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Oral manifestations of Crohn's disease in relation to patient's hematinic status

Zmiany patologiczne w jamie ustnej w przebiegu choroby Crohna z uwzględnieniem statusu hematologicznego pacjentów

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Aim: Crohn's disease (CD) is a chronic, immune-mediated inflammatory condition that develops in various parts of the gastrointestinal tract, with a multifactorial, but not fully understood etiology. Both abdominal and extra-abdominal symptoms may accompany this entity.

Material/Methods: The aim of the present study was to evaluate the state of the oral mucosa in patients with Crohn's disease in relation to their hematinic status. Seventy patients with CD aged 18–79 years were enrolled in the study. The mean duration of the disease was 6.3 years; the subjects presented with assorted clinical stages of CD. The control croup consisted of 70 generally healthy subjects aged 22–78 years. All the participants underwent a detailed oral examination, mycological testing on *Candida*-selective media and blood serum iron level evaluation. The results were statistically analyzed with $p<0.005$ being considered significant level.

Results: Commonly observed pathologic lesions in patients with CD included: white coated tongue, buccal cobblestoning, and recurrent aphthous stomatitis (RAS). RAS and several types of glossitis, including: atrophic, median rhomboid and geographic type appeared more often in iron deficient subjects. RAS, angular cheilitis, atrophic glossitis and white coated tongue appeared frequently in the high-active CD subgroup, although the differences were statistically insignificant. The occurrence of *Candida* was similar in the tested subgroups, but significantly higher than in the controls.

Conclusions: Pathologic oral lesions like RAS and glossitis may indicate the development of iron deficiency and deterioration of CD. Iron status and disease activity do not influence the occurrence of oral *Candida*.

Keywords: **Crohn's disease • iron deficiency • oral candidiasis • oral mucosa • recurrent aphthous stomatitis**

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INTRODUCTION

Crohn's disease (CD) is a chronic immune-mediated condition affecting the gastrointestinal (GI) tract that belongs to the group of inflammatory bowel diseases (IBD). The etiology of CD is still not fully understood but it is considered to be multifactorial, with a contribution genetically mediated interaction between the immunologic system, gut microbiota, and environmental factors [8, 34, 41]. In recent years, several genes localized on chromosomes 6, 12, 14, 15 and 16 have been identified as being responsible for the IBD. The crucial role in the development of CD has been assigned to the mutation of NOD2/CARD15 (nucleotide-binding oligomerisation domain)/(caspase activating recruitment domain) gene on chromosome 16q12, which has been associated with an impaired ability to recognize bacterial particles, disturbed NFκB protein metabolism and altered immune reaction [34, 41]. Hyperactivation of Th1-mediated cellular immune response with the enhanced release of proinflammatory cytokines, like IL 12, 18, IFN-γ and TNF-α, has been observed in CD [7, 37]. As the incidence of Crohn's disease in the industrialized countries has increased in the past decades, the contribution of the environmental component in the etiopathogenesis of the entity has been suggested. Environmental factors known to modify the course of the condition include: smoking tobacco, air pollution, dietary habits with an increased ratio of omega-6 to omega-3 polyunsaturated fatty acids and exposure to several drug types and food additives [14, 17, 30, 32, 39]. The causal role of gut microbiota in the development of CD remains controversial; damaged mucosal layer and an impaired ability to clear certain bacteria from gastrointestinal tract may enhance the growth of several microorganisms. Participation of *Escherichia coli, Listeria monocytogenes, Chlamydia trachomatis* and *Mycobacterium paratuberculosis* has been suggested in some studies [1, 12, 31, 33, 34].

Inflammation in CD presents as transmural and discontinuous, creating a characteristic picture of "skip lesions", where the abrupt transition between unaffected tissue and ulcers may be observed. Histopathologic examinations reveal a focal infiltration of neutrophils into the epithelium. In approximately 50% of cases, non-caseating granulomas composed of giant cells may appear. Blunting of the intestinal villi, atypical branching of the crypts and features of metaplasia may be also found in bioptates from CD patients [4, 10, 41].

