. The concordance in affected monozygotic twins ranges between 70 and 100% [19–21]. The increased frequency of specific serologically defined lymphoid cell surface proteins (HLA class II molecules) in CD patients was observed [9, 11, 13]. The recent research focused on the following locations: 6p23, 7q31.3, 11p11, 15q26, and 22cen [22, 23], 10q23.1 and 16q23.3 [24], CTLA4/CD28 region, on chromosome 2q33 [25, 26], showing ambiguous results.

Environmental modifiers include gluten-rich diet, prolonged stress, pregnancy, viral infections, antibiotic therapy, or even long-distance, burdensome journeys [3].

CD diagnoses are based on the recommendations of the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) [5, 11, 12, 14]. It focuses on characteristic symptoms and a specific result of a duodenal biopsy. High serum levels of CD-specific markers, such as antibodies against tissue transglutaminase (tTG), endomysial antibodies (EMA), antibodies against deaminated gliadin peptides (DGP), and deaminated gliadin analogous fragments (GAF), are also found to be a reliable diagnostic tool for CD [5, 7, 11, 27]. Moreover, the genetic tests' results are considered [9, 11]. For several years, it has been considered a condition affecting mainly small children; meanwhile, coeliac disease in adults used to be regarded as a sporadic condition. In this age group, the typical gastrointestinal symptoms are often silent, which makes the disease underdiagnosed [28–31]. Currently, with the progress of diagnostic approaches, the frequency of CD in the adult population is estimated as 1/130–250 [9, 32]. It mainly affects people between the 4th and 6th life decades [33] with a female predilection [8, 9, 33, 34]. The CD frequency in the general population varies depending on the geographic region; in Europe, it ranges from 1:85 in Hungary to 1:130 in Finland, 1:230–300 in Italy and Ireland, and 1:340 in the Netherlands and Norway [34–36].

The treatment includes a gluten-free diet and sulphones to diminish the symptoms. Eliminating gluten from the diet results in regression of intestinal and systemic symptoms and intestinal villi regeneration [3, 11, 19, 37]. As CD is often accompanied by lactose intolerance, a lactose-free diet is also recommended [30, 31].

While several reports on the analysis of various aspects of the oral hard and soft tissue condition in CD patients have been published so far, the attempts to evaluate the immunological markers of the oral mucosa specimens are unique.

The aim of this study was to evaluate the oral mucosa state by defining the occurrence of oral lesions, Candida carriage, and the presence of IgA, IgG, IgM, and C3 deposits in the oral mucosa specimens by direct immunofluorescence in CD patients.

Methods

The study group consisted of 30 patients with CD aged 16–65 (mean age: 39.4 years), including 24 females aged 20–65 (mean age: 40.3 years) and six males aged 16–55

(mean: 35.8 years), who were treated in the Department of Gastroenterology, Human Nutrition and Internal Diseases, Department of Dermatology, and Department of Oral Mucosa Diseases, Poznań University of Medical Sciences (PUMS). The CD was diagnosed based on clinical presentation, endoscopy, laboratory tests (full blood count, anty-gliadin and anty-endomysial antibodies), and histopathologic examination of the intestinal biopsies with the evaluation of villi atrophy, by the criteria accepted in the Department of Gastroenterology, Human Nutrition and Internal Diseases, PUMS, following the recommendations of ESPGHAN, and British Society of Gastroenterology [38, 39]. All those tests were performed on all 30 study participants.

