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CASE REPORT

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Persistent oral mucosal lesions preceding diagnosis of Crohn's disease and primary sclerosing cholangitis

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Abstract

Oral mucosal lesions may persist years before symptoms or diagnosis of inflammatory bowel disease (IBD) and subsequent primary sclerosing cholangitis (PSC). Since a dental practitioner may be the first clinician to suspect IBD with extraintestinal manifestations (EIMs), early referral, and close collaboration with a gastroenterologist are recommended.

KEYWORDS

dentistry, gastroenterology and hepatology, inflammatory bowel disease (IBD), oral medicine

1 | INTRODUCTION

Inflammatory bowel disease (IBD) comprises two major pathological conditions affecting the gastrointestinal tract, i.e., Crohn's disease (CD) and ulcerative colitis (UC). CD can affect any part of the GI, while UC affects the large intestine. IBD can also involve many other organs of the body from mouth to anus, including the oral cavity.

The incidence of IBD is increasing, especially in newly industrialized countries.[1] In Europe, the incidence of CD ranges between 0.4 and 22.8 per 100,000 people per year and UC between 2.4 and 44.0 per 100,000 people per year.[2] The prevalence is approximately 0.2% of the European population.[2]

Patients with IBD might suffer from different symptoms such as abdominal pain, diarrhea, weight loss, secondary anemia, and fistulas.[3] Oral manifestations may appear years before systemic symptoms.[3] These include aphthous ulcers, mucogingivitis, lip swelling, angular cheilitis, mucosal tags, cobblestoning, and deep linear ulcerations. Histopathologically, granulomatous inflammation can be seen. The etiology of IBD remains unknown, but it is believed to be multifactorial, involving genetic, immunologic, and environmental factors.[2–5] IBD should

be considered a systemic disease, since extraintestinal manifestations (EIMs) present in 5% to 50% of all IBD cases. EIMs can affect nearly every organ and might appear prior to the first diagnosis of IBD, simultaneously, or after resection of the affected bowel segment. EIMs, such as primary sclerosing cholangitis (PSC) as a hepatobiliary manifestation, must be recognized early to prevent severe morbidity and mortality. We report the case of a young female with oral manifestation 4 years before diagnosis of Crohn's disease and subsequent PSC.

2 | CASE REPORT

An otherwise healthy 18-year-old female was referred for gingival overgrowth and desquamative gingivitis to the Department of Oral and Maxillofacial Diseases Head and Neck Center, Helsinki University Hospital, Helsinki, Finland.

The patient did not have any systemic diseases, medications, or gastrointestinal symptoms; neither did she smoke or use alcohol regularly. She had an allergy to cats, dogs, and horses. There was no family history of IBD or other autoimmune diseases.

Histopathological examination of a biopsy from gingival overgrowth in the right incisal-premolar region of the maxilla revealed normal surface epithelium with a slight decrease in cell cohesion. Under the epithelium, among the inflammatory cells, granuloma structures with histiocytic and multinucleated giant cells were seen (August 2017) (Figure 1). Having found this granulomatous inflammation, the pathologist raised the possibility of Crohn's disease. Consequently, the patient was referred for gastro- and colonoscopy with biopsies, which all turned out normal. Liver and kidney laboratory tests, including celiac antibodies and CRP, were normal. Microcytic anemia was considered to be associated with menstruation and was treated with iron supplementation. Sarcoidosis was ruled out by an ear, nose, and throat specialist.

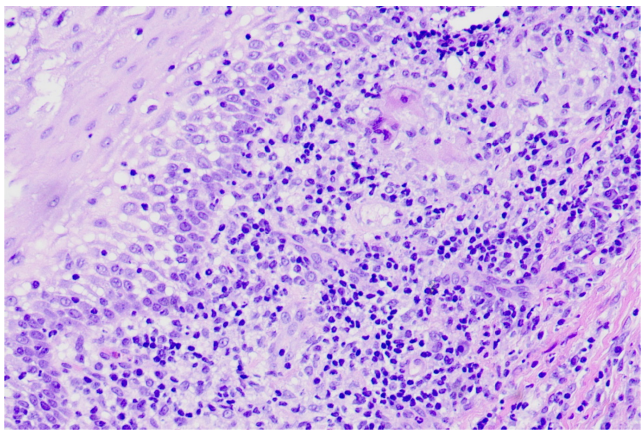

FIGURE 1 Granulomatous inflammation from gingival overgrowth.

