Crohn's & Colitis 360, 2025, **7**, otaf027
https://doi.org/10.1093/crocol/otaf027
Advance access publication 1 April 2025
Observations and Research

Oral Extraintestinal Manifestations of Inflammatory Bowel Disease: The Temporal Relationship Between Oral and Intestinal Symptoms

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Objectives: Oral extraintestinal manifestations (OEIMs) of inflammatory bowel disease (IBD) may impact IBD treatment. The aims of this study were to: (1) determine which OEIMs are most prevalent among patients with IBD, (2) investigate the presence of a temporal association between GI luminal disease activity and OEIMs, and (3) determine how often changes in therapeutic management of IBD are needed in the presence of OEIMs.

Study Design: A retrospective cohort study was performed for adult patients with IBD evaluated between January 2017 and November 2021 with at least 1 oral complaint. Demographic data were collected from the charts of these patients. Kruskal-Wallis test for continuous measures and Fisher's Exact test for categorical measures were used.

Results: A total of 116 patients with IBD who had presented with at least 1 oral finding during the study time period were identified. Aphthous ulcers were the most common oral presentation in both Crohn's disease (CD) (85.1%) and ulcerative colitis (UC) (75.0%). OEIMs were associated with CD activity in the small intestine ($P = .004$) and colon ($P < .001$). UC pancolitis was associated with OEIMs ($P = .002$). In 32.7% of patients, OEIMs led to either an increase in dose or frequency of IBD therapy. In an additional 16.4% of patients, new systemic agents were started because of the OEIMs.

Conclusions: This study provides evidence that patients with IBD may develop OEIMs synchronous with IBD flares and may require escalation of IBD therapy when OEIMs occur.

Lay Summary

Patients with IBD may develop oral extraintestinal manifestations (OEIM) synchronous with IBD flares and may require escalation of IBD therapy when OEIMs occur.

Key Words: oral EIM, aphthous ulcers, stomatitis, mucositis

Introduction

Inflammatory bowel diseases (IBD), including both Crohn's disease (CD) and ulcerative colitis (UC), may present with a multitude of symptoms both within and outside of the gastrointestinal (GI) tract. Extraintestinal manifestations (EIMs) of IBD span nearly every organ, resulting in the need for multidisciplinary education and collaboration. EIMs occur in 5%-50% of patients with IBD.[1,2] EIMs can either be associated with IBD activity while others, such as primary sclerosing cholangitis and pyoderma gangrenosum, do not parallel activity of luminal IBD.[3] Oral extraintestinal manifestations (OEIMs), predominately aphthous ulcers, are the focus of this article due to the pervasive nature of this EIM among patients with IBD.[4]

Received for publication: October 31, 2024. Editorial Decision: February 18, 2025

There is limited literature on standardized identification and treatment of OEIMs. In order to help contextualize scientific and clinical research on OEIMs, the European Crohn's and Colitis Organization (ECCO) brought together 15 ECCO members and 6 experts in subspecialties often involved in the multidisciplinary management of OEIMs, including rheumatologists, dermatologists, ophthalmologists, and immunologists, to outline criteria for diagnosing OEIM in IBD.[5] The panel agreed that an EIM of any organ system is "an inflammatory pathology in a patient with IBD that is located outside the gut and for which the pathogenesis is either dependent on extension/translocation of immune response from the intestine, or is an independent inflammatory event perpetuated by IBD or that shares a common environmental or genetic predisposition with IBD."[5] The variable definition of OEIMs of IBD is further mystified by the concept of extraintestinal complications (ECs) of IBD. As opposed to OEIMs, ECs are a direct or indirect sequela of GI inflammation.[1] For example, nausea, abdominal pain, and loss of appetite that can result from IBD activity can result in ECs including osteoporosis, anemia, and micronutrient deficiencies.[6] The mutually exclusive concepts of EIMs versus ECs of IBD contribute to the difficulty that exists in the recognition and optimal treatment of these conditions.