Although the ileocolic location of the entity is most common, the entire GI duct may be affected with CD. Both abdominal and extra-abdominal symptoms may be present in the course of the disease. Typical intestinal manifestations that include recurrent episodes of abdominal pain, diarrhea, bloody stools, and weight loss, are often accompanied by extra-intestinal inflammatory lesions involving skin, eyes, joints and the mouth [29, 35, 37]. The incidence of extra-abdominal manifestations in IBD ranges from 21-41%, depending on the study qualification criteria and population. Oral symptoms have been found to occur in 0.5-20% adults. A much higher prevalence of oral CD symptoms which range between 48 and 80% has been described in children [3, 11, 24, 37]. Oral lesions in CD were classified by Malins et al. (with a further modification of Sheper and Brand) into specific and non-specific groups. The first group comprises of polypoid tags, mucosal swellings, mucosal cobblestoning and granulomatous cheilitis. The second group includes: oral ulcerations, aphthae, angular cheilitis and gingivitis. Generally, the clinical presentation of oral CD symptoms correlates with the severity and extent of gut involvement [26, 35].

The chronic, relapsing course of this entity with the periods of remissions and exacerbations requires repeated and prolonged administration of antibiotics and anti-inflammatory agents, including steroids. Hospitalization and surgical treatment is very often introduced [4, 24]. Therefore, the true extra-intestinal manifestations and secondary complications, resulting from side-effects of the therapy, malnutrition or vitamin and microelement deficiency in CD may overlap. The prevalence of anemia in patients with CD treated in specialized European centers has been reported to be 27%, where 57% of the anemic patients were iron deficient [18, 22, 36]. Both functional and absolute type of anemia may accompany CD. In the functional type of anemia, insufficient availability of iron for incorporation into erythroid precursors appears, despite normal or elevated body iron. The absolute iron deficiency occurs when the amount of stored iron is inadequate to meet the demands for red blood cell production. Poor dietary intake of iron, reduced iron absorption and blood loss, which very often accompany CD, may deplete the monocyte-macrophage stores, making iron unavailable for erythropoiesis [18, 22, 36].

Oral cavity is easily accessible for direct examination; therefore, such an examination could be used to define the type and frequency of oral lesions in CD and may be useful in creating a diagnostic algorithm to help monitor disease deterioration and treatment efficacy.

The aim of the present study was to evaluate the condition of the oral mucosa in patients with Crohn's disease in relation to their hematinic status and disease activity.

Table 1. Characteristics of patients with Crohn's disease and healthy controls

	Number of patients		Age [yrs]		Number of women		Age of ♀ [yrs]		Number of men		Age of ♂ [yrs]	
	n	% of Total	Range	Mean	n	%	Range	Mean	n	%	Range	Mean
Total	140	100	18-79	35.5	79	56.4 (of Total)	18-78	35.9	61	43.6 (of Total)	18-79	35.9
CD	70	50	18-79	37.4	33	47.1 (of CD)	18-75	37.5	37	52.8 (of CD)	18-79	37.4
Control	70	50	22-78	31.6	46	65.7 (of Control)	22-78	33.5	24	34.3 (of Control)	22-75	30.4
		% of CD										
CD↓Fe	29	41.4	18-79	38.2	12	41.4 (of CD↓Fe)	20-75	38.4	17	58.6 (of CD↓Fe)	18-79	38.2
CD↑Fe	41	58.6	18-67	36.3	21	51.2 (of CD↑Fe)	18-67	39.4	20	48.8 (of CD↑Fe)	19-52	33.1
CDact	19	27.1	18-59	37.8	11	57.9 (of CDact)	18-59	37.8	8	42.1 (of CDact)	18-42	39.6
CDinact	17	24.3	19-67	37.4	9	52.9 (of CDinact)	20-67	37.6	8	47.1 (of CDinact)	19-52	38.1

CD - patients with Crohn's disease, CD↓Fe - patients with Crohn's disease and decreased serum iron, CD↑Fe - patients with Crohn's disease and normal serum iron, CDact - patients with Crohn's disease in active stage, CDinact - patients with Crohn's disease in non-active stage.

MATERIAL AND METHODS

Patients

The study was performed in the Department of Human Nutrition, Gastroenterology and Internal Diseases and in the Department of Oral Mucosa Diseases, Poznań University of Medical Sciences, Poland between November 2007 and December 2009.

The study group comprised of 70 patients aged 18–79 years (mean 37.4) with CD, including 33 women aged 18–75 years (mean 37.5) and 37 men aged 18–79 years (mean 37.4). All the patients were diagnosed based on the algorithm used in the Department of Human Nutrition, Gastroenterology and Internal Diseases, Poznań University of Medical Sciences, Poland, which involved the analysis of clinical symptoms and the results of laboratory, endoscopic, histopathologic and radiographic tests. The duration of CD varied from 0.5 to 25 years (mean 6.3). The examined subjects presented with assorted clinical stages of the disease. Depending on serum iron levels, CD patients were assigned to low- and normal-iron level subgroups.

