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Gastrointestinal diseases and their oro-dental manifestations: Part 1: Crohn's disease

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In brief

Highlights that a wide variety in the incidence of oral manifestations has been described in patients with Crohn's disease.

Demonstrates that Crohn's disease has negative effects on oral health and therefore patients need special attention from dental clinicians.

Points out that oral manifestations may precede gastrointestinal symptoms and recognition can lead to early referral to a gastroenterologist, which is important especially in children

Widely varying prevalence rates of oral lesions in patients with Crohn's disease have been reported, ranging from 0.5% to 37%. These manifestations may coincide with or precede intestinal symptoms. Oral manifestations can be classified as specific lesions, when macroscopic examination shows similar changes to those observed endoscopically in the intestine, and non-specific lesions including aphthous ulcerations. The most frequently observed oral lesions are oedema, ulcers and hyperplastic lesions on the buccal mucosa. In most patients these lesions are asymptomatic, however, some patients may experience discomfort. In this review we describe the most relevant oro-dental manifestations observed in patients with Crohn's disease and discuss the potential implications for oro-dental management.

Introduction

Crohn's disease and ulcerative colitis represent the two main types of inflammatory bowel disease, which is a broad term that describes conditions with chronic and recurring inflammation of the gastrointestinal tract. Bowel symptoms are predominant, but extra-intestinal manifestations may occur, including involvement of the oral cavity. In this review we will focus on the oral manifestations of Crohn's disease.

Burrill Crohn and co-workers first described a chronic granulomatous inflammation of the intestinal wall (*enteritis regionalis*) in 1932.[1] This chronic bowel inflammation was later named Crohn's disease (CD). CD usually has a patchy, rather than continuous distribution throughout the gut ('skip lesions') and may affect any part of the gastrointestinal tract from the oral cavity to the anal canal, but mainly involves the terminal ileum and colon (Figs 1 and 2). The diagnosis of CD depends on the demonstration of typical clinical, endoscopical, radiological, histopathological and/or biochemical findings.[2]

The incidence of CD differs between geographical regions. The disease is relatively infrequently diagnosed in developing countries but is increasing.[3] The age-standardised incidence rates in the Netherlands between 1991 and 2002 in males and females were respectively 4.84 and 7.58 per 100,000 person-years.[4] Symptoms can start at any age with peaks in early and late adulthood.[5,6]

Clinical symptoms include abdominal pain, diarrhoea, rectal blood loss, decreased appetite, weight loss, fever and growth failure in children.[2] The disease usually shows episodes of clinical activity (exacerbations or flares) interspersed with asymptomatic intervals or remissions.

There are three phenotypes of CD: the stricturing, penetrating and non-stricturing non-penetrating types.[7] In the stricturing type of CD, gradual thickening of the intestinal wall will lead to stenosis or obstruction of the bowel lumen with subsequent pain,