The first appointment at the Department of Oral and Maxillofacial Diseases Head and Neck Center, Helsinki University Hospital was 1 year after initial examinations (August 2018). The patient still had no gastrointestinal symptoms at that time. According to the patient, the only symptom was bleeding gums when brushing her teeth. The patient brushed her teeth twice a day with fluorine toothpaste, but interdental cleaning was not performed regularly. Non-foaming, sodium lauryl sulfate free toothpaste and interdental cleaning with a silicone brush were recommended. Eating and drinking habits were recorded in more detail. The patient consumed cola drinks three times per week; accordingly, she was asked to stop drinking cola drinks with benzoate compounds.

Extra- and intraoral clinical examination with panoramic tomography was performed. Extraoral findings were normal; facial skin and lips were healthy. Intraorally, the interproximal gums were swollen, with some periodontal pseudopockets 4 mm deep. The bleeding on probing (BOP) index was 18%, measured from six sites per tooth. There were no infection foci, no alveolar bone loss, no caries, and no periapical lesions in panoramic tomography. Professional anti-infective treatment was performed, and oral self-care instructions were given. After 5 months, oral self-care was improved and the BOP index dropped under 10%; however, swollen gums in interproximal areas were still seen in the upper jaw. A biopsy was taken in March 2019 from the marginal gingiva in the maxillary canine region, revealing chronic inflammation.

Clinical examination with new laboratory tests were carried out after 6 months (October 2019). Clinically, the lower lip was slightly swollen, angular cheilitis with cracks in the corners of the mouth was seen (Figure 2A), and gingiva in right upper maxilla was swollen (Figure 2B). Other oral mucosal lesions (OMLs) included small tissue tags in the sulcus in the lower jaw (Figure 2C) and in the base of the mouth. In laboratory tests, complete blood count, antinuclear antibody (ANCA), and angiotensin-converting enzyme (ACE) turned out to be normal, but fecal calprotectin, which reflects inflammation in the colon and is a useful marker for IBD, was slightly elevated—115 μg/g (reference <100 μg/g). Gastroenterologist was consulted but since no intestinal symptoms were found, and calprotectin was only slightly elevated; no further examinations were made at that point. Oral mucosal monitoring was recommended in our department.

A new biopsy was taken in November 2019 from the buccal sulcular fold and revealed chronic inflammation.