All the study participants underwent a thorough oral cavity examination, performed in all cases by the two dental specialists experienced in oral pathology. The oral cavity exam included medical history, physical examination, and a *Candida* smear from the oral mucosa. Moreover, the evaluation of the presence of IgA, IgG, IgM, and C3 deposits was performed in the oral mucosa specimens in 10 subjects. Oral mucosa diseases were diagnosed based on typical clinical findings and accessory test results if required. Material for mycologic tests was collected with sterile swabs in the morning, before the first meal, and toothbrushing. A solid growth-transport medium selective to yeast-like fungi (Sabouraud agar with chloramphenicol, pH 6.5, by Graso Biotech, bioMerieux) was utilized. Microbiologic analysis was performed in the Department of Medical Mycology and Dermatology, PUMS. The material was incubated at 37 °C, and the growth was verified after 24, 48, 72 h, and 7 days. Drug sensitivity was checked with Fungitest (Bio-Rad), and the results were verified within 48 h. In 10 subjects (8 females and two males), the specimens were taken from the clinically intact buccal mucosa in local anesthesia (2% lidocaine) with forceps, and no stitches were needed. Collected tissue samples were then transported, within a few hours, in plastic containers with a saline solution to the Laboratory of Skin Immunopathology and Histopathology of the Department of Dermatology, PUMS. The samples were refrigerated and cut in a cryostat. Polyclonal FITC-conjugated rabbit anti-human IgG, IgM, IgA, and C3 antibodies were used as reagents (Dako, 1:100 dilution in a phosphate buffer-PBF, pH = 7.6), and the specimens were then incubated with the reagents in a humid chamber at room temperature for an hour. The slides were subsequently washed in the PBF, a drop of 10% PBF glycerine solution was added, and the glass covers were placed over the specimens. A fluorescent microscope (Zeiss) and a digital camera (Olympus) were used for the immunopathological assessment of the specimen slides. The images obtained by the digital camera were not photo-edited. The results were presented in a semi-quantitative scale, describing the fluorescence intensity from "–" to "++."A negative result was the reference value.

The study design was approved by the local Ethics Committee of Poznań University of Medical Sciences, Poland (Resolution No. 355/10; 08.10.2010) and complied with the Declaration of Helsinki's guidelines. Written informed consent was obtained from all the study participants.

Statistical analysis

Data were organized in MSExcell® spreadsheets and presented descriptively. Dell Statistica (data analysis software system), version 13 (Dell Inc., 2016; Palo Alto, CA, USA) was used where appropriate.

Results

Oral complaints

Oral complaints were reported by 23 patients with CD (76.6%). Most of the patients presented more than one complaint at a time. Most common complaints included oral pain related to oral erosion or ulcer (20 patients; 66.6%), dry mouth (15 patients; 50%), gum bleeding and pain (13 patients; 43.3%), burning sensation, and taste disturbances (8 patients; 26.6%). Burning was described as chronic discomfort in 6 cases, while the burning provoked by food stimuli was found in 2 cases. Chronic burning was mostly located on the tongue (4 patients). In single cases, it was limited to the gingivae and buccal mucosa. The food-provoked burning affected the tongue surface.

Table 1 Oral mucosal changes in the study population

Oral finding	*n* (%)
Acute atrophic glossitis	8 (26.6)
Buccal oedema	7 (23.3)
Recurrent aphthous stomatitis	5 (16.6)
Angular cheilitis	5 (16.6)
Mucosal pallor	3 (10)
Tongue depapillation	3 (10)
Fissured tongue	3 (10)
Plaque-induced gingivitis	1 (3.3)
Recurrent labial herpes	1 (3.3)

Oral signs

Oral mucosal changes were revealed in 29 patients (96.6%). Table 1 depicts the oral findings on the oral mucosa in the study population.

The most common findings related to oral mucosa included white-coated tongue (11 persons; 36.6%) and *linea alba* due to mechanical irritation (9 persons; 30%). Atrophic erythematous tongue lesions were observed in 8 persons (26.6%), buccal mucosa oedema with a pebbly structure was found in 7 patients (23.3%), recurrent aphthous stomatitis (RAS) in 5 patients (16.6%), of whom

three subjects suffered minor RAS (miRAS) and 2- major RAS (maRAS). Also, angular cheilitis was revealed in 5 subjects. Less frequently observed findings included fissured tongue, tongue depapillation, and mucosal pallor.

Figures 1 and 2 show oral mucosal lesions in patients from the study group.

Mycologic evaluation

Oral candidiasis was revealed in 13 CD patients (43.3%). The diagnosis was established in all the study participants based on clinical lesions typical of candidiasis, accompanied by subjective complaints, and confirmed by detecting *Candida* fungi in culture. In 6 cases, acute pseudomembranous candidiasis was detected, and in 3 cases, chronic atrophic type was revealed. Acute atrophic candidiasis and angular cheilitis were found in 2 cases, respectively. Three (10%) of the study participants had asthma; all of them were treated with steroid inhalers, and all of them developed candidiasis in atrophic form- one of acute and two of chronic course. The patient with acute atrophic candidiasis and asthma presented concomitant angular cheilitis. However, we did not reveal a significant correlation between asthma and candidiasis in the CD group ($p = 0.0704$).

Immunologic assay

The evaluation of IgA, IgG, IgM, and C3 immunoglobulin deposits with the direct immunofluorescence method did not reveal the presence of granular deposits along the basal membrane of the oral mucosa epithelium in any of the subjects.

Systemic conditions and genetic predisposition

Systemic conditions that most accompanied CD in the study population were anemia (12 patients, 40%) and allergy (8 patients, 23.6%). Thyroid gland disorders and dermatologic conditions unrelated to coeliac disease were found in 6 cases (20%), respectively. Gastrointestinal diseases other than CD were reported by five patients (16.6%). Hypertension, cardiovascular disorders, and asthma, which required the regular application of steroid inhalers, were revealed in 3 patients (10%), respectively.

