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PERSISTENT ORAL MUCOSAL LESIONS PRECEDING DIAGNOSIS OF CROHN'S DISEASE AND PRIMARY SCLEROSING CHOLANGITIS A CASE REPORT AND LITERATURE REVIEW

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Abstract

Oral mucosal lesions may persist years before diagnosis of inflammatory bowel disease (IBD) and subsequent primary sclerosing cholangitis (PSC). It may be that a dental practitioner may be the first clinician to suspect IBD. Suspect IBD; early referral and close collaboration with a gastroenterologist are recommended.

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 suffer from 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 lesions can be seen. The etiology of IBD remains unknown, but it is believed to be multifactorial, involving genetic, immunologic, and environmental factors.[2,3,4,5] 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 four years before diagnosis of Crohn´s disease and subsequent PSC.

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.

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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.

The first appointment at the Department of Oral and Maxillofacial Diseases Head and Neck Center, Helsinki University Hospital was one 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 five 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 six 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). The patient had a gastroenterology consultation, 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. 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 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 four 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

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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, swollen gingiva/folded mucosa) persisted (Figure 2F-I). She was switched to subcutaneous ustekinumab in May 2022.

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.

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] 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% to 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,

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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 should be considered a systemic disease, since extraintestinal manifestations (EIMs) present in 5% to 50% of all IBD cases. Some EIMs correlate with intestinal disease activity, other manifestations are activity independent, such as primary sclerosing cholangitis (PSC).[54,17,18] Musculoskeletal manifestations such as spondyloarthopatia, cutaneous manifestations such as oral aphthous lesions, 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] 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% to 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 four years of initial symptoms, she developed diarrhea and fecal calprotectin was elevated (186 ug/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.

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.

Credit author statement: Karita Nylund: conceptualization, writing original draft, project administration Jaana Helenius-Hietala: conceptualization, writing original draft Fredrik Åberg: writing original draft Jaana Hagström: writing – reviewing and editing Hellevi Ruokonen: conceptualization, writing reviewing and editing, supervision

Consent statement:

This statement confirms that the authors have obtained written informed consent from patient.

References

1. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, Panaccione R, Ghosh S, Wu JCY, Chan FKL, Sung JJY, Kaplan GG. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017 Dec

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23;390(10114):2769-2778. doi: 10.1016/S0140-6736(17)32448-0. Epub 2017 Oct 16. Erratum in: Lancet. 2020 Oct 3;396(10256): e56. PMID: 29050646.