Perhaps the lack of consistent criteria to define EIMs is a product of the lack of clarity on the pathogenesis of these conditions. Given the appreciation of the increased likelihood of additional EIMs after the development of 1 EIM, it is possible that a common pathogenic pathway exists.[7] Aphthous ulcers have previously been found to be the most common OEIM of IBD.[8] These typically present as sharply marginated ulcers with a fibrinous base surrounded by erythema (Figure 1). Patients often present with oral symptoms that can significantly impair quality of life due to pain and result in decreased oral intake which may worsen underlying nutritional deficiencies. Importantly, about a quarter of patients with IBD present with OEIMs before intestinal symptoms prompt evaluation for IBD.[1] One study by Plauth and colleagues found OEIMs to be the presenting symptom of newly diagnosed CD in 60% of patients.[9] However, OEIMs can precede, coincide, or come after intestinal inflammation with IBD.[10] This highlights the importance of collaboration across specialties including gastroenterology, dermatology, rheumatology, dentistry, and primary care to recognize OEIMs and facilitate appropriate evaluation and management. New or worsening recurrent aphthous ulcers should prompt providers to consider screening for IBD.

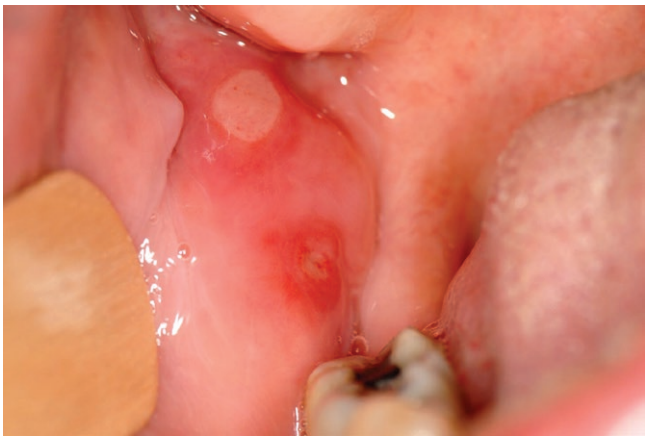

Figure 1. Aphthous ulcers typically present as sharply marginated ulcers with a fibrinous base surrounded by erythema (by permission of Mayo Foundation for Medical Education and Research. All rights reserved).

OEIMs have been recognized as having a direct relationship with the activity of IBD.[11] Flares of OEIMs may serve as an indicator of disease activity in a patient with IBD. Flares of OEIMs may also indicate that alternative or escalated IBD therapy is needed.

The aims of this study were to: (1) determine which OEIMs are most prevalent among patients with IBD, (2) investigate the presence of a temporal association between GI luminal disease activity and OEIMs, and (3) determine how often changes in therapeutic management of IBD are needed in the presence of OEIMs. Primary outcome measured endoscopic disease activity. Secondary outcomes included time between active OEIM and GI disease activity, and the need for adding, escalating, or changing advanced therapies.

Materials and Methods

Patients with IBD who were evaluated for at least 1 oral complaint between January 2017 and November 2021 were identified and included. Patients were identified using the SlicerDicer function of our institution's electronic medical record (EPIC). This search was performed using ICD-10 codes to identify patients 18 and over with a diagnosis of CD or UC and one of the following oral diagnosis codes: K12.0 "recurrent aphthous stomatitis," K13.4 "granuloma and granuloma-like lesions of oral mucosa," K12.30 "mucositis (ulcerative); non-specified," K12.1 "other forms of oral stomatitis," or G51.2 "Melkersson' s syndrome." Patients were stratified by IBD diagnosis (CD or UC). All included patients had to have a visit at 1 of the 3 Mayo Clinic sites for their oral complaint and clinical notes were reviewed by the study team to confirm inclusion in the study. Patients were excluded if they did not have a confirmed diagnosis of IBD or if they did not have at least 1 oral diagnosis for which they were evaluated at our center during the study period. OEIMs were temporally related to GI inflammation if both were active within 4 weeks of each other.

Clinical notes of providers caring for included patients were retrospectively reviewed to determine demographic information, extent of intestinal involvement by location, previous treatments for IBD, oral symptoms and diagnoses rendered, OEIM treatment, IBD treatment during OEIM symptomatology, synchronicity between oral and GI findings, and other medical comorbidities. Information was recorded regarding whether the patient's oral findings were deemed to be related to IBD by the treating clinicians, whether IBD was active at the time of oral findings, and at what site of involvement. Additionally, data on whether changes were made to IBD medical therapy due to the OEIM were collected. To determine the activity of IBD at the time of oral findings, clinical notes as well as procedural and lab data from 4 weeks of pre and post-oral complaints were reviewed, including endoscopic findings. In patients who expressed active symptoms, an endoscopy was required to confirm if they truly had disease activity or not. Patients under the age of 18 years were excluded. Institutional Review Board approval was obtained for this minimal risk chart review study, which complies with the Helsinki Declaration.

Statistical Analysis

The data were analyzed separately with respect to specific IBD diagnoses of either CD or UC. Kruskal–Wallis test for continuous measures and Fisher's Exact test for categorical measures were performed to identify an association between active IBD flare and oral findings. Numerical variables were summarized with median and range and categorical variables were summarized with frequency and percentage. All tests were 2-sided and *P*-values less than .05 were considered statistically significant. All the analysis programming was done by R-studio with R version 4.1.2.

Results

Demographic Information

A total of 116 patients with IBD were included. Patient and disease characteristics are summarized in Table 1. Patients with CD made up just over half (57.8%) of our sample size. The median age at CD diagnosis was 30.7 (range 18.1-77.8) years. Extentof CD activity in the small intestine was most common (79.1%), followed by activity in the colon (71.6%). There were 49 patients with UC in our study cohort. The median age at UC diagnosis was 38.9 (range 19.6-74.7) years. Pancolitis was the most common site of disease activity extent in the UC cohort (67.3%). The most frequent medical comorbidities in all patients included anemia (50.9%), nutritional deficiencies (37.1%), anxiety (36.2%), inflammatory arthritis (34.5%), and depression (32.8%).

Oral Extraintestinal Manifestations in Relation to IBD

Table 2 summarizes the oral diagnoses given and IBD characteristics at the time of oral findings. The most common oral diagnosis was aphthous ulcers, which was found in 80% of our cohort. Other OEIM diagnoses including angular cheilitis, granulomatous diseases, and pyostomatitis vegetans were infrequent

Table 1. Patient and disease characteristics of the 116 included patients.

Variable	Median (minimum, maximum) or No. (%) of patients
Diagnosis of Crohn's disease (*n* = 67)	67 (56.3%)
Age at Crohn's disease diagnosis (years)	30.7 (18.1, 77.8)
Crohn's disease site, extent of involvement	
Small intestine	53
Colon	48
Perianal disease	23
Gastroduodenal	7
Esophageal	4
Diagnosis of ulcerative colitis (*n* = 49)	49 (42.2%)
Age at ulcerative colitis diagnosis (years)	38.9 (19.6, 74.7)
Ulcerative colitis site,extent of involvement	
Extensive colitis/Pancolitis	34
Rectum/proctitis	7
Left-sided colitis	6
Proctosigmoiditis	2
Medical comorbidities	
Anemia	59 (50.9%)
Nutritional deficiency	43 (37.1%)
Anxiety	42 (36.2%)
Inflammatory arthritis	40 (34.5%)
Depression	38 (32.8%)
Cardiovascular disease	36 (31.0%)
Dyslipidemia	36 (31.0%)
Neurologic disorder	33 (28.4%)
Obesity	21 (18.1%)
Thyroid disease	15 (12.9%)
Renal disease	12 (10.3%)
Diabetes mellitus	12 (10.3%)
Chronic liver disease	10 (8.6%)
Primary sclerosing cholangitis	4 (3.4%)
Solid organ transplantation	4 (3.4%)
Cervical cancer	2 (1.7%)
Spondylitis	1 (0.9%)
Uveitis	1 (0.9%)

Table 2. Most common oral diagnoses given.

Oral diagnosis given, CD cohort	Overall ($N = 67$)
Aphthous ulcer	57 (85.1%)
Stomatitis unspecified	8 (11.9%)
Oral candidiasis	6 (9.0%)
Mucositis unspecified	5 (7.5%)
Angular cheilitis	4 (6.0%)
Oral Crohn's disease	3(4.5%)
Glossitis	2 (3.0%)
Mucogingivitis	2 (3.0%)
Granulomatous cheilitis	1 (1.5%)
Orofacial granulomatosis	1 (1.5%)
Pyostomatitis vegetans	1 (1.5%)
Oral diagnosis given, UC cohort	**Overall ($N = 52$)**
Aphthous ulcer	39 (75.0%)
Stomatitis unspecified	7 (13.5%)
Mucositis unspecified	6 (11.5%)
Oral candidiasis	3 (5.8%)
Mucogingivitis	2 (3.8%)
Angular cheilitis	1 (1.9%)
Cobblestone/hyperplastic oral mucosa	1 (1.9%)
Pyostomatitis vegetans	1 (1.9%)

Abbreviations: CD, Crohn's disease; UC, ulcerative colitis.

(Table 2). The most common CD sites active at the time of oral findings were the small intestine (46.3%) and the colon (34.3%). Pancolitis was the most common site of activity in patients with UC at the time of presentation with oral findings (19.2%).

Table 3 demonstrates the relationship between oral findings and IBD in this cohort. In 47.4% of patients, treating clinicians attributed the oral findings to the patient's IBD, and oral findings were associated with flares of IBD in 40.5% of patients. Amongst patients deemed to have oral findings related to IBD, in 32.7% of patients, OEIMs led to either an increase in dose or frequency of IBD therapy. In an additional 16.4% of these patients, new systemic agents were started because of OEIMs.

Amongst the CD cohort, treating clinicians attributed oral findings to CD in 56.7% of patients. In the remaining 43.3% of patients, this relationship was not explicitly recognized by the treating clinicians. Oral findings were found to be associated with CD flares in 44.8% of patients (Table 3). OEIMs led to a change in CD treatment in 42.1% of patients with OEIMS deemed related to IBD, including dose adjustments or increasing the frequency of medications given; and a new systemic agent was added in an additional 13.2% of patients with OEIMs that were deemed related to CD (Table 3). In 66.7% ($P = .004$) of patients with CD, CD activity in the small intestine coincided with OEIMs (Table 4). In 56.7% ($P < .001$) of patients with CD, there was CD activity in the colon that coincided with OEIMs (Table 4). Patients with flares of CD that were esophageal, gastroduodenal, and perianal did not show statistically significant overlap with active OEIMs (Table 4).

About a third of oral findings (34.7%) in patients with UC were interpreted by treating clinicians to relate to their IBD diagnosis (Table 3). In 34.7% of patients with UC, these oral findings were associated with UC flares (Table 3). Amongst patients with UC, when treating clinicians determined their OEIMs related to IBD, OEIMs led to a change in IBD treatment in 11.7% of patients, and a new systemic agent was added in an additional 23.5% of patients (Table 3). In 47.1% of patients with UC, there was pancolonic UC activity that was synchronous with OEIMs ($P = .002$, Table 5).

Discussion

Our retrospective study of oral findings in patients with IBD has produced several clinically significant findings. The most commonly active sites for both CD and UC during flares of OEIMs were similar to those identified historically. The majority of the existing literature on the temporal relationship between intestinal IBD activity and OEIMs support a relationship between IBD activity and OEIMs. Several studies have shown that patients with active CD experience a greater frequency of OEIMs than patients with inactive CD.[9,12–14] A prospective case-control study by Brito and colleagues, however, comparing the prevalence of periodontal disease, a nonspecific OEIM of IBD, in 179 patients with IBD to 74 patients without IBD, failed to show this association. Although patients with IBD were found to have significantly worse oral health than matched controls, there was no difference between the groups in the number of active oral lesions and this study did not find a relationship between IBD disease activity and periodontitis.[15] Another study found that aphthous ulcers were diagnosed before IBD in 27.8% of patients.[16] Our data reinforces that some oral findings may be associated with IBD and this supports a role for screening for oral symptoms

Table 3. Relationship between oral findings and IBD.

	Crohn's disease (*N* = 67)	Ulcerative colitis (*N* = 49)	Total (*N* = 116)
Treating clinicians attributed oral findings to patient's IBD?			
No	9 (13.4%)	21 (42.9%)	30 (25.9%)
Yes	38 (56.7%)	17 (34.7%)	55 (47.4%)
Not determined	20 (29.9%)	11 (22.4%)	31 (26.7%)
Did flares of oral findings correlate with flares of IBD?			
No	26 (38.8%)	29 (59.2%)	55 (47.4%)
Yes	30 (44.8%)	17 (34.7%)	47 (40.5%)
Not determined	11 (16.4%)	3 (6.1%)	14 (12.1%)
Did oral findings lead to changes in IBD treatment or new systemic agents being given?			
No	40 (59.7%)	37 (75.5%)	77 (66.4%)
Yes, IBD treatment changed	20 (29.9%)	5 (10.2%)	25 (21.6%)
Yes, new systemic agents added	6 (9.0%)	4 (8.2%)	10 (8.6%)
Not determined	1 (1.5%)	3 (6.1%)	4 (3.4%)
Did oral findings lead to changes in IBD treatment or new systemic agents being given among patients with oral findings attributed to IBD	*N* = 38	*N* = 17	*N* = 55
No	16 (42.1%)	9 (52.9%)	25 (45.4%)
Yes, IBD treatment changed	16 (42.1%)	2 (11.7%)	18 (32.7%)
Yes, new systemic agents added	5 (13.2%)	4 (23.5%)	9 (16.4%)
Not determined	1 (2.6%)	2 (11.7%)	3 (5.4%)

Abbreviation: IBD, inflammatory bowel disease.

Table 4. Correlation between IBD flares and oral findings by active CD site.

Active CD site at time of oral findings	No flare correlation (*N* = 26)	Flare correlation (*N* = 30)	Total (*N* = 56)	*P* value
Esophageal				.115
No	26 (100.0%)	26 (86.7%)	52 (92.9%)	
Yes	0 (0.0%)	4 (13.3%)	4 (7.1%)	
Gastroduodenal				.055
No	26 (100.0%)	25 (83.3%)	51 (91.1%)	
Yes	0 (0.0%)	5 (16.7%)	5 (8.9%)	
Small intestine				.004
No	19 (73.1%)	10 (33.3%)	29 (51.8%)	
Yes	7 (26.9%)	20 (66.7%)	27 (48.2%)	
Colon				<.001
No	23 (88.5%)	13 (43.3%)	36 (64.3%)	
Yes	3 (11.5%)	17 (56.7%)	20 (35.7%)	
Perianal disease				.517
No	22 (84.6%)	23 (76.7%)	45 (80.4%)	
Yes	4 (15.4%)	7 (23.3%)	11 (19.6%)	

Abbreviations: IBD, inflammatory bowel disease; CD, Crohn's disease.

in patients who report GI symptoms as it may allow for earlier identification of IBD. Similarly, patients with new or worsening recurrent aphthous ulcers should be screened for symptoms of IBD.[17] Earlier identification and treatment of IBD may help prevent disease progression associated with delayed diagnosis and also help improve patient's quality of life through earlier therapy. As for patients who already have IBD and are on IBD therapy, in the presence of OEIMs, they may benefit from escalation of therapy.

In our patient sample, nearly half (47.4%) of the oral findings were attributed to underlying IBD and 40.5% of oral findings occurred in association with an IBD flare. Our results support those of prior studies which have shown that aphthous ulcers can occur with increased IBD activity.[18] The synchronous presentation of OEIMs with IBD flares further supports that better control of IBD promotes better patient outcomes. Despite this correlation, only one-fifth of patients in this study received changes to their IBD treatment.