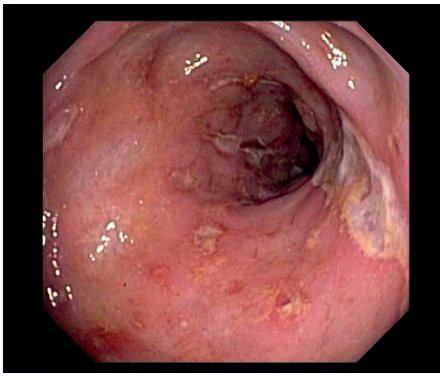

Fig. 1 Endoscopy of the colon shows ulceration of the mucosa

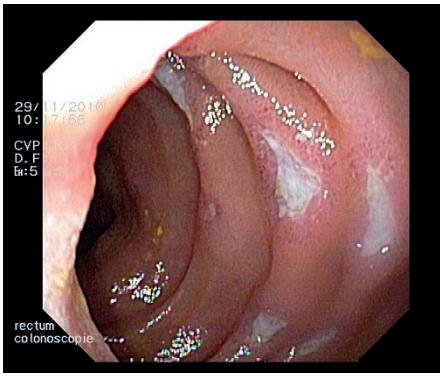

Fig. 2 Endoscopy of the terminal ileum shows typical skip lesions

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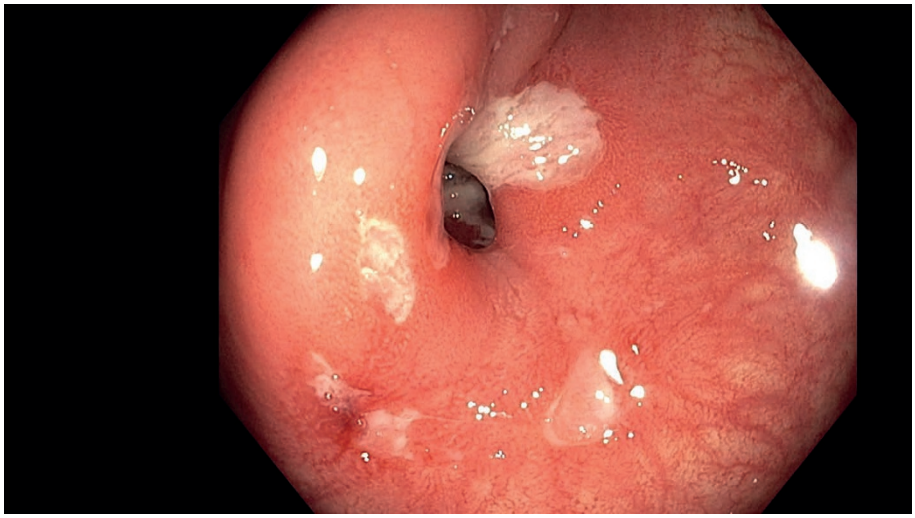

Fig. 3 Endoscopy showing stenosis of the colon with ulcera

vomiting and weight loss (Fig. 3). The penetrating disease pattern is characterised by formation of internal fistulas between the gastrointestinal tract and other organs, such as vagina or bladder, as well as external fistulas draining intestinal contents to the skin. Anal and perianal fissures, abscesses, or fistulas are frequently observed in patients with CD and cause perianal pain, itching, or faecal incontinence.

Although the exact underlying pathogenesis has not been clearly elucidated, increasing evidence suggests that CD results from an inappropriate inflammatory response to intestinal microbes and other environmental factors in a genetically susceptible host.[8] The influence of genetic factors was initially demonstrated by epidemiological data, including differences in prevalence between different ethnic groups, familial aggregation, concordance in twins and association with genetic syndromes. In total, over 150 risk genes/loci that might play a role in susceptibility for CD have been reported.[9]

Several authors have described the potential role of environmental factors in the aetiology. An increase in carbohydrate intake, particularly simple carbohydrates, has been suggested as a risk factor for the development of CD.[10] Smoking cigarettes clearly increases the risk for CD and worsens its clinical course.[11] Some ingredients of toothpaste, such as tricalcium phosphate, magnesium trisilicate and quartz, are capable of penetrating the epithelium and creating enteric lesions similar to CD.[10,12]

Since CD is neither medically nor surgically 'curable', treatment is pragmatically aimed at symptomatic relief, reduction of inflammation during exacerbations, increasing quality of life, maintenance of remissions and prevention of surgical intervention or complications. Therapeutic approaches depend on the disease location, disease severity, and disease-associated complications.[13] The main drugs used in therapy are glucocorticoids, immunomodulators and biologicals.[14] Thiopurines and methotrexate are primarily used as maintenance immunosuppressive therapy to minimise the risk of future exacerbations. Glucocorticoids, given systemically or locally, are mainly prescribed to induce a remission, as long term usage leads to unacceptable high rates of steroid-induced adverse events. The most frequently administered biologicals in CD patients comprise two monoclonal antibodies directed against tumour necrosis factor-α (TNF-α). Many patients with CD ultimately require surgical intervention with intestinal resection because of intractability of symptoms, obstruction, or perforation.

Epidemiology of oral manifestations

Oral lesions in a patient with CD were initially described by Dudeney in 1969.[15] Since then, widely varying prevalence rates of oral lesions have been reported, ranging from 0.5% to 37% per cent.[5,16–20] This variation in the prevalence of oral lesions might be related to a variety of factors, including age and ethnicity of the population studied, experience of the examiner, definition of disease-specific lesions, and whether the patients received medication for CD at the time of the study.[17]

Oral lesions are more prevalent in children compared to adults – a prospective three year study showed oral lesions in 41.7% of the children with CD.[21] Oral lesions are also more prevalent in CD patients with proximal gastrointestinal tract and/or perianal involvement.[21,22]