2. Zhao M, Gönczi L, Lakatos PL, Burisch J. The Burden of Inflammatory Bowel Disease in Europe in 2020. J Crohns Colitis. 2021 Sep 25;15(9):1573-1587. doi: 10.1093/ecco-jcc/jjab029. PMID: 33582812.
3. Zbar AP, Ben-Horin S, Beer-Gabel M, Eliakim R. Oral Crohn's disease: is it a separable disease from orofacial granulomatosis? A review. J Crohns Colitis. 2012 Mar;6(2):135-42. doi: 10.1016/j.crohns.2011.07.001. Epub 2011 Aug 9. PMID: 22325167.
4. Lauritano D, Boccalari E, Di Stasio D, Della Vella F, Carinci F, Lucchese A, Petruzzi M. Prevalence of Oral Lesions and Correlation with Intestinal Symptoms of Inflammatory Bowel Disease: A Systematic Review. Diagnostics (Basel). 2019 Jul 15;9(3):77. doi: 10.3390/diagnostics9030077. PMID: 31311171; PMCID: PMC6787704.
5. Woo VL. Oral Manifestations of Crohn's Disease: A Case Report and Review of the Literature. Case Rep Dent. 2015; 2015:830472. doi: 10.1155/2015/830472. Epub 2015 Jul 9. PMID: 26240765; PMCID: PMC4512596.
6. Rogler G, Singh A, Kavanaugh A, Rubin DT. Extraintestinal Manifestations of Inflammatory Bowel Disease: Current Concepts, Treatment, and Implications for Disease Management. Gastroenterology. 2021 Oct;161(4):1118-1132. doi: 10.1053/j.gastro.2021.07.042. Epub 2021 Aug 3. PMID: 34358489; PMCID: PMC8564770.
7. Alawi F, Shields BE, Omolehinwa T, Rosenbach M. Oral Granulomatous Disease. Dermatol Clin. 2020 Oct;38(4):429-439. doi: 10.1016/j.det.2020.05.004. PMID: 32892852.
8. Zippi M, Corrado C, Pica R, Avallone EV, Cassieri C, De Nitto D, Paoluzi P, Vernia P. Extraintestinal manifestations in a large series of Italian inflammatory bowel disease patients. World J Gastroenterol. 2014 Dec 14;20(46):17463-7. doi: 10.3748/wjg.v20.i46.17463. PMID: 25516659; PMCID: PMC4265606.
9. SIRCUS W, CHURCH R, KELLEHER J. Recurrent aphthous ulceration of the mouth; a study of the natural history, aetiology, and treatment. Q J Med. 1957 Apr;26(102):235-49. PMID: 13432144.
10. Laranjeira N., Fonseca J., Meira T., Freitas J., Leitão J. Oral Mucosa Lesions And Oral Symptoms In Inflammatory Bowel Disease Patients. *Arq. Gastroenterol.* 2015; 52:105–110.
11. Muhvić-Urek M, Tomac-Stojmenović M, Mijandrušić-Sinčić B. Oral pathology in inflammatory bowel disease. World J Gastroenterol. 2016 Jul 7;22(25):5655-67. doi: 10.3748/wjg.v22.i25.5655. PMID: 27433081; PMCID: PMC4932203.
12. Philpot HC, Elewski BE, Banwell JG, Gramlich T. Pyostomatitis vegetans and primary sclerosing cholangitis: markers of inflammatory bowel disease. Gastroenterology. 1992 Aug;103(2):668-74. doi: 10.1016/0016-5085(92)90863-t. PMID: 1634082.
13. Rowland M, Fleming P, Bourke B. Looking in the mouth for Crohn's disease. Inflamm Bowel Dis. 2010 Feb;16(2):332-7. doi: 10.1002/ibd.20983. PMID: 19705418.
14. Byrd KM, Gulati AS. The "Gum-Gut" Axis in Inflammatory Bowel Diseases: A Hypothesis-Driven Review of Associations and Advances. Front Immunol. 2021 Feb 19;12:620124. doi: 10.3389/fimmu.2021.620124. PMID: 33679761; PMCID: PMC7933581.
15. Nijakowski K, Gruszczyński D, Surdacka A. Oral Health Status in Patients with Inflammatory Bowel Diseases: A Systematic Review. *Int J Environ Res Public Health* . 2021;18(21):11521. Published 2021 Nov 2. doi:10.3390/ijerph182111521Rikardsson S, Jönsson J, Hultin M, Gustafsson A, Johannsen A. Perceived oral health in patients with Crohn's disease. Oral Health Prev Dent. 2009;7(3):277-82. PMID: 19780435.
16. Rikardsson S, Jönsson J, Hultin M, Gustafsson A, Johannsen A. Perceived oral health in patients with Crohn's disease. Oral Health Prev Dent. 2009;7(3):277-82. PMID: 19780435.
17. Malik TF, Aurelio DM. Extraintestinal Manifestations of Inflammatory Bowel Disease. 2022 Mar 9. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 33760556.
18. Ott C, Schölmerich J. Extraintestinal manifestations and complications in IBD. Nat Rev Gastroenterol Hepatol. 2013 Oct;10(10):585-95. doi: 10.1038/nrgastro.2013.117. Epub 2013 Jul 9. PMID: 23835489.

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