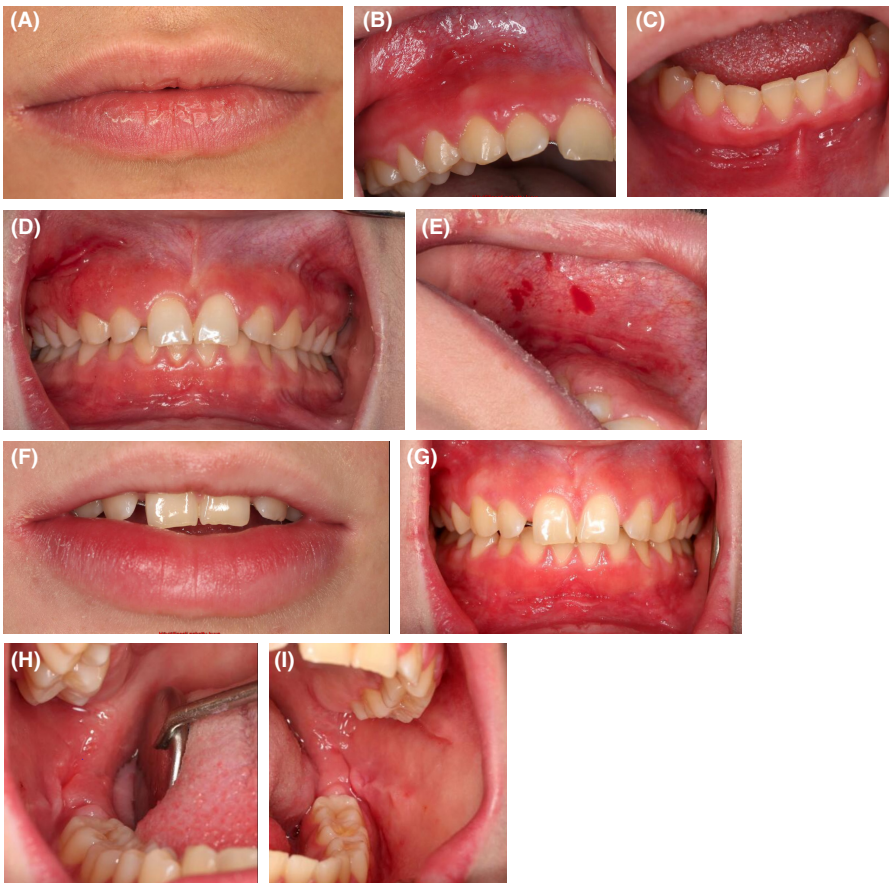

FIGURE 2 Oral manifestations. (A) swollen lips, cracked lip corners, (B) swollen gingiva in right upper maxilla, (C) mucosal folds in the lower sulcus, (D) strawberry-like gingiva, inflamed mucosa, (E) ulcerative tissue tags, (F) swollen lower lip, (G) mucosal folds in the lower sulcus, (H,I) mucosal folds in the retromolar area and in the cheeks, (A–C 2019, D–E 2021, F–I 2022).

Since the gums still bled easily, some extra laboratory tests (S-Ferrit, P-TfR, S-B12-TC2, fS-Folaat, P-D 25) were made. Ferritin (S-Ferrit) 11 μg/L (15–125 μg/L) and vitamin D (P-D-25) 23 nmoL/L (>50 nmoL/L) were under the reference values. Ferritin and vitamin D supplementation were recommended. Still, no other symptoms except bleeding on brushing were noticed by the patient. Laboratory values were controlled, and both ferritin and vitamin D values were corrected.

The patient was closely followed up in our clinic, and supportive periodontal therapy was arranged on regular basis.

Almost 4 years after oral granulomatous inflammation was first diagnosed, the patient complained of abdominal pain for the first time (February 2021). Beginning autumn 2020, she suffered from diarrhea twice a week. The gums were swollen and the mouth was sore, she had cracked lips and angular cheilitis. Intraoral examination revealed swollen marginal hyperplastic strawberry-like gingivitis and slightly folded mucosa in the sulcus areas of the maxilla (Figure 2D,E). The gingiva bled easily on probing. A biopsy was taken from the swollen, inflamed area of the left premolar area of the maxilla. Histopathologically, granulomatous inflammation was diagnosed. Fecal calprotectin was elevated—186 μg/L. fS-ACE, P-Ferrit, S-D-25, and ANCA were within the reference limits. See Table 1 for details for main oral and systemic symptoms, manifestations, and pathology, laboratory, and endoscopy findings.

A colonoscopy performed in April 2021 showed segmental mild inflammation in the colon and rectum. Mucosal biopsies confirmed a diagnosis of Crohn's disease. Gastroscopy was normal. Magnetic resonance imaging (MRI) revealed an uncomplicated and asymptomatic perianal fistula. The patient was started on standard intravenous infliximab. A repeated colonoscopy in March 2022 showed moderate pancolitis, and the patient was shown to be a non-responder to infliximab therapy. In addition, oral lesions (sore mouth, lips and corners of the mouth cracking easily, and swollen gingiva/folded mucosa) persisted (Figure 2F–I). She was switched to subcutaneous ustekinumab in May 2022 and since then she has been able to be managed medically.

At the time of the diagnosis of Crohn's disease, alkaline phosphatase (ALP) was elevated—425 U/L (reference 35–105 U/L)—and alanine aminotransferase (ALT) was 214 U/L (reference <35 U/L). A liver biopsy showed findings consistent with primary sclerosing cholangitis (PSC). An endoscopic retrograde cholangiography (ERC) in November 2021 showed slight biliary narrowing of the common hepatic duct and choledochus, in line with mild PSC.

TABLE 1 Main oral and systemic symptoms, manifestations, and pathology, laboratory and endoscopy findings.

Date	Oral symptoms	Oral manifestations	Biopsy, oral pathology	Systemic symptoms	Laboratory	Endoscopy
August 2017	Bleeding gums	Gingival hyperplasia desquamative gingivitis	Granulomatous inflammation	None	B-Hb 109 g/L (Ref 117–155)	Normal
June 2018	Bleeding gums	Swollen gingiva, pseudopockets		None		
March 2019	Bleeding gums	Swollen gingiva in upper jaw, ulceration in lower sulcular area, angular cheilitis	Chronic inflammation (upper gingiva)	None		
October, November, December 2019	Bleeding gums, cracked corners of the mouth, swollen lips	Ulcerations, tissue tags in upper and lower sulcular area, angular cheilitis	Chronic inflammation (lower sulcular area)	None	F-Calpro 115 µg/g (Ref < 100) S-Ferritin 11 µg/l (Ref 15–125) S-D-25 23 nmoL/L (Ref > 50)	Not performed
February, March 2021	Bleeding gums, painful mouth	Ulcerations	Granulomatous inflammation (upper jaw)	Severe diarrhea twice a week	F-Calpro 186 µg/g S-D-25 46 nmoL/L	
June 2021	Bleeding gums, painful mouth	Ulcerations			F-Calpro 1037 µg/g ALP 425 U/L (Ref 35–105) ALAT 214 U/L (Ref < 35) ASAT 147 U/L (Ref 15–35)	Crohn's disease primary sclerosing cholangitis
May, July 2022	Bleeding gums, better but painful sometimes	Swollen lower lip, tissue tags in cheeks in sulcus and in floor of the mouth		Mild	F-Calpro 211 µg/l ALP 88 U/L ALAT 44 U/L Ferrit 5 µg/l S-D-25 72 nmoL/L	

3 | DISCUSSION

Oral manifestations may precede diagnosis of IBD; thus, the role of the dental practitioner is important in early detection, and collaboration between an oral specialist and gastroenterologist is important. We reported a case of an otherwise healthy young female with desquamative gingivitis and gingival overgrowth, which revealed granulomatous inflammation in the biopsy specimen (Figure 1). Granulomatous inflammation is rare in the oral cavity but can be seen in CD, sarcoidosis, foreign body reaction, perioral dermatitis, infectious disease, mycobacterial infections (tuberculosis), granulomatosis with polyangiitis, and orofacial granulomatosis.[6] Orofacial granulomatosis (OFG) is an uncommon granulomatous disorder in which systemic granulomatous diseases have been excluded. Cinnamon or bentzoate compounds, among others, have been suggested as playing an important role as hypersensitivities in OFG patients.[6]

The presence of oral manifestations that precede or follow intestinal symptoms of IBD must be taken into serious consideration by both dentists and gastroenterologists in order to allow early diagnosis. The prevalence of oral manifestations in IBD has been reported to range from 0.7% to 37% in adults and 7% to 23% in children.[3,7] The variability in the incidence may be due to different study design and due to the number and type of the population. The etiopathogenesis is unknown. Genetic susceptibility altered gut microbiota and environmental factors are suggested (smoking, antibiotic exposure in childhood).

A healthy oral mucosa is dependent on several vitamins and minerals. The integrity of the oral mucosa may be compromised in IBD due to intestinal malabsorption, leading to a deficit of iron, zinc, or vitamin B12.

Oral manifestations of IBD were first reported in the 1950s and initially focused on aphthous ulcerations, which are the most common type of oral lesions in Crohn's disease (CD), with a prevalence of 0.7%–50% in adults.[5,8] Aphthous ulcerations are strongly associated ($p = 0.001$) with the active phase of CD and they resemble the ulcers present in the gastrointestinal (GI) tract.[9] Other oral manifestations characteristic of CD include swelling of the lips, cobblestoning or edema of the buccal mucosa, deep linear ulcerations, mucosal tags, and mucogingivitis.[3,4,10,11] Pyostomatitis vegetans, a rare disorder characterized by friable pustules on the gingiva and mucosa, has been described in connection with IBD and PSC and liver disease.[12] Pyostomatitis vegetans is more often associated with UC than CD.[3] The most common non-specific manifestations, such as aphthous stomatitis and angular cheilitis, occur in both diseases. Non-specific lesions in the oral cavity can also be the result of malnutrition and drugs. These oral manifestations may be either asymptomatic or symptomatic with pain and impairment of oral function.[4,13]