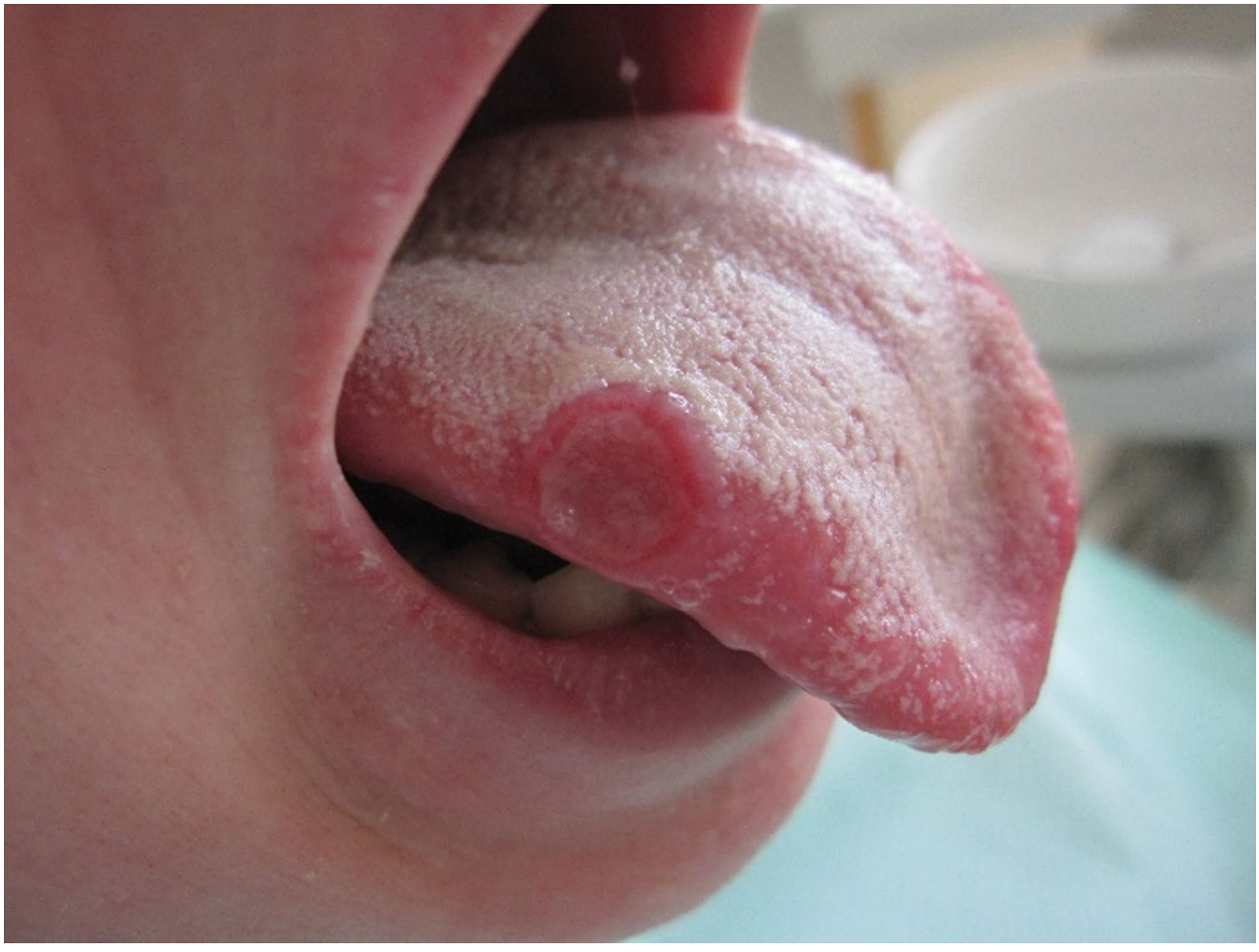

Fig. 1 Major aphtha on the side of the white-coated tongue

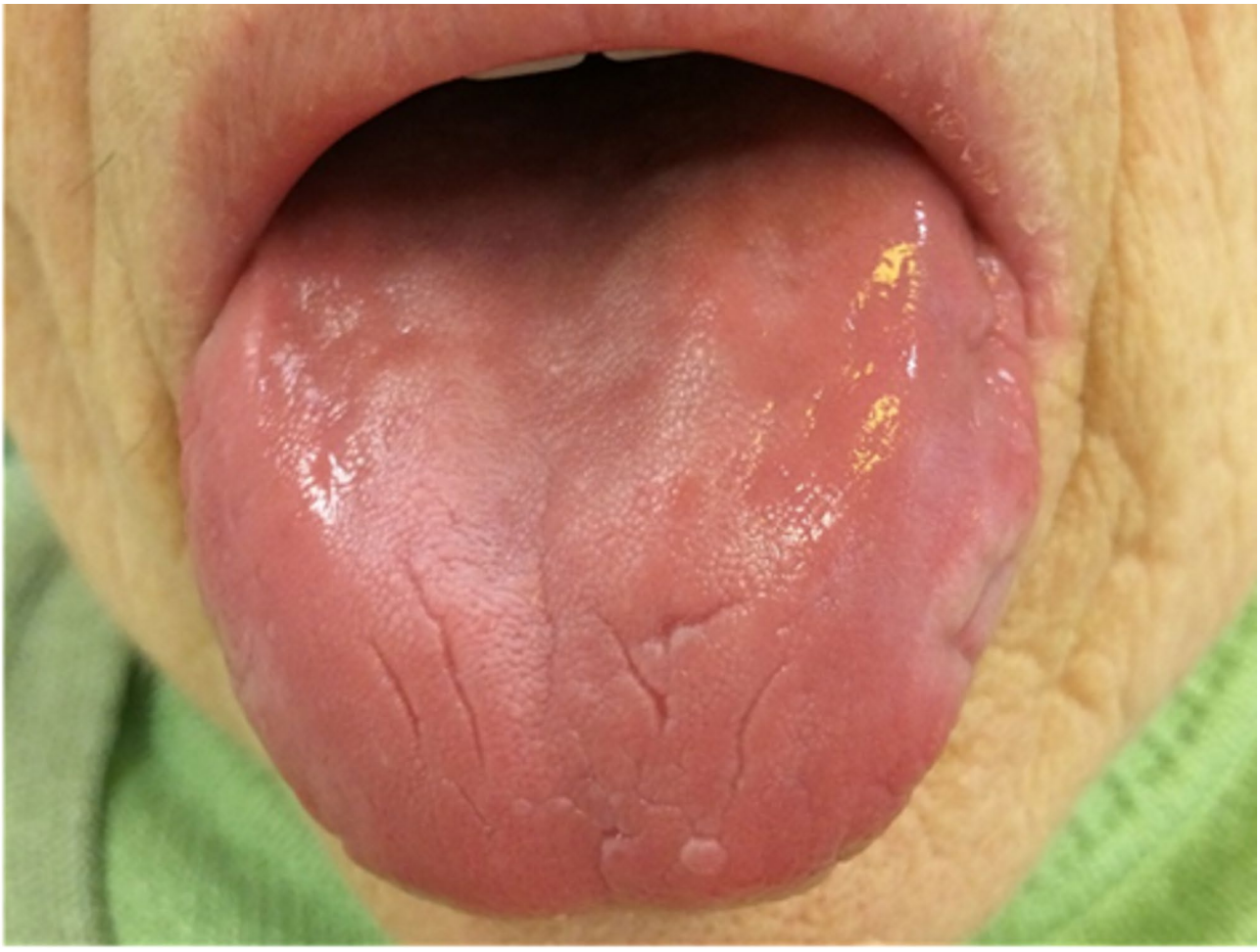

Fig. 2 Acute atrophic glossitis

Neoplasms, urinary tract diseases, and rheumatic and ocular disorders were reported by two patients (6.6%), respectively. HBS and HCV infection and diabetes mellitus were found in 1 case (3.3%) each. Some of the systemic diseases appeared in one patient simultaneously.

All patients were treated with dietary measures during the study period and did not require pharmacotherapy due to CD. Loss of weight a year prior to the study was reported by 29 CD patients (96.6%). Twenty-two patients were on a gluten-free diet (77.3%).

Coeliac disease in first-degree relatives was found in 15 patients (50%).

Discussion

Oral mucosal lesions are observed in various systemic conditions and very often may be an initial sign of developing a generalized disease. Oral involvement in gastrointestinal diseases has recently been emphasized [1, 2]. In the present study, we aimed to determine the oral mucosa condition in patients with coeliac disease, which was expanded with mycologic testing. We also evaluated the presence of IgA, IgG, IgM, and C3 immunoglobulin deposits in mucosal bioptates to determine whether this approach could benefit the diagnosis of CD.

The most reported complaints in our study group included pain related to oral ulcers (66.6%), dry mouth (50%), and bleeding gums (43.3%). The burning sensation was reported in 26.6% of cases, and included a chronic discomfort located mainly on the tongue (6 cases), while the burning provoked by food stimuli was found in 2 cases. Similar results were shown in the Lähteenoja et al. study [40], which found oral burning in 26.5% of their study population with CD. They, however, revealed xerostomia in a lower percentage of patients than we did- it was reported in 22.6% of cases. In their case report, Lucchese et al. described a 72-year-old female patient with CD who had suffered a burning sensation on the tongue. As all the results of accessory investigations, including blood work, microelements evaluation, and microbiologic assays, were within the norm, the symptom was attributed to coeliac disease. Oral symptoms such as soreness, burning, erythema, or atrophy are often falsely

not considered by clinicians as indicators of an ongoing pathologic process [41]. CD patients seem, therefore, at high risk of developing oro-facial pain for several reasons: on the one hand, they are commonly malnourished and show microelement deficiency; on the other hand, as presented in the above-cited case report, the CD itself may lead to glossalgia. Oral pathologists should, therefore, also consider CD in the differential diagnosis of idiopathic sore tongue.

Meanwhile, Da Silva et al. [42] mentioned xerostomia as a serious problem related to coeliac disease, describing the case of a 39-year-old female CD patient who developed severely reduced salivation. In the recent study by Liu et al., xerostomia, mucosal lesions, dry/cracked lips, and focal lymphocytic sialadenitis were more prevalent and extensive in patients with CD than in healthy controls. However, according to their observations, the major salivary gland function was unaffected in CD patients. Therefore, dry mouth in those patients may be somewhat related to minor salivary gland inflammation and subsequent impaired mucosal lubrication [43].

