Asymptomatic Inflammatory Bowel Disease Presenting With Mucocutaneous Findings

Sheila S. Galbraith, MD*; Beth A. Drolet, MD*; Subra Kugathasan, MD‡; Amy S. Paller, MD§; and Nancy B. Esterly, MD*

ABSTRACT. Although inflammatory bowel disease (IBD) typically presents with gastrointestinal complaints, mucocutaneous lesions are commonly associated and can precede gastrointestinal symptoms, thereby alerting the clinician to the diagnosis of IBD before the onset of gastrointestinal symptoms. Nine children are reported who had no gastrointestinal symptoms suggestive of IBD but presented with mucocutaneous findings of IBD and were subsequently diagnosed with Crohn’s disease or ulcerative colitis based on characteristic features on gastrointestinal endoscopy and/or biopsies. The majority of the patients had oral and perianal lesions. We believe that IBD is a common etiology for persistent oral lesions in the pediatric population. In addition to a good history, children with unexplained oral mucous membrane lesions should have an examination of the rectal and genital mucosa as well as tests for complete blood count, iron levels, sedimentation rate, albumin, and occult blood in the stool with endoscopy and biopsies to rule out IBD if indicated.

Representative Cases

Patient 1

A 6-year-old white boy presented with a 5-month history of intermittent upper-lip swelling associated with eczematous skin changes and gingival edema (Fig 1). Over the subsequent 3 years, he developed worsening of the upper-lip swelling as well as angular cheilitis and lower-lip involvement (Fig 2). He denied any systemic symptoms including facial paralysis, abdominal pain, and diarrhea. A biopsy specimen from the oral mucosa showed a hyperplastic mucosa with spongiosis and a dense lymphocytic infiltrate with small granulomas in the submucosa. Patch tests, complete blood count, tuberculin skin tests, chest radiograph, and pulmonary function tests were within normal limits.

A repeat biopsy was planned because of lack of improvement with several therapies including topical steroids, antihistamines, amoxicillin-clavulanate, and minocycline for presumed Melkersson-Rosenthal syndrome. On returning to the clinic for biopsy, his mother mentioned a perianal pustule that had been present for some time. Given this new information, the oral biopsy was not performed; he instead was referred to a gastroenterologist. The patient was found to have microcytic anemia (hemoglobin: 11.1 g/dL; mean corpuscular volume: 75 fL) and hypoalbuminemia (3.3 g/dL) at that time. Esophagastroduodenoscopy was unremarkable; however, patchy erythema, erosions, and pseudopolyps were seen during colonoscopy. Biopsies from the colon showed...
gastritis, terminal ileum granulomas, and granulomatous colitis, confirming the diagnosis of Crohn’s disease. The perianal lesion proved to be a fistula, and 6-mercaptopurine (6-MP) was started. Metronidazole was added intermittently to treat the fistula further. There was mild improvement of the granulomatous cheilitis; however, the fistula remained patent. Infliximab was started, with complete resolution of the oral lesions, closure of the fistula, and normalization of laboratory abnormalities after 3 infusions. He is in clinical and biochemical remission without intestinal or extraintestinal manifestations while maintained on scheduled 8- to 10-week-interval infliximab therapy.

Patient 2
An 8-year-old white boy had a 2-year history of recurrent oral ulcerations with hyperplastic ridges in the inferior gingival sulcus bilaterally (Fig 3). He denied any gastrointestinal symptoms. A previous oral biopsy was reviewed and showed a small granuloma in the submucosa. He also had a history of perianal skin tags and fissures. Gastrointestinal evaluation revealed esophagitis, gastritis, and multiple aphthous ulcers in the sigmoid colon. Biopsy specimens showed esophagitis with granulomas and granulomatous colitis consistent with Crohn’s disease. Work-up subsequently revealed hypoalbuminemia (3.2 g/dL) and an elevated erythrocyte sedimentation rate (ESR) (32 mm/hour). Monotherapy with 6-MP resulted in resolution of his oral ulcers.

Patient 3
A 12-year-old obese white boy (body mass index: 97th percentile) presented with a 6-month history of an erythematous plaque on his right lower extremity that more recently had become warm to the touch, tender, and ulcerated with indurated violaceous borders (Fig 4). The patient denied any trauma to the area. Two biopsies performed elsewhere were consistent with folliculitis, and the patient had been treated with Augmentin and topical antibiotics with no improvement. Repeat biopsy showed suppurative folliculitis which, along with the typical clinical presentation, was consistent with pyoderma gangrenosum. Fungal culture and acid-fast bacillus stains were negative. His ESR was slightly elevated (14 mm/hour). The patient denied any gastrointestinal complaints, but upper and lower endoscopy showed multiple ulcerations in the gastric antrum and ileum. Biopsy specimens showed gastritis, ileitis, and crypt destruction with giant-cell reaction in the colon consistent with Crohn’s disease. He initially received intralesional corticosteroids for the pyoderma gangrenosum; however, after the diagnosis of Crohn’s disease was made,

TABLE 1. Case Presentations

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age, y</th>
<th>Presentation</th>
<th>Perianal Lesions</th>
<th>Mucosal/Cutaneous Biopsy</th>
<th>Endoscopic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>Male</td>
<td>6</td>
<td>Upper-lip swelling; gingival edema; eczematous patches</td>
<td>Perianal pustule (fistula)</td>
<td>Dense lymphocytic infiltrate and small granulomas in the submucosa of oral mucosa</td>
<td>EGD normal; erythema, erosions, and pseudopolyps in colon</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>8</td>
<td>Oral ulcers with hyperplastic ridges</td>
<td>Perianal skin tags and fissures</td>
<td>Small submucosal granuloma of oral mucosa</td>
<td>Multiple ulcers in the sigmoid colon</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>12</td>
<td>Pyoderma gangrenosum, right preordial; obesity</td>
<td>None</td>
<td>Suppurative folliculitis consistent with pyoderma gangrenosum</td>
<td>Multiple ulcers in the ileum</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>5</td>
<td>Cutaneous pustules; oral erosions</td>
<td>Perianal ulcer</td>
<td>Pustular dermatosis of left leg and left trunk</td>
<td>Upper and lower endoscopies grossly normal</td>
</tr>
<tr>
<td>5†</td>
<td>Female</td>
<td>8</td>
<td>Right vulvar erythema and swelling</td>
<td>Perianal skin tags</td>
<td>Perirectal tag granulomas</td>
<td>Erosions in the rectum and sigmoid colon</td>
</tr>
<tr>
<td>6*</td>
<td>Male</td>
<td>13</td>
<td>Pyoderma gangrenosum, right lower extremity</td>
<td>None</td>
<td>Pyoderma gangrenosