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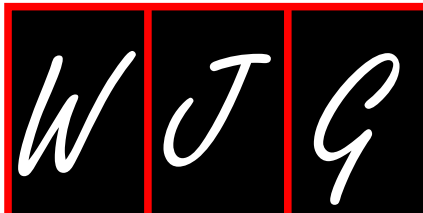
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2016 Inflammatory Bowel Disease: Global view

Oral pathology in inflammatory bowel disease

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Abstract

The incidence of inflammatory bowel diseases (IBD) - Crohn's disease (CD) and ulcerative colitis (UC) - has been increasing on a global scale, and progressively, more gastroenterologists will be included in the diagnosis and treatment of IBD. Although IBD primarily affects the intestinal tract, extraintestinal manifestations of the disease are often apparent, including in the oral cavity, especially in CD. Specific oral manifestations in patients with CD are as follows: indurate mucosal tags, cobblestoning and mucogingivitis, deep linear ulcerations and lip swelling with vertical fissures. The most common non-specific manifestations, such as aphthous stomatitis and angular cheilitis, occur in both diseases, while pyostomatitis vegetans is more pronounced in patients with UC. Non-specific lesions in the oral cavity can also be the result of malnutrition and drugs. Malnutrition, followed by anemia and mineral and vitamin deficiency, affects the oral cavity and teeth. Furthermore, all of the drug classes that are applied to the treatment of inflammatory bowel diseases can lead to alterations in the oral cavity due to the direct toxic effects of the drugs on oral tissues, as well as indirect immunosuppressive effects with a risk of developing opportunistic infections or bone marrow suppression. There is a higher occurrence of malignant diseases in patients with IBD, which is related to the disease itself and to the IBD-related therapy with a possible oral pathology. Treatment of oral lesions includes treatment of the alterations in the oral cavity according to the etiology together with treatment of the primary intestinal disease, which requires adequate knowledge and a strong cooperation between gastroenterologists and specialists in oral medicine.

Key words: Crohn's disease; Ulcerative colitis; Drug-related side effects and adverse reactions; Inflammatory bowel disease; Extraintestinal manifestations; Malnutrition

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Core tip: Inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis affect the intestinal tract, but can also present with extraintestinal manifestations and complications. In CD, disease-specific lesions with granulomatous changes can occur in the oral cavity. However, non-specific lesions are more common in IBD and are mostly caused by malnutrition and medications. All of the drug classes that are applied in the treatment of IBD can lead to lesions in the oral cavity. This paper offers an overview of the oral pathology with a detailed description of the complications related to malnutrition and IBD therapy.

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) belong to the group of chronic inflammatory bowel diseases (IBD). Although the etiology of these diseases has not been completely ascertained, it is well known that the factors contributing to disease pathogenesis include environmental aspects, intestinal microflora, genetic predisposition and pathological immune responses^[1-3]. North America and North-Western Europe exhibit the highest incidence and prevalence of the disease, but an increase in the number of patients has been observed worldwide, indicating its emergence as a global disease^[4,5]. It appears that the global increase in the disease is related to a "Western" lifestyle and diet, which shows the strong impact of the environment on the occurrence of the disease^[1,3,6].

In addition to affecting the intestinal tract, the disease can manifest with extraintestinal symptoms in almost every organ system and significantly influence the quality of life and the functional state of the patient. There is a distinction between extraintestinal manifestations (EIM) and extraintestinal complications, although they are sometimes difficult to distinguish. EIMs occur in 6% to 47% of patients^[7-10] with different rates of occurrence in relation to the primary disease. Peripheral arthropathy type I, aphthous stomatitis, erythema nodosum and episcleritis are usually related to an active disease. Ankylosing spondylitis and peripheral arthropathy type II have their own course of disease, independent of the activity of the bowel disease. Primary sclerosing cholangitis, uveitis and pyoderma gangrenosum have a variable course and can be associated with, but do not have to be related to, the activity of the bowel disease^[10]. Patients with perianal CD, patients with colonic disease and smokers are at an increased risk of developing EIMs^[9,10]. Furthermore, patients can develop several EIMs at the

same time, and the occurrence of one EIM increases the risk of developing another EIM^[10].

The pathogenesis of EIMs is still not fully identified. It appears that the inflamed intestinal mucosa can trigger immunological responses by sharing common epitopes (e.g., intestinal bacteria and synovial). Bacteria that can translocate because of greater permeability of the intestinal mucosa trigger an acquired immune response that does not distinguish between a bacterial epitope and a joint or skin epitope^[10]. In patients with extraintestinal disease manifestations, there is also a strong genetic predisposition; the connection between the EIMs and the major histocompatibility complex loci has been demonstrated, and there is a concordance for EIMs in 84% of siblings^[8,9].

Extraintestinal complications of inflammatory bowel diseases frequently occur due to malnutrition, chronic inflammation and side effects of drugs^[2,8-10].

Oral lesions are common in patients with IBD and epidemiology data vary over a wide range of 5%-50% due to contradictory studies^[11,12]. The goal of our paper is to present the oral pathology of IBD, whether it includes extraintestinal manifestations of the disease or its complications.

ORAL MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE

Oral manifestations of CD include specific and non-specific lesions, while in patients with UC, only non-specific lesions in the oral cavity are observed. Characteristics of specific lesions include the presence of non-caseous granulomas, which occur only in CD patients. CD manifestations in the oral cavity can precede the intestinal manifestations, occur at the same time as the intestinal manifestations or occur after the occurrence of the intestinal manifestations. Oral lesions can be of significance when diagnosing CD because of a characteristic non-caseous granulomatous inflammation^[12-17]. This condition can be easily confirmed by a histopathological examination of accessible lesions in the oral cavity. Turchi *et al.*^[18] described a rare case of tonsillar granuloma as a manifestation of CD. Oral manifestations of the disease are more common in males^[15,19,20] and children^[12,19,21,22]. They are also more common in patients with CD than in patients with UC^[23,24], and their prevalence in CD patients ranges from 20%-50%^[11], while in UC the prevalence is 8%^[25]. However, some studies have not demonstrated a statistically significant difference^[26]. Furthermore, data from the literature are contradictory; in some studies, it has been stated that the changes in the oral cavity are not related to the CD activity index^[27] or to the localization of intestinal manifestations^[23,24,28,29], although there are papers that do link and attribute the changes in the oral cavity to inflammatory responses following the exacerbation of CD^[26,30].



Figure 1 Cobblestoning and ulcerations in Crohn's disease.

Specific oral lesions in patients with CD include a cobblestone appearance of the oral mucosa; deep linear ulcerations; mucosal tags; swelling of the lips, cheeks and face; lip and tongue fissures; and mucogingivitis^[15,19,21,22,25,31]. The mucosa of the oral cavity is hyperplastic and resembles a "cobblestone", which marks the nodular, granulomatous swelling of the oral mucosa (Figure 1). In addition, there are also indurated polypoid fringe-like lesions of the vestibule and the retromolar region. Mucosal tags and deep ulcerations with hyperplastic edges, firm or boggy to palpation, are mostly present in the labial and buccal mucosa and in retromolar regions. Attached gingiva and alveolar mucosa become swollen, granulated and hyperplastic with or without ulcerations^[19,32]. Edema of the face, of one or both lips and of the buccal mucosa may also occur. This condition is unpleasant for patients because it can lead to facial deformation^[15,19,22,25]. Non-caseous granulomatous inflammation^[33] can be histologically detected in such lesions. The lips are the most commonly affected, and they are usually painless, tender and firm to palpation^[34]. Numerous patients with swollen lips also develop painful vertical fissures where many microorganisms can be isolated^[35].

Furthermore, patients with CD often experience autoimmune changes of the minor salivary glands and dry mouth^[23,36]. Mills *et al.*^[36] reported a case of patient with CD in which characteristic granulomatous lesions caused rupture of the excretory salivary duct leading to the formation of a cutaneous salivary duct fistula. Chronic inflammatory processes near the parotid duct resulted in partial to total duct obstruction and caused dilated ducts and cyst formation, which can lead to the formation of cutaneous fistula. All of these changes can cause reduction in saliva and dry mouth^[23].

Non-specific oral lesions associated with CD and UC include aphthous stomatitis, angular cheilitis, pyostomatitis vegetans, glossitis and lichen planus^[13,17,19,23,31,37,38]. Non-specific lesions, present in both CD and UC patients, are more common than specific lesions, which makes the differential diagnosis very difficult^[13]. Non-specific lesions occur due to

chronic inflammation, malnutrition and as a side effect of drugs. The occurrence of halitosis^[23], dental erosion, dental caries^[20,30,39,40], candidiasis, odynophagia and dysphagia^[23,26] is more common in patients with IBD than in the general population. Furthermore, patients with UC exhibit diffuse pustules and non-specific gingivitis in the oral cavity^[19].

Aphthous stomatitis, which occurs in both CD and UC patients, presents as shallow, round ulcers surrounded by an erythematous "halo" with a central fibrin membrane^[19,31]. Aphthous stomatitis does not differ from the stomatitis that occurs in the general population. If aphthous ulcerations are present, the presence of inflammatory bowel disease must be suspected, although intestinal symptoms may not yet be present^[28,29]. Because oral lesions are more common in children and can precede the development of inflammatory bowel disease, cooperation between a specialist in oral medicine and a gastroenterologist is crucial to detect the disease as early as possible^[12,13].

Angular cheilitis is clinically manifested as erythema with or without painful fissures and sores at the corners of the mouth. It can occur due to anemia or as a manifestation of a fungal or bacterial infection^[25,41-43].

Pyostomatitis vegetans is a rare benign chronic inflammatory mucocutaneous disorder characterized by pustules of an unknown etiology. It is related to inflammatory bowel disease, occurs more often in combination with UC (although it can occur in CD) and is more common in male patients. It represents a specific inflammatory marker of UC^[19,33]. Only about fifty cases of this disorder have been described to-date^[37,38,44-50]. Macroscopically, the disease manifests as small exophytic lesions with an erythematous perimeter and a creamy white or yellow surface. They are covered with vulnerable membranes and their cracking results in small superficial erosions or ulcers. The confluence of those lesions results in the characteristic morphology sign of a "snail track"^[33]. The alterations occur in the upper and lower frontal vestibule, on the tongue (Figure 2) and gingiva, as well as on the soft and hard palate^[33]. Microscopically, there are no granulomas in the lesions.

Although IBD complications lead to non-specific lesions in the oral cavity, the consequences of two of the most common complications, malnutrition and medications administered for the treatment of inflammatory bowel disease, must be emphasized. Table 1 summarizes the oral manifestations and complications of IBD.

ORAL PATHOLOGY CAUSED BY MALNUTRITION

Malnutrition is present in 23% of outpatients and 85% of hospitalized patients suffering from IBD^[51]. It is caused by a reduced food intake, reduced resorption of nutrients, gastrointestinal losses, increased metabolic

Table 1 Oral manifestations and complications in inflammatory bowel disease

Oral tissue	Manifestations	Etiology
Lips	Lips swelling with or without fissures ^[12,15,16,21,22,34,36,156] Angular cheilitis ^[15,22,31]	Crohn's disease Fungal and bacterial infections, nutritional deficiency
Tongue	Erythema multiforme, Stevens-Johnson syndrome ^[143,144] Fissuring ^[23] Cobblestone plaques ^[17] Pyostomatitis vegetans ^[17,37,38,45] Aphthous stomatitis ^[11,31] Taste disturbance ^[17,23,147,155]	Infliximab; adalimumab Crohn's disease Crohn's disease Ulcerative colitis (more common) and Crohn's disease Nutritional deficiency; decreased heat shock protein 27 expression Related to disease activity and nutritional habits; sulfasalazine; metronidazole
Oral mucosa (labial/buccal/palatal/vestibular)	Candida infections ^[78,131,132,141] Erythema multiforme, Stevens-Johnson syndrome ^[143,144] Buccal edema ^[15,34,48] Cobblestoning ^[12,14,15,21,24,34] Deep linear ulceration ^[15,16,21-24,34,38] Mucosal tags ^[12,16,21,29,34] Buccal sulcus ulcerations ^[20,34] Palatal ulcerations ^[20,44] Pyostomatitis vegetans ^[33,37,45-47,49,50] Aphthous stomatitis ^[11,22,29,31,45] Lichen planus/lichenoid reaction ^[29,85,140,142]	Corticosteroids; thiopurines; cyclosporin A; infliximab Infliximab; adalimumab Crohn's disease Crohn's disease Crohn's disease Crohn's disease Crohn's disease Ulcerative colitis (more common) and Crohn's disease Nutritional deficiency; decreased heat shock protein 27 expression Sulfasalazine; mesalazine; infliximab;
Periodontal tissue	Erythema multiforme, Stevens-Johnson syndrome ^[143,144] Mucogingivitis ^[12,21,22,32,34] Cobblestoning ^[29,32] Pyostomatitis vegetans/pustular ulcerations ^[17,32,33,37,44,46,50] Nonspecific gingivitis ^[13,19,147] Periodontal diseases/periodontitis ^[20,156]	certolizumab pegol Infliximab; adalimumab Crohn's disease Crohn's disease Ulcerative colitis (more common) and Crohn's disease Cause not clearly specified Cause not clearly specified
Alveolar bone	Periapical lesions ^[30] Alveolar bone loss ^[156]	Related to disease activity Cause not clearly specified
Teeth	Caries ^[20,30,39,40] Hypoplasia of enamel ^[40]	Related to disease activity and malabsorption Related to disease activity and malabsorption
Salivary glands	Hyposalivation/dry mouth ^[23,36] Salivary duct fistula ^[36]	Granulomatous inflammation Autoimmune changes in minor salivary glands Crohn's disease

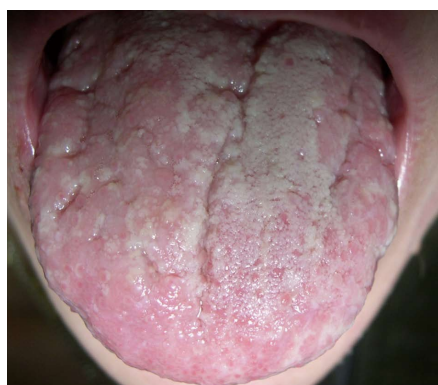


Figure 2 Pyostomatitis vegetans in ulcerative colitis.

needs and as a side effect of drugs^[51,52]. As a result of a nutrient deficiency, patients develop anemia due to lower iron, vitamin B₁₂ and folate levels. In addition to anemia, a deficiency of electrolytes, trace elements and vitamins is also quite common^[52,53]. Anemia is a common complication of inflammatory bowel disease, which can be manifested in oral pathology. Suffering from anemia can strongly influence the patient's quality of life. Bleeding and reduced iron reabsorption (due to inflammatory changes in the duodenum and upper

jejunum) lead to a microcytic, hypochromic anemia, while the presence of proinflammatory cytokines causes chronic anemia with a high hyperferritinemia. The deficiency of B₁₂ and folates leads to macrocytic anemia. The deficiency of B₁₂ occurs most often in Crohn's disease due to reabsorption deficiency in the terminal ileum, while the deficiency of folates can be caused by reduced reabsorption, inadequate dietary intake and as a side effect of methotrexate and sulfasalazine^[7,54].

Anemia caused by an iron deficiency is manifested as paleness of the oral mucosa^[55], generalized oral mucosal atrophy, pricking^[56,57], atrophic glossitis with tongue pain^[57] and angular cheilitis^[43,55]. The deficiency of vitamin B₁₂ is manifested in the oral cavity as a painful atrophy of the oral mucosa and the tongue, recurrent aphthous ulcerations^[58,59], angular cheilitis, oral candidiasis, diffuse erythematous stomatitis and pale yellowish mucosa, especially on the palate^[60]. Patients can also complain of altered taste, a burning sensation in the mouth and dysphagia^[43]. If anemia is caused by a folate deficiency, the manifestations in the oral cavity are the same as in anemia caused by vitamin B₁₂ deficiency but without neurological symptoms^[43]. In more severe cases, ulcerative stomatitis and pharyngitis^[43] are also detected.

Today, it is well known that vitamin D not only plays an important role in the mineralization of bones and teeth but also contributes to numerous metabolic processes and has a protective role in immune-mediated diseases as well as allergies. A vitamin D deficiency, in addition to disorders in the metabolism of calcium and phosphate in the oral cavity, is accompanied by the development of bone hypomineralization and an increased risk of fractures^[61]. Malabsorption of calcium, vitamin K and other nutrients, treatment with corticosteroids, inflammatory cytokines in IBD and hypogonadism caused by IBD are additional factors that contribute to the decreased bone mineral density^[62]. A vitamin D deficiency is also associated with the increased prevalence of periodontal diseases (gingivitis and periodontitis), dental caries and tooth loss^[63-65]. Vitamin D also exerts an immunomodulatory effect, and its deficiency increases the risk of infection, malignancy and autoimmune disease^[66] with possible oral manifestations. Calcium is a mineral that plays an important role in tooth development and mineralization. Experimental studies have shown that a calcium deficiency causes a disorder affecting the mineralization of dentin and enamel^[40,67]. A decreased mineralization of bones and teeth is expected in children, who have developed IBD with a deficiency of calcium and vitamin D. However, according to the literature, there are no studies addressing this issue.

Vitamin A and vitamin C deficiencies are also described in IBD patients. A vitamin A deficiency is manifested in the oral cavity as angular cheilitis, atrophy and dryness of oral mucosa. The lips are described as "retreating" because the mucosa contracts towards the oral cavity^[68]. A vitamin C deficiency is manifested in the oral cavity as generalized gingival swelling and spontaneous bleeding, ulcerations, tooth mobility, increased severity of periodontal infections and bone loss^[55,69]. Spontaneous bleeding of the mucosa can be observed as well^[70]. The development of bones and teeth is disrupted in children because both dentin and osteoid depend on vitamin C.

A zinc deficiency is quite common in CD patients. It is manifested in the oral cavity with erosions, ulcers and fissures, a crusting and scaling rash on the lips^[29,71], burning mouth syndrome^[56] and altered taste^[72].

ORAL PATHOLOGY CAUSED BY MEDICATION

Treatment of inflammatory bowel diseases includes 5-aminosalicylic acid (5-ASA) derivatives, corticosteroids, immunomodulators, calcineurin inhibitors, biological therapy and antibiotics. The selection of treatment depends on the site of the disease, the disease activity and the course or behavior of the disease^[73,74]. Currently, the personalized approach to

therapy is advocated, and "risk matrices" for assessing the risk of developing severe forms of the disease have been developed^[75,76]. The therapy applied to treating inflammatory bowel diseases can lead to alterations in the oral cavity due to the direct toxic effect of the drug on the oral tissue, the indirect immunosuppressive effect which increases the risk for opportunistic infections or bone marrow suppression. The immunomodulators commonly used in IBD treatment include the following: corticosteroids (a total dose equivalent to ≥ 20 mg of prednisolone for ≥ 2 wk), thiopurines, methotrexate, anti-tumor necrosis factor alpha (anti-TNF) agents and other biologics, which increase the risk of opportunistic infections^[77]. The incidence of infection is higher if the patients simultaneously receive several immunosuppressive drugs, are malnourished, suffer from other associated diseases or have a prior history of serious infections^[77-80]. The risk of infection also increases with age^[77-79]. Potential myelotoxicity of the drugs, including the development of leucopenia and agranulocytosis, also increases the risk of developing opportunistic and serious infections^[79-81]. In addition to the risk of developing gastrointestinal tumors, patients with inflammatory bowel diseases are at risk of developing hematological malignancies. Compared to the general population, patients suffering from CD are at risk of developing lymphoma, especially non-Hodgkin lymphoma, while patients with UC are more likely to develop leukemia^[82]. Early disease onset, male gender and age > 65 are risk factors for developing hematological malignancies. With regard to malignancies related to IBD therapy, patients receiving thiopurines have an increased risk of developing cancer. The risk of developing lymphoma is also increased but can be reversed by thiopurine withdrawal. There is no evidence of an increased risk of developing cancer or lymphoma in patients who received monotherapy with anti TNF drugs^[82].

Thus far, only one study addressing the risks of developing malignancies in the oral cavity of patients with IBD has been published^[83]. Katsanos *et al.*^[83] have established that patients with IBD are at a higher risk of developing tumors in the oral cavity, especially on the tongue. The authors have also concluded that female IBD patients are at a higher risk than male patients. However, this study did not include a risk analysis based on the type of treatment.

Oral complications of aminosalicylates

Sulfasalazine has been used to treat UC for 50 years^[84]. It is a prodrug made of sulfapyridine and an active substance of 5-aminosalicylic acid (5-ASA). Sulfapyridine, or more precisely the sulfur component, is considered to be responsible for numerous side effects and allergic reactions caused by this drug. In the oral cavity, sulfasalazine causes an oral lichen planus/oral lichenoid reaction^[85-87]. The occurrence of these lesions in the oral cavities of patients with IBD



Figure 3 Pseudomembranous candidiasis on the palatal mucosa and atrophic candidiasis on the tongue in a Crohn's disease patient treated with anti-TNF and prednisone.

is rare, and only a few cases have been described^[85]. Some patients receiving sulfasalazine may complain of a metallic taste in the mouth^[72]. Patients suffering from inflammatory bowel diseases who are receiving sulfasalazine can also develop oral complications caused by myelotoxicity and hepatotoxicity due to the sulfasalazine treatment, presented through signs of aplastic anemia, bleeding (ecchymosis and petechiae) and oral infections. Side effects of 5-ASA derivatives (non-sulfa-containing drugs) are less numerous^[88] but have been described in the literature^[89]. Mesalazine can cause hematological side effects, such as leucopenia, thrombocytopenia and aplastic anemia^[89], resulting in alterations in the oral cavity. Alstead *et al.*^[85] presented a case of a patient who developed oral lichen as a reaction to sulfasalazine, which was replaced with mesalazine, but the lesions did not withdraw. After withdrawing the mesalazine, the oral lesions withdrew, and the authors concluded that the lesions were related to 5-ASA.

Oral complications of corticosteroids

Despite their efficiency, corticosteroids were declared unsuitable for long-term use due to a high percentage of side effects (reported in 50% of patients)^[90]. Early adverse effects in the orofacial region, which occur as a result of a supra-physiological dose, include acne, moon face, petechiae and ecchymosis due to blood vessel vulnerability^[90-92]. The long-term use

of corticosteroids increases the risk of opportunistic infection^[78,79]. The risk of infection also depends on the dose^[78]. The use of these drugs is related to the occurrence of candidiasis in the oral cavity, pharynx and esophagus^[78]. Pseudomembranous candidiasis and chronic atrophic candidiasis are the most prevalent forms of oral candidiasis in such patients (Figure 3)^[92,93]. Patients receiving corticosteroids and thiopurines simultaneously have an increased risk of developing opportunistic infections than patients who receive corticosteroids only^[78]. Tournier *et al.*^[78] observed a 10% prevalence of *Candida albicans* infections in patients with IBD receiving corticosteroid therapy only. However, the clinical site of these infections was not specified. Numerous case reports and clinical studies on primary varicella zoster virus and herpes zoster virus infections^[78,79,81,94] in patients with IBD were published, but checking the literature, no papers on these infections occurring in the oral cavity and orofacial region have been published. Herpes simplex virus (HSV) infections in such patients are also common, whether they are of primary or recurrent character^[78,95-98]. Tournier *et al.*^[78] have described an 18% prevalence of HSV infections on the face, in the esophagus or on the extremities of patients with IBD.

In children with IBD, especially with CD, the disease itself^[99] and the use of corticosteroids^[100] can affect growth. There are no studies analyzing bone development in the orofacial region of children with IBD, especially in children who have received long-term corticosteroid therapy. Long-term corticosteroid use can also result in osteoporosis, affecting the patients' jawbones and increasing the risk of periodontal diseases and fractures. Experimental and clinical studies have shown that the long-term use of corticosteroids leads to the occurrence of calcifications in the dental pulp and pulp obliteration^[101-103].

Oral complications of thiopurines

Azathioprine (AZA) and 6-mercaptopurine (6-MP) are thiopurine drugs that have been used in the treatment of IBD for the past 50 years, primarily for the maintenance of disease remission^[90]. Unfortunately, in addition to the beneficial treatment effects in some patients with IBD, these drugs can also cause complications and lead to adverse effects. AZA has been shown to cause taste disturbances in the form of ageusia/hypogeusia and dysgeusia^[72]. Other side effects of thiopurines include opportunistic infections, myelotoxicity and hepatotoxicity as well as a risk of developing malignant lymphomas, which can also lead to alterations in the oral cavity. The use of AZA/6-MP increases the risk of opportunistic infections for patients taking steroids from approximately 2-3-fold to approximately 15-fold^[78]. Atypical clinical features and longer disease duration are characteristics of these infections. Cases of recurrent HSV infections with large and irregular ulcerations occurring in any region of the

oral mucosa and lasting for weeks or months have been described. The lesions can also occur on non-keratinized mucosa (a region not usually affected) and are not easily distinguished from aphthous lesions^[104]. Due to a potential myelotoxic effect of thiopurines, such as the development of leucopenia and neutropenia^[105,106], the risk of developing opportunistic infections is increased.

It is well known that the use of thiopurines increases the risk of developing lymphoma and cancer^[82,107,108]. However, clinical studies on the prevalence of malignant diseases in the oral cavity of patients with IBD receiving thiopurines are lacking. Only one clinical study was published on this subject. Pasternak *et al.*^[109] established that patients with IBD who are receiving thiopurines are at no greater risk of developing lip, oral cavity or pharynx cancer. Dojcinov *et al.*^[110] were the first to present the cases of two rheumatoid arthritis (RA) patients with an azathioprine-related lymphoproliferative disorder (LPD) in the oral cavity.

Oral complications of methotrexate

Methotrexate is a stomatotoxic drug, which causes oral ulcers, ulcerative stomatitis and mucositis^[87,111-113]. The occurrence of lesions in the oral cavity is associated with a folic acid deficiency and toxic effects of the drug^[112]. The effects of the drug in the oral cavity depend on the administered dose. Lower doses cause ulcers and stomatitis, while higher doses, administered to treat malignant diseases, cause mucositis^[114]. Several clinical studies and cases have described oral ulcers, stomatitis and mucositis in patients treated with methotrexate due to RA, psoriasis and malignancies^[113,115,116]. Furthermore, methotrexate can cause agusea/hypogeusia in the oral cavity^[72]. However, there are no published papers on the occurrence of oral ulcers, stomatitis and taste disturbances in patients with IBD treated with methotrexate.

Bone marrow suppression (in the form of leucopenia, thrombocytopenia or pancytopenia) is also described in patients receiving methotrexate (more often in patients treated with high doses and less often in patients treated with low doses)^[117,118]. Oral alterations can develop as a consequence of bone marrow suppression. The only study on oral infections in patients receiving low doses of methotrexate that we found was published by Pedrazas *et al.*^[119]. The authors described a significantly higher prevalence of oral candidiasis (10.7%) and oral ulcers (60.7%) in patients with RA receiving methotrexate than in patients who were not treated with methotrexate.

Several clinical cases of methotrexate-related Epstein-Barr virus associated lymphoproliferative disorders in the oral cavity in patients with RA and Still's disease^[110,111,120-126] have been published. Clinical LPD is manifested in the oral cavity as swelling or painful ulcers of irregular edges on the gingiva, tongue, floor of the mouth and buccal mucosa^[110,111,120-126]. In some cases,

the bone^[111,122,125] was also affected. The common characteristic of these disorders is that the majority of lesions regress completely following the withdrawal of methotrexate^[123]. According to the literature, there are no descriptions of these disorders in the oral cavity caused by methotrexate in patients with IBD.

Oral complications of calcineurin inhibitors (cyclosporine and tacrolimus)

Gingival hyperplasia (or gingivae overgrowth) is common in patients receiving cyclosporine (CsA). The severity of gingival hyperplasia depends on the duration of CsA therapy, but its occurrence is also influenced by bacterial plaque, local irritants and possibly the simultaneous use of other drugs that cause gingival hyperplasia (*e.g.*, nifedipine)^[127,128]. Gingival hyperplasia can interfere with oral functions and speech and can cause delayed and/or ectopic dentition and difficulties in maintaining oral hygiene, increasing the risk of caries, infection and periodontal disease^[129].

Furthermore, in patients receiving CsA, filiform papillae hypertrophy on the tongue^[130], opportunistic infections (candidiasis)^[131,132], squamous-cell carcinomas on the lip^[133], non-Hodgkin lymphomas^[134,135] and lymphoproliferative disorders^[110,136,137] have been described in the oral cavity. The side effects of tacrolimus are less common compared to cyclosporine^[138], and currently there is no evidence of complications associated with tacrolimus treatment in the oral cavity.

Oral complications of biologic drugs

In addition to exerting a revolutionary effect in treating inflammatory bowel diseases, TNF alpha inhibitors have numerous side effects. These drugs can cause oral lichen/lichenoid reactions and opportunistic infections in the oral cavity^[87,139-142]. Asarch *et al.*^[139] reported two cases of oral lichenoid reaction in patients with psoriasis receiving infliximab and adalimumab. Moss *et al.*^[140] described a case of a patient with CD receiving infliximab that resulted in an oral lichenoid reaction. Cases of erythema multiforme and Stevens-Johnson syndrome in the oral cavity and on the skin in patients with CD receiving infliximab and adalimumab^[143,144] were also reported. Oral opportunistic infections (primarily candidiasis) can be expected in patients with IBD treated with anti-TNF drugs but so far only one case report has been published^[141]. There are no clinical studies on the prevalence of opportunistic oral infections in these patients. One of the most often described side effects of vedolizumab (a gut selective anti-integrin) is pharyngitis^[145,146].