Table 5. Correlation between IBD flares and oral findings by active UC site.

Active UC site at time of oral findings	No flare correlation ($N = 31$)	Flare correlation ($N = 17$)	Total ($N = 48$)	*P* value
Proctosigmoiditis				.99
No	28 (90.3%)	15 (88.2%)	43 (89.6%)	
Yes	3 (9.7%)	2 (11.8%)	5 (10.4%)	
Left-sided colitis				.99
No	29 (93.5%)	16 (94.1%)	45 (93.8%)	
Yes	2 (6.5%)	1 (5.9%)	3 (6.2%)	
Extensive colitis/Pancolitis				.002
No	29 (93.5%)	9 (52.9%)	38 (79.2%)	
Yes	2 (6.5%)	8 (47.1%)	10 (20.8%)	
Rectum				.651
No	28 (90.3%)	14 (82.4%)	42 (87.5%)	
Yes	3 (9.7%)	3 (17.6%)	6 (12.5%)	

Abbreviations: IBD, inflammatory bowel disease; UC, ulcerative colitis.

Recognition of the temporal relationship between OEIMs and active IBD should prompt providers to consider adjusting IBD therapy to address OEIMs in order to optimize patient quality of life and outcomes.

The most frequent medical comorbidities in our patient population were anemia (50.9%), nutritional deficiency (37.1%), anxiety (36.2%), inflammatory arthritis (34.5%), and depression (32.8%). OEIMs likely contribute to many of these comorbidities. For example, pain associated with swallowing could prevent adequate oral intake resulting in weight loss and nutritional deficiencies. Additionally, recurrent or refractory oral pain and ulcers could certainly promote feelings of anxiety and depression. Another concept worthy of consideration is the possibility that ECs of IBD may beget OEIMs. For example, iron deficiency anemia is appreciated as the leading cause of anemia in patients with IBD with an average prevalence of 45%.[19,20] However, there is likely a multifactorial origin of anemia in patients with IBD, as anemia of chronic disease is another common etiology of anemia in this patient population.[21] There are several elements at play in patients with IBD contributing to such a robust portion of the population experiencing anemia. These include blood loss through intestinal ulcerations, poor iron absorption in patients with duodenal disease, inflammatory upregulation of hepcidin resulting in reduced intestinal absorption, and inflammatory inhibition of erythropoiesis.[22] Appreciation of this EC of IBD is relevant due to the implications of anemia on aphthous ulceration. Studies have established a significant association between anemia and nutrient deficiencies and the development of recurrent aphthous stomatitis.[23–26] Therefore, it is difficult to discern which aphthous ulcers are an OEIM or EC of IBD.

There are several limitations to this study including the relatively small number of patients with active IBD that coincided with oral findings thus limiting statistical power to detect an association between the 2. Other factors that may contribute to oral findings as well as OEIMs refractory to IBD treatment should be further analyzed. Additionally, the oral diagnoses and the relationship of these diagnoses to IBD in our study were provided by medical doctors. Given the retrospective nature of a chart review, we are not able to better clarify some of these diagnoses. Given the lack of consistent criteria to define OEIMs, and variable knowledge of OEIMs and their pathogenesis, this may have impacted the frequency at which the oral findings in this cohort were thought to be related to the patient's IBD. As these patients were not evaluated by dentists, other known OEIMs, such as periodontitis, may have been underreported and the relationship to IBD unrecognized.

In conclusion, recognition of the temporal relationship between OEIMs and active IBD can help clinicians to optimize patient outcomes. Persistent OEIMs should prompt providers to consider adjusting IBD therapy. Awareness of this relationship may also help to identify patients with IBD earlier in the course of the disease, thus minimizing long-term morbidity.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

Dr. Jana G. Hashash holds the position of associate editor for Crohn's and Colitis 360 and has been recused from reviewing or making decisions for the manuscript. No disclosures or conflicts of interest related to the content of this manuscript exist.

Ethics Approval

The Mayo Clinic Institutional Review Board approved a search of the electronic health record.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data not publicly available.

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