Caries and periodontitis are also common oral diseases in CD.[3] Over 50 systemic diseases or conditions are associated with periodontal diseases, including inflammatory bowel diseases.[14] In a meta-analysis by Nijakowski et al, the risk of periodontal disease in IBD patients was almost two and a half times more than that of controls.[15] Dry mouth, dysphagia, taste alterations, and halitosis have also been reported.[3] As said, oral manifestations may precede diagnosis of IBD, and they can significantly impact the quality of life (QoL) of IBD patients, sometimes more so than the intestinal disease itself.[5] In a study by Rikardsson conducted in Sweden, CD patients themselves also perceived their oral health to be worse and have a greater need for dental treatment compared to a control group. That study comprised 1943 patients with CD recruited from the Swedish National Patients Organization of IBD and 1000 randomly selected controls. Patients with CD reported significantly more mouth-related problems than controls (OR 3.2), such as significantly more caries and more gingival bleeding.[16]

IBD in should be considered a systemic disease, since extraintestinal manifestations (EIMs) are present 5%–50% of all IBD cases. Some EIMs correlate with intestinal disease activity, other manifestations are activity independent, such as primary sclerosing cholangitis (PSC).[4,5,17,18] Musculoskeletal manifestations such as spondyloarthopatia, cutaneous manifestations such as oral aphthous lesions and pyostomatitis vegetans, ocular manifestations such as uveitis, pulmonary, renal, and urological manifestations, neurological manifestations, anemia, osteopenia, osteoporosis and hepatobiliary manifestations such as primary sclerosing cholangitis (PSC), autoimmune and granulomatous hepatitis, and fatty liver disease should be kept in mind.[5,12] PSC is the most common hepatobiliary manifestation of IBD, since 75% of PSC patients are diagnosed with IBD. Intestinal diseases might occur years before the liver disease is diagnosed. UC is far more common, since 90% of PSC patients with IBD have UC and only 10% have CD. Still, only about 3%–8% of colitis patients may have PSC, which results in inflammation and fibrosis of the intra- and extrahepatic biliary tract.[17] PSC is also associated with a high risk of cholangiocarcinoma.

The frequency for at least one EIM varies between 6% and 47%. Just one EIM seems to increase the risk for developing further manifestations. Autoimmune and genetic factors (HLA) may have an important role for EIMs.[18]

In the present case, a healthy young female with no abdominal or other systemic symptoms presented desquamative gingivitis and gingival overgrowth with granulomatous inflammation in a biopsy. However, initial gastro- and colonoscopy with biopsies and laboratory tests

turned out normal. Oral mucosal lesions (OMLs) were followed up on a regular basis. In addition to the existing mucogingivitis, linear ulceration and tissue tags with pain were noted later on. After 4 years of initial oral symptoms, she developed diarrhea and fecal calprotectin was elevated (186 μg/l). She was referred to a gastroenterologist for further investigation, and IBD, namely Crohn's disease, was diagnosed together with primary sclerosing cholangitis (PSC). Early recognition and follow-up are, thus, crucial, and a dental practitioner may be the first clinician to suspect IBD.

4 | CONCLUSION

To conclude, we reported a case of a young female with oral manifestation of IBD several years before diagnosis of Crohn's disease and subsequent PSC. The role of the dental practitioner is important in early detection, and in terms of treatment, close collaboration with a gastroenterologist is recommended.

AUTHOR CONTRIBUTIONS

Jaana Helenius-Hietala: Writing – original draft; writing – review and editing. **Fredrik Åberg:** Writing – review and editing. **Jaana Hagström:** Writing – review and editing. **Hellevi Ruokonen:** Writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Karita Nylund declares no conflict of interest. Jaana Helenius-Hietala presented a poster about this subject at the AAOM annual meeting in May 2022 in Memphis, USA. She declares that there is no conflict of interest. Hellevi Ruokonen declares no conflict of interest. Fredrik Åberg declares no conflict of interest. Jaana Hagström declares no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable – no new data generated.Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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