Almost all CD patients in our study had some oral mucosa changes. The most common oral findings included white-coated tongue (11 persons; 36.6%), *linea alba* (9 persons; 30%), atrophic erythematous tongue lesions (8 persons; 26.6%), buccal mucosa oedema with a pebbly structure (7 patients; 23.3%), RAS and angular cheilitis (5 patients; 16.6%). The white-coated tongue was common in patients with Crohn's disease, as shown in a previous study by Ślebioda et al. [44]. As reported by Seerangaiyan et al. [45], systemic conditions like fever, dehydration, and malnourishment may increase the deposits on the dorsal tongue surface, while several drugs may influence its color. The frequency of coated tongue was comparable to that observed in our study in the report by Dalirsani et al., who had examined a large cohort of institutionalized elderly subjects in Iran [46]. However, it was much lower in the study by Gupta et al., which reached only 4.17% [47]. Buccal mucosa oedema with a pebbly structure, found in 23.3% of our CD patients, has been a condition attributed so far rather to chronic inflammatory conditions of the intestines than to coeliac disease [44, 48]. We did not find other reports relating this feature to CD. Atrophic erythematous tongue lesions found in our study in 8 persons (26.6%) could be explained by microelement insufficiency, namely the vitamin B group [41, 44]. In the Pastore et al. study [49], the authors revealed atrophic glossitis in 59%, combined with iron and vitamin B12 deficits in CD patients. Atrophic tongue lesions were observed in the study by da Silva et al. [42]. Another common oral condition found in our study population was RAS, detected in 5 patients (3 cases of miRAS and 2 cases of maRAS). The systematic review by Turska-Szybka et al. showed that RAS was three times more common in patients with CD compared to healthy controls, with an incidence of about 50% compared to 10–20% in the general population [50]. Although the increased frequency of RAS has been described by several authors [1, 2, 4, 8, 31, 51], some researchers did not observe RAS as a crucial oral finding in CD. In the Lähteenoja et al. [40] study, the RAS prevalence was 3.1%, while in the Seyhan et al. study, it reached 1.8% [3]. A case of rapid improvement of RAS after implementing a gluten-free diet was described in the Biel et al. report. A patient with long-lasting aphthae refractory to conventional treatment underwent a duodenal biopsy, which revealed CD's features. Moreover, a granular deposition of IgA at the dermo-epidermal junction characteristic of Duhring disease (DHD) but not of CD without DHD was found.

Meanwhile, the direct immunofluorescence of uninvolved oral mucosa was negative. Within 1 month after introducing a gluten-free diet, the aphthous lesions relapsed [52]. Similarly, like in glossitis, most researchers explain the higher prevalence of RAS in coeliac disease with microelement deficits, mainly iron, folate, and vitamin B12 [1]. These findings could also possibly be associated with common pathogenetic mechanisms [53]. Angular cheilitis, revealed in 16.6% of our CD patients, is another common indicator of microelement deficiencies. Comparable results were shown in the da Silva et al. [42] study. We also observed frequent oral pallor, which can be attributed to coeliac-induced anemia. The fissured tongue was revealed in 10% of our study population, which aligns with Seyhan et al.'s results [3], while Gupta et al. reported this finding only in nearly 2% of their study cohort from Nepal [46]. However, the frequency in our study did not exceed the average prevalence in the general population. A common oral disorder revealed in our study population was oral candidiasis. The diagnosis was confirmed by subjective symptoms, clinical signs, and the presence of *Candida* in the culture. It was revealed in 13 patients (43.3%). Candidiasis is a common opportunistic infection promoted by several local and systemic factors, including dry mouth, exposure to certain drugs, like antibiotics and steroids, malnourishment, and immunologic imbalance [54]. That puts CD patients at a high risk of developing candidiasis.

Immunofluorescence (IF) studies diagnose various dermatological diseases as an adjunct to clinical and histological examinations. These conditions include bullous and connective tissue disorders, vasculitides, lichen planus, and scaling dermatoses, notably psoriasis.