Oral lesions may precede intestinal involvement. A retrospective study of 40 patients found that 42% had orofacial lesions 1 to 39 years before they were diagnosed as having CD, and 50% developed oral lesions 1 to 45 years after gastrointestinal involvement.[23] Oral lesions might be more severe during active intestinal disease, but approximately 30% of the patients continue to manifest oral lesions despite control of their intestinal disease activity.[17,24]

Oral manifestations

CD may present with several types of oral manifestations.[23] An evaluation of 147 patients with CD showed that 42 patients (29%) presented with one lesion only, whereas 12 patients (8%) presented more than one lesion simultaneously.[18] Oral manifestations can be classified as specific lesions, when macroscopic examination shows similar changes to those observed endoscopically in the intestinal tract, and non-specific lesions[25] (Box 1). The non-specific lesions may be related to nutritional

Box 1 Specific and non-specific oral lesions in Crohn's disease

Specific lesions:

Diffuse labial and buccal swelling

Cobblestones

Other specific lesions

- mucosal tags
- deep linear ulcerations
- mucogingivitis
- granulomatous cheilitis

Non-specific lesions:

Aphthous ulcerations

Pyostomatitis vegetans

Dental caries

Gingivitis and periodontitis

Other non-specific lesions

- angular cheilitis
- glossitis
- gingival hyperplasia
- lichen planus
- halitosis
- dysphagia
- altered taste perception
- reduced salivation
- lymphadenopathy
- secondary fibrosis
- candidiasis

deficiency, resulting from chronic diarrhoea, reduced oral feeding, overgrowth of intestinal flora, intestinal resection, malabsorption, or to adverse reactions of drug therapy.[25,26] The most frequently observed oral lesions are oedema, ulcers and hyperplastic lesions on the buccal mucosa.[18] These lesions may be painful, impair proper oral function and hygiene, and even lead to psychological problems.[24,27]

Specific lesions

Diffuse labial and buccal swelling

One of the most obvious and common presentations of oral CD is diffuse swelling.[23] This swelling is usually persistent, firm on palpation, painless and tends to involve the lips, buccal mucosa, and facial soft tissues[28,29] (Fig. 4). Most commonly the swelling involves the lips, but it may extend to the perioral area and involve other parts of the face. The lip swelling can be diffuse and symmetrical or localised. In most cases it involves only one lip, but it can also affect both lips. The prevalence of upper and lower lip involvement is similar.[23,30] Lip involvement can lead to vertical fissuring.[6,24,29]

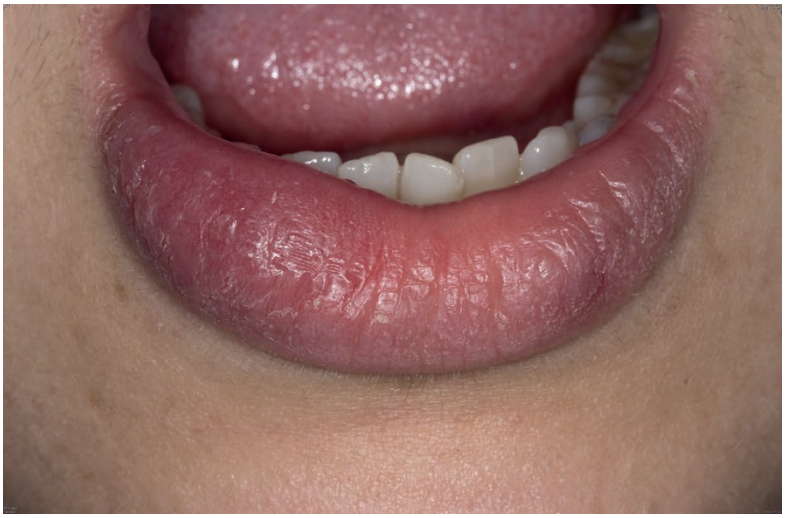

Fig. 4 Swelling of the lower lip

Cobblestones

Granulomatous swelling in the oral cavity sometimes may resemble the swelling of the intestinal mucosa at endoscopy and give a similar 'cobblestone' appearance[23] (Figs 5 and 6). The mucosal nodularity consists of papules forming firm plaques. These plaques may have a hyperplastic appearance with corrugation and a fissured swollen mucosa. These lesions are usually observed in the buccal mucosa and may be alternated with mucosal folds with normal epithelium.[24,31] Cobblestoning may be painful and interfere with speaking and eating.[19]