The control croup consisted of 70 generally healthy subjects aged 22–78 years (mean 31.6), including 46 women aged 22–78 years (mean 33.5) and 24 men aged 22–75 years (mean 30.4). Pregnancy, drug intake and hormonal supplementation were the exclusion criteria from the control group. The examined subjects were the patients, students and staff of the Department of Human Nutrition, Gastroenterology and Internal Diseases and the Department of Oral Mucosa Diseases, Poznan University of Medical Sciences.

A detailed characteristic of the study participants is presented in Table 1.

METHODS

Oral examination. All the participants underwent a detailed oral examination comprised of anamnesis and a clinical evaluation. Age, sex, subjective complaints related to the oral cavity, dental hygiene habits and addictions were included in the patients' history. The clinical evaluation of the oral cavity was performed by a qualified dental specialist in artificial light with a standard diagnostic dental set, and included the detailed assessment of type, localization and frequency of pathologic lesions. Oral mucosa diseases were diagnosed based on typical clinical symptoms and the results of accessory tests performed when indicated. If a histopathologic examination was required, bioptates of oral mucosa were fixed in 10% buffered formalin, then paraffin-embedded and stained with H+E. Pathologic findings were photographed in all cases.

Mycological test. All the participants underwent a mycological evaluation. Smears were collected with a sterile swab from the dorsal tongue surface, buccal area and pathologic lesions, if detected, and were then cultured in a *Candida*-selective solid medium (Sabouraud glucose agar with chloramphenicol; Mycomedium, Biomed S.A.,

Table 2. Classification criteria used in the study in relations to CDAI values

CDAI	Subgroup
0-220	Patients with low activity of CD (CDinact)
> 221	Patients with high activity of CD (CDact)

Poland) at a temperature of 37°C according to the manufacturer's instructions. Results were checked after 24, 48 hours and 7 days. *Candida* yeasts appeared as white or creamy, round, smooth colonies. The number of colonies was evaluated with a half-quantitative method.

Blood test. Routine full blood count was performed in all patients. Blood serum iron levels were estimated with a colorimetric ferrozine-based assay, according to Walmsley et al. [43].

Crohn's disease activity evaluation. The activity of CD was assessed based on Crohn's Disease Activity Index (CDAI) according to Best et al. [5]. This scoring system based on several clinical abdominal and extra-abdominal symptoms enables the classification of patients as remissive or active and helps to quantify the disease symptoms. The classification includes the following aspects: the number of liquid or soft stools, abdominal pain, subjectively assessed general well-being, presence of complications (including oral mucosa inflammation), use of antiperistaltic agents, the presence of an abdominal mass, decreased hematocrit and percentage deviation from a standard weight. Summarized values of each symptom were used to illustrate the current activity of the disease. According to Best et al., a level <150 points indicates remission, values between 150 and 220 points are related to low activity of the disease, values between 220 and 450 points indicate moderate disease activity, while the values above 450 points appear in patients with highly active CD. For the purpose of our study, patients were assigned into 2 subgroups, as presented in Table 2.

Statistical analysis. The results were statistically analyzed with StatExact for Windows with Mann-Whitney and Kruskal-Wallis nonparametric tests (Mann-Whitney test to compare the two groups, Kruskal-Wallis test in comparisons of more than two groups), with $p<0.05$ considered as a significance level.

Ethical approval. The study was approved by the Poznan University of Medical Sciences Ethics Committee (approval code: 924/07) and complied with the guidelines of the Declaration of Helsinki. All patients were informed in detail about the nature of the study before written consent was obtained for participation in this project.