Oral complications of antibiotics (metronidazole and ciprofloxacin)

The most common side effect of metronidazole is a metallic taste in the mouth^[147]. In addition to the metallic taste, there are no other described side effects

of these antibiotics in the oral cavity.

TREATMENT OF THE ORAL LESIONS

The goal of treating oral lesions in patients with IBD is to reduce pain, accelerate the healing of lesions and prevent secondary infections. The treatment depends on the etiology, severity of the clinical presentation and the symptoms of the oral lesions. Treatment options include topical or/and systemic medications. Although the first European evidence-based consensus on extraintestinal manifestations in inflammatory bowel disease has been recently published^[148], there are still no statements on the treatment of oral manifestations and complications of IBD.

Treatment of specific oral lesions in Crohn's disease and pyostomatitis vegetans (which occur in both diseases) is always aimed at treating and controlling the underlying disease, and lesions usually respond well to IBD treatment^[37-39,41-43,46,50]. In addition to systemic therapy, topical agents can be used; therefore, a multidisciplinary approach is essential. Topical treatments include steroids (topical or intralesional injections), topical tacrolimus, 5-ASA mouthwashes, topical anesthetics for pain relief, non-steroidal anti-inflammatory pastes and antiseptic mouthwash for preventing secondary infections^[11,14,19,33,34,149].

In IBD patients, the treatment of aphthous stomatitis includes nutrition supplements and topical or systemic medication therapy. The choice of therapy depends on the severity of symptoms and the type and numbers of aphthous lesions. Choices for therapy include steroids (topical, intralesional or systemic) as a first line of treatment, topical anesthetics, antiseptic mouthwash or non-steroidal anti-inflammatory pastes^[150]. Furthermore, non-medical treatments, such as ozone therapy and low-level laser therapy, can be used for pain relief and to accelerate lesion healing^[151,152]. When the aphthous lesions are numerous and very painful, systemic steroids, immunosuppressive agents and thalidomide are indicated^[11,150].

Angular cheilitis and glossitis are frequently caused by anemia and malnutrition; in cases with specific deficiencies, the replacement of iron, B₁₂, folate and zinc is necessary^[52-54]. Angular cheilitis can also be caused by fungi (*Candida* spp.) and bacteria (*Staphylococcus aureus* or β -hemolytic streptococci). In the case of fungal etiology, treatment options include topical antifungals (e.g., nystatin, miconazole, ketoconazole or clotrimazole). When the infection is caused by *Staphylococcus aureus*, topical treatments include combinations of mupirocin or fusidic acid and 1% hydrocortisone cream^[153].

Most often, oral infections occur as a consequence of immunosuppressive drug therapy, and candidiasis is the most commonly occurring infection. Oral candidiasis does not require the interruption of therapy^[77]. Topical therapy options include nystatin, amphotericin B, miconazole, fluconazole, ketoconazole or clotrimazole.

In some cases, systemic therapy with fluconazole, itraconazole or ketoconazole is necessary^[154].

HSV infection is not a contraindication for immunosuppressive therapy. In recurrent oral HSV infections, oral antiviral therapy should be considered^[77].

When oral lichen/oral lichenoid reactions or taste disturbances are present, the interruption and replacement of medication can be considered.

The occurrence of erythema multiforme or Stevens-Johnson syndrome requires the prompt interruption of biologic drugs^[143,144]. The patients with erythema multiforme can be treated as out-patients with systemic and topical steroids^[143]. Stevens-Johnson syndrome requires treatment in a hospital setting^[144].

CONCLUSION

Oral lesions in patients with inflammatory bowel disease can be extraintestinal manifestations of the disease or can occur as complications of the disease and treatment. They occur more often in CD patients than in UC patients, although pyostomatitis vegetans is more common in UC patients. One or more oral lesions can simultaneously appear in the oral cavity. The severity of their clinical presentation can range from mild and painless to extensive and painful. The lesions can compromise oral functions. Cooperation between specialists in oral medicine and gastroenterologists is essential for the successful diagnosis of IBD (in cases when oral pathology precedes intestinal manifestations), as well as in the diagnosis and treatment of oral lesions in such patients.

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