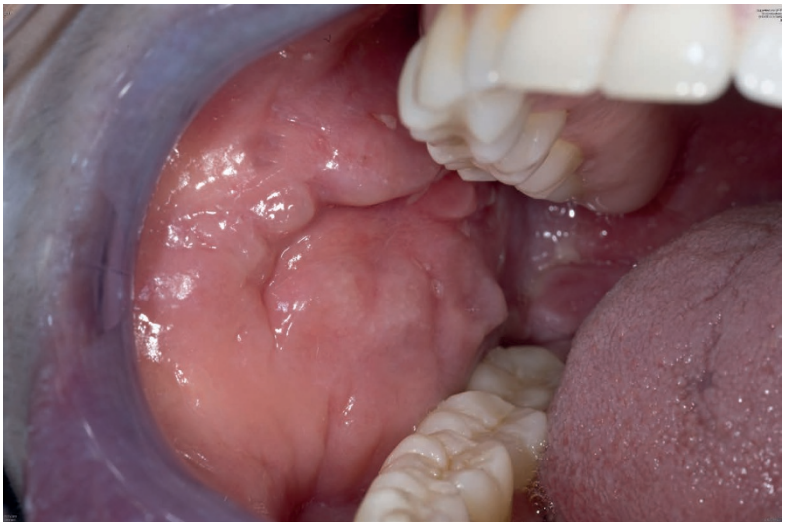

Fig. 5 Folded and swollen buccal mucosa known as cobblestoning

Other specific lesions

Mucosal tags can be observed at various locations in the oral cavity. They are small, localised swellings and often asymptomatic.[23,32,33] (Fig. 7). Deep linear ulcerations may be surrounded by hyperplastic margins and are usually seen at the buccal vestibule[28] (Fig. 8). These ulcers are not only linear and deep, but also persistent and could be confused with aphthous ulcers.[34] Mucogingivitis might affect the whole gingiva up to the mucogingival line. The gingiva may become oedematous and hyperplastic and may be associated with ulceration.[24] A prospective three year study of 49 children with CD shows that mucogingivitis was the most common oral finding.[17,21] Granulomatous cheilitis is a swelling

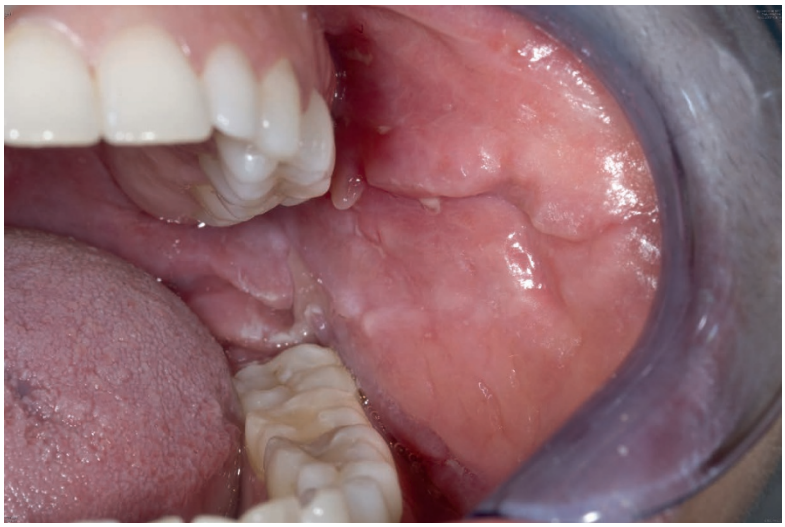

Fig. 6 Typical cobblestone appearance of the buccal mucosa

of the lip due to granulomatous inflammation. It is a rare condition and the onset is usually in young adulthood.[35]

Non-specific lesions

Aphthous ulcerations

Oral ulcerations are one of the most common lesions associated with CD and occur in about 20–30% of the CD patients,[23,24,36] however, these ulcerations also frequently occur in the general population with a prevalence of approximately 20%.[24] Aphthous ulcers are shallow round to oval shaped lesions and may feel granular below the epithelium on palpation.[34] They are often painful and can have negative effects on daily activities.[23] Their onset is usually sudden and they may occur with or precede intestinal disease activity.[5] The association with flare-ups of intestinal disease is unclear.[37]

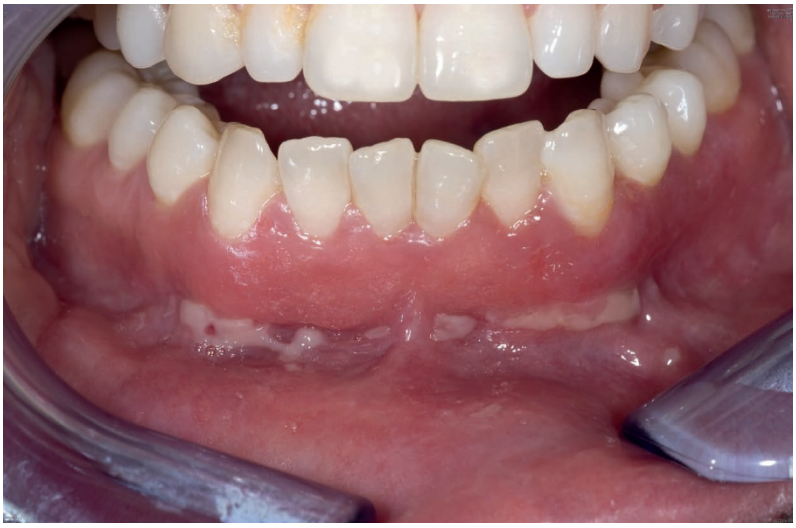

Fig. 7 Linear ulceration with mucosal tags

Pyostomatitis vegetans

Pyostomatitis vegetans can occur in CD, but is more frequently associated with ulcerative colitis.[19,24,26] The lesions are characterised by multiple pustules, erosions, vegetative plaques and mucosal folds.[17,19,26,27,38] They appear mostly on the buccal and gingival mucosa but can also appear on the tongue or the floor of the mouth. The pustular lesions may easily rupture and fuse, leading to linear or 'snail track' ulcerations.[19,38] The histologic features of these lesions are dominated by eosinophilic micro abscesses.[39]

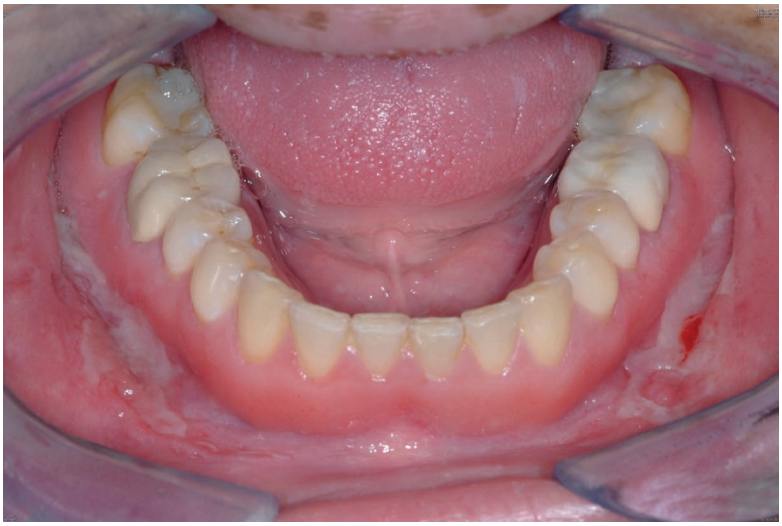

Fig. 8 Linear ulceration of the mandibular buccal vestibule

Dental caries

A number of studies have reported higher caries prevalence rates in CD patients compared to controls.[40–42] One study did not report any differences in the decay-missing-filled-surface (DMF-S) index but found a significantly higher prevalence of dentine caries amongst IBD patients compared to controls. A possible explanation could be the difference in study groups, since the latter group also included patients with ulcerative colitis.[43] The levels of lactobacilli and *Streptococcus mutans* were higher in CD patients compared to control groups.[42] Szymanska *et al.* revealed in a study with 235 CD patients that patients who had undergone resective surgery had higher DMF-S scores compared to the control group, while there was no difference between CD patients who had not undergone resective surgery and the control group. They also found more dental plaque in the CD groups, and male CD patients had a significantly higher prevalence of dental plaque than females. The study also showed a higher consumption of sweetened drinks between meals. This is in agreement with a study that showed a higher sugar intake in CD patients.[41,42]

Gingivitis and periodontitis

Gingival bleeding is common in patients with CD and occurs in approximately 20%.[40] A study of 53 patients with long-standing CD did not reveal any statistically significant differences in gingival index between patients with active and inactive disease. Patients with active disease more often had high counts of lactobacilli and mutans streptococci compared to patients with inactive disease.[44]

Several studies have revealed that the prevalence of periodontitis is higher among patients with CD compared to controls.[18,40,45] Brito *et al.* found periodontitis in 81.8% of the CD patients compared to 67.6% in the controls.[40] Stein *et al.* suggest that CD patients have a moderate severity of periodontitis with a community periodontal index of treatment needs (CPITN) score 3 in 57.8% of the patients.[18] Periodontitis in the primary dentition may be indicative for CD and could precede intestinal symptoms.[46]

Other non-specific lesions

Some of the other non-specific oral lesions include angular cheilitis, glossitis due to nutritional deficiencies, gingival hyperplasia, lichen planus, halitosis, dysphagia, altered taste perception, reduced salivation, lymphadenopathy, secondary fibrosis and candidiasis.[25,28,40,41,47]

Orofacial granulomatosis

The term orofacial granulomatosis (OFG) is used to describe patients with orofacial signs and symptoms similar to those seen in Crohn's disease but in absence of any evident intestinal involvement.[48] It is an uncommon chronic inflammatory disorder with lip and facial swelling as the most common clinical signs. Less commonly, it may also affect gingivae, buccal mucosa, tongue, floor of the mouth and other sites in the oral cavity. OFG may occur at any age but appears to be more prevalent in children and young adults. Childhood onset has a higher risk to be related to systemic disease, which can manifest years after initial presentation.[49,50] A systematic review showed that concurrent CD is described in about 40% of the children diagnosed with OFG and suggests that OFG may be a subtype of CD.[51] However, the debate about whether OFG is just an oral manifestation of CD or rather a separate inflammatory disease is still open.[30]

Observational studies have shown that dietary elimination of some provoking elements is an effective treatment. A cinnamon- and benzoate-free diet provides benefit in 54–78% of the patients with 23% not requiring adjunctive therapy so this is recommended as primary treatment, especially in younger patients.[52]

Dental management

As described above, CD can have negative effects on oral health and therefore CD patients need special attention from dental clinicians. A study of 2085 CD patients demonstrates that there is a significantly higher total number of dental procedures compared to the control group. The most pronounced difference were for removable dentures, front teeth fillings and endodontic treatments.[53] Clinical implications include frequent dental check-ups with oral hygiene instruction and application of fluoride varnishing.[25] It is important to advise the patients to reduce the amount and frequency of sugar- and carbohydrate-containing consumptions. In addition, sugar substitutes are relatively contraindicated because of the risk of gastrointestinal disturbances.[25] In patients treated with the immunomodulator methotrexate, use of non-steroidal anti-inflammatory drugs and penicillin is contraindicated because combination increases the risk of bone marrow depression caused by an impaired renal methotrexate clearance.[54]

In most patients, the oral lesions are asymptomatic and in these patients no special treatment is necessary.[24] However, some patients may experience discomfort and for them there are several treatment options. The first and foremost step in treatment of the specific and non-specific oral lesions is gastrointestinal disease control,[34] so referring to a gastroenterologist is recommended at this point. To relieve the pain of aphthous ulcerations, topical agents such as lidocaine and/or topical steroids such as triamcinolone 0.1% can be used. Topical application of 0.1% dexamethasone seems also effective. Severe and recurrent cases of aphthous ulceration can be treated with systemic or intra-lesional steroids. Lip swelling and deep linear ulcerations can be treated with topical tacrolimus (0.5 mg/kg) and intra-lesional steroid injections. Treatment of cobblestoning consists of application of topical steroids.[17,24,25]

As described previously, oral manifestations may precede gastrointestinal symptoms of CD. General practitioners may suspect CD in patients with the aforementioned oral lesions, especially when combined and with a positive family history of CD and/or clinical symptoms such as frequent abdominal pain, diarrhoea, unwanted weight loss and failure to thrive in children. In these cases, referral to a gastroenterologist for further investigation seems warranted.

Conclusion

Crohn's disease may have negative effects on oral health and therefore patients with CD need special attention from dental clinicians. In complex cases, dedicated specialist teams consisting of dental clinicians and gastroenterologists are to be consulted.

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