RESULTS

Serum iron levels were estimated in all 70 patients with CD. Decreased serum iron level was observed in 29 patients with CD (41.4%), where values between 50

Table 3. Oral mucosal lesions and Candida occurrence regarding to patient serum iron levels in Crohn's disease

Oral pathologic lesion	CD↓Fe n=29		CD↑Fe n=41		Control n=70	
	n (% of CD↓Fe)	Candida + n (% of subjects with oral lesion)	n (% of CD↑Fe)	Candida + n (% of subjects with oral lesion)	n (% of Control)	Candida + n (% of subjects with oral lesion)
White coated tongue	15 (51.7)	11 (73.3)	28 (68.3)	16 (57.1)	36 (51.4)	14 (38.9)
Buccal cobblestoning	8 (27.6)	4 (50)	14 (34.1)	11 (78.6)	3 (4.3)	1 (33.3)
Recurrent aphthous stomatitis (RAS)	8 (27.6)	8 (100)	11 (26.8)	6 (54.5)	6 (8.6)	2 (33.3)
Atrophic glossitis	3 (10.3)	2 (66.7)	5 (12.2)	4 (80)	0	0
Median rhomboid glossitis	3 (10.3)	2 (66.7)	1 (2.4)	1 (100)	0	0
Geographic tongue	2 (6.9)	1 (50)	2 (4.8)	1 (50)	2 (2.8)	2 (100)
Fissured tongue	2 (6.9)	2 (100)	1 (2.4)	1 (100)	1 (1.4)	0
Angular cheilitis	2 (6.9)	2 (100)	5 (12.2)	4 (80)	2 (2.8)	2 (100)
Ulcer	1 (3.4)	0	2 (4.8)	1 (50)	0	0

CD↓Fe - patients with Crohn's disease and decreased serum iron, CD↑Fe - patients with Crohn's disease and normal serum iron.

Fig. 1. Minor aphtha on a tip of the tongue in a patient with Crohn's disease

and 175 µg/dL were considered as normal in accordance with the current hospital laboratory recommendations. The remaining 41 subjects from the CD group (58.9%) were within the normal range of serum iron levels. Table 3 lists the oral mucosal findings and the *Candida* occurrence with respect to patient serum iron levels.

The most commonly observed oral mucosal findings in both groups where the following: white coated tongue (51.7% and 68.3%), buccal cobblestoning (27.6% and 34.1%) and recurrent aphthous stomatitis (RAS) (27.6% and 26.8%). The lesions which appeared more often in patients with decreased serum iron levels included the following: RAS and several types of glossitis. RAS was found to be insignificant in patients with decreased serum iron when compared to CD subjects with the normal serum iron (27.6% vs 26.8%). There was, however, a significant difference in the RAS occurrence between the CD↓Fe group and the healthy controls (27.6% and 8.6%; p< 0.05). Figure 1 depicts minor aphtha on the tip of the tongue in a female patient from the study group.

Erythematous and atrophic types of glossitis were observed in 8 CD subjects with decreased serum iron (27.5%). The lesions included atrophic glossitis (10.3%) median rhomboid glossitis (10.3%) and geographic tongue (6.9%). The frequency of tongue inflammations in CD patients with normal serum iron values was lower and reached 19.4%: atrophic glossitis in 12.2%, geographic tongue in 48%, and median rhomboid glossitis in 2.4%.

Table 4 shows the results of mycological analysis in iron deficient and CD patients with normal serum iron levels.

Oral *Candida* appeared in similar frequency in CD patients with decreased serum iron levels and with normal iron values (62.1% *vs* 65.8%; the difference statistically insignificant). However, in the CD↓Fe group, the growth of multiple yeast colonies was significantly more frequent when compared to the subgroup with normal iron levels (38.9% vs 9.7%; p< 0.05).

The disease activity according to CDAI was assessed in 36 patients with CD who required hospitalization. According to the described criteria, 19 patients (52.8%) were classified as belonging to the high-active stage of the disease. In this subgroup, CDAI ranged from 44 to 219 points (mean 131.1). Low active CD was found in 17 subjects (47.2%), with CDAI values between 228 and 440 points (mean 233.1). The frequency of oral mucosal findings in active and inactive CD subgroups is compared in Table 5.

Oral pathologic lesions which appeared more often in the high-active CD subgroup than in the low-active included: RAS, angular cheilitis, atrophic glossitis and white coated tongue. However, the differences were statistically insignificant. Ulcerative lesion on the dorsal tongue surface in a female patient with high-active CD and the microscopic image of histopathologic specimen is presented in Figure 2.

Table 6 lists the results of mycological analysis in relation to the disease activity.