The immunologic findings may be disease-specific and diagnostic. They are considered as such in pemphigus and pemphigoid (all types), linear bullous IgA dermatosis, dermatitis herpetiformis, epidermolysis bullosa acquisita, and lupus erythematosus (discoid and

sclerosus). IgA, IgG, IgM, and C3 belong to a routine immunoglobulin panel utilized for immune-bullous disease diagnostics [55, 56, 59–61]. Granular IgA deposits in skin biopsies were found in celiac patients without dermatitis herpetiformis by direct immunofluorescence in the study by Antiga et al. [57]. The authors show that granular IgA deposits may represent a low-sensitivity but highly specific skin marker for celiac disease.

Meanwhile, reports on examining the oral mucosa biopsies in search of immunoglobulin deposits in a CD are scarce [58]. In our study, where we decided to utilize the immunoglobulin panel typical for immune-bullous diagnostics, the evaluation of IgA, IgG, IgM, and C3 immunoglobulin presence did not reveal the presence of granular deposits along the basal membrane of the oral mucosa epithelium in any of the subjects. In the Harrison et al. study [58], minor C3 deposits were revealed in one of 10 examined CD subjects. They compared the results with those of dermatitis herpetiformis (DH) patients, wherein IgA and C3 deposits were found in all seven patients. That stands in line with the results shown in the previous study by Mania-Końsko et al. [59], where the granular IgA and C3 deposits were found in 6 patients (60%) with DH, and C3 deposits were found in 5 subjects (50%). Fraser et al. [20], Russell et al. [60], and Hietanen et al. [61] presented similar results regarding the immunoglobulin deposits in DH. Although further research on a larger study sample is indicated, these results indicate that such a diagnostic approach is not valuable for diagnosing CD. However, it could be considered to support the diagnostics of DH.

This study has its weaknesses and strengths. The main limitation is the relatively small sample size, which refers to clinical evaluation and immunopathological assay. We did not examine the control group of healthy adults, although we included the comparisons with the literature reports on the general prevalence of oral mucosal lesions. The results do not show the impact of systemic medications on the oral cavity condition. However, we discuss the presence of co-morbidities. Our results may contribute to expanding the knowledge on oral mucosal involvement in CD, especially since the number of original research studies based on local cohorts from our region is scarce. The main innovative part described in this manuscript is related to immunopathological assay and the evaluation of immunoglobulin deposits in the oral mucosa specimens. While that kind of examination has until now been performed in a few studies on Duhring disease, oral mucosa testing has not been widely performed in CD patients.

Conclusions

The most common oral mucosal changes in CD patients were white-coated tongue and *linea alba*. Frequently observed oral pathologies included atrophic glossitis, RAS, angular cheilitis, and candidiasis, and their presence should alert a primary medical care supervisor to perform a meticulous inspection, including a detailed history, physical examination, and accessory tests, often covering also gastrointestinal assays.

In none of the study participants, the granular deposits of IgA, IgG, IgM, and C3 immunoglobulin were revealed along the basal membrane of the oral mucosa epithelium. The direct immunofluorescence method may act as an accessory test to exclude coeliac disease.

Author contributions

A.M.-K. and A.D.-P. designed the work; A.M.-K. was responsible for investigation and data acquisition; A.M.-K., Z.Ś., M.L.W., and A.D.-P. interpreted the data; A.M.-K. and Z.Ś. wrote the main manuscript text. M.L.W. and A.D.-P. revised the text. All authors reviewed the manuscript.

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Data availability

The data that support the findings of this study are available from the authors upon request.

Declarations

Ethics approval and consent to participate

The study design was approved by the local Ethics Committee of Poznań University of Medical Sciences, Poland (Resolution No. 355/10; 08.10.2010) and complied with the Declaration of Helsinki's guidelines. Written informed consent to participate in the study was obtained from all the study participants.

Consent for publication

Written informed consent for information about the patients to be published was obtained from all the study participants.

Competing interests

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