Table 4. Candida occurrence in CD patients with respect to serum iron levels

Oral Candida occurrence	**CD↓Fe n=29**	**CD↑Fe n=41**
	n (%)	
Positive result	18 (62.1)	27 (65.8)
	n (% of positive CD↓Fe)	n (% of positive CD↑Fe)
+	7 (38.9)	6 (14.6)
++	3 (16.7)	13 (31.7)
+++	7 (38.9)	4 (9.7)
cg	2 (6.9)	3 (7.3)

CD↓Fe - patients with Crohn's disease and decreased serum iron, CD↑Fe - patients with Crohn's disease and normal serum iron, C – controls, cg - confluent growth, - statistically significant difference (Mann-Whitney test; p<0.05 considered significant).

Table 5. Oral mucosal lesions in relation to the disease activity

Oral pathologic lesion	CDact n=19		CDinact n=17		Control n=70	
	n (% of CDact)	Candida + n (% of subjects with oral lesion)	n (% of CDinact)	Candida + n (% of subjects with oral lesion)	n (% of Control)	Candida + n (% of subjects with oral lesion)
White coated tongue	12 (63.2)	10 (83.3)	8 (47)	6 (75)	36 (51.4)	14 (38.9)
Recurrent aphthous stomatitis	7 (36.8)	7 (100)	2 (11.8)	2 (100)	6 (8.6)	2 (33.3)
Buccal cobblestoning	6 (31.6)	4 (66.6)	6 (35.3)	5 (83.3)	3 (4.3)	1 (33.3)
Atrophic glossitis (Hunter's)	3 (15.8)	2 (66.6)	2 (11.8)	2 (100)	0	0
Angular cheilitis	3 (15.8)	3 (100)	1 (5.9)	1 (100)	2 (2.8)	2 (100)
Erythematous macules on palate	2 (10.5)	2 (100)	4 (23.5)	3 (75)	3	4,3
Median rhomboid glossitis	2 (10.5)	2 (100)	0	0	0	0
Papillary hyperplasia on palate	1 (5.3)	1 (100)	0	0	0	0
Fissured tongue	1 (5.3)	1 (100)	0	0	1 (1.4)	0
Geographic tongue	0	0	1 (5.9)	1 (100)	2 (2.8)	2 (100)
Ulcer	0	0	1 (5.9)	1 (100)	0	0
Black hairy tongue	0	0	1 (5.9)	1 (100)	0	0

CDact - patients with Crohn's disease in active stage, CDinact- patients with Crohn's disease in non-active stage.

No statistically significant differences were found in the total oral occurrence of *Candida* between the compared subgroups nor during the quantitative analysis of the yeast growth.

DISCUSSION

Oral pathologic lesions appear in several systemic diseases, very often in mucocutaneous and gastro-intestinal disorders. Defining the type and the frequency of those findings may facilitate the diagnostics and the treatment of the general disease. Commonly described digestive disorders, where the oral cavity may be involved, include gastro-oesophageal reflux disease, coeliac disease, bulimia and anorexia [19, 32]. The reports on oral involvement in the course of inflammatory bowel diseases in a Polish cohort of patients are rather limited [2, 6, 9, 21, 23, 25, 37, 38].

In this study we attempted to define the influence of iron deficiency and disease activity into oral mucosa condition in CD patients. We demonstrated the presence of CD nonspecific oral lesions in the examined subjects.

One of the diseases which appeared more often in patients in the highly active stage of CD, compared to low-active CD subjects, was RAS (36.8% *vs.* 11.8). At the same time, the decreased serum iron levels did not significantly enhance the development of RAS in CD. There was, however, a significant difference in the RAS occurrence between the CD↓Fe group and healthy controls (27.6% and 8.6%). As described by several authors, RAS occurred more frequently in patients with Crohn's disease than in the general population [27, 35, 40, 42]. On the other hand, according to Górska, the impact of gastro-intestinal diseases on the development of RAS is limited and less evident than the role of other factors, including oral hygiene, dental carries and local irritants

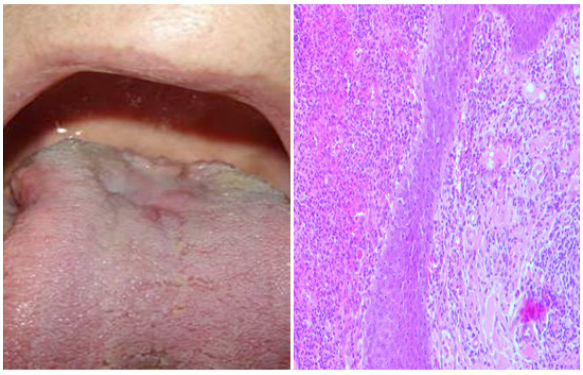

Fig. 2. Ulcer on the dorsal surface of the tongue in a female patient from high-active CD group and microscopic image of histopathologic specimen, which reveals chronic, granulomatous, partially purulent inflammation with moderately numerous eosinophils (H+E stain, 100x)

Table 6. Candida occurrence in CD patients regarding the disease activity

Oral Candida occurrence	CDact n=19	CDinact n=17
	n (%)	
Positive result	15 (78.9)	12 (70.6)
	n (% of positive CDact)	n (% of positive CDinact)
+	5 (33.3)	4 (33.3)
++	5 (33.3)	3 (25)
+++	4 (26.7)	3 (25)
cg	1 (6.7)	2 (16.6)

CDact - patients with Crohn's disease in active stage, CDinact - patients with Crohn's disease in non-active stage
cg- confluent growth, ■- statistically significant difference (Mann-Whitney test; $p<0.05$ considered significant).

in the oral cavity [13]. Our study confirms a higher incidence of RAS in patients with CD, especially those in a high active stage of the disease, when compared to the generally healthy population. Also, Szczeklik et al. demonstrated a higher incidence of RAS in patients with active CD compared to non-active and controls (26.9% vs 7% vs 4.4%) [37]. This phenomenon may partially result from similar etiologic pathways involved in CD and RAS. Although in both cases the direct pathomechanism remains elusive, genetically conditioned immunologic disturbances involving disrupted cytokine profile participate in the development of these two entities and appear to be a contributing factor [13, 40, 42].

In our observations, a high activity of the disease is correlated with an increased frequency of erythematous or atrophic glossitis and angular cheilitis. Atrophic tongue inflammation was also a common finding in iron deficient CD subjects in this study. Patients with CD are predisposed to develop microcytic and megaloblastic anemia and very often they suffer from general malnourishment, especially during the period of the disease activation [11, 18, 36]. Microelement and vitamin deficiency may contribute locally to glossitis, mucosal atrophy, palor, burning and paresthesia of the oral cavity [2, 11, 18]. Glossitis and angular cheilitis in the course of CD were observed by Mdinaridze et al. [27] and Androsz-Kowalska et al. [2]. In agreement with our observations, Szczeklik et al. demonstrated a significantly higher incidence of glossitis and angular cheilitis, especially in the highly active stages of CD [37]. Jędrzejowska et al. listed glossitis as one of the important, early signs of gastro-intestinal diseases and anemias. In their observations, complaints related to GI tract were reported by 67.4% of patients with atrophic glossitis [16]. Also, Katz et al., who evaluated the oral mucosa condition in relation to the disease activity, reported a higher incidence of removable coating on the tongue and inflammatory lesions of the tongue in patients in active stage of CD [20]. In contrast to these findings, in the Halme et al. study, the activity of CD did not influence the oral mucosa condition [15]. The discrepancy in the presented study outcomes may partially result from the non-uniform qualification criteria used while stratification into study subgroups, non-homogenous structure of the control groups and the different methods of the oral mucosa evaluation.

In our study, the oral *Candida* occurrence was comparable in all the studied subgroups, although *Candida* carriage was most frequent in patients with a high active disease (78.9%). There were, however, significant differences between all the subgroups of patients with CD and the controls, where the *Candida* occurrence reached 35.7%. Our results remain consistent with the observations of Meurman et al., who did not find a difference in *Candida* occurrence in active and non-active CD patients. They described, however, a trend towards enhanced yeast colonization in subjects during the exacerbation of CD [28]. Disrupted immunologic response, which occurs in the course of CD that includes the impaired ability of neutrophils to kill *Candida albicans*, together with immunosuppressive therapy and bacteriostatic effects of sulpha-containing preparations, may partially explain the higher risk of candidiasis in CD patients. A higher rate of colonization could be, however, expected in patients with a high activity of the disease. Some further studies are required on a larger sample of patients in this matter.

Oral lesions in patients with CD can be either extra-intestinal manifestations of the disease, or they can develop as complications of accompanying nutrient deficiency and treatment. Those belonging to the second group appear quite often and can be considered as a potential indicator of the disease deterioration or remission. The lesions may compromise oral functions and decrease patients' quality of life. Cooperation between dentists, specialists in oral medicine and gastroenterologists is important for the successful treatment of oral symptoms in CD. This may facilitate the diagnosis of CD, especially if oral lesions precede gastrointestinal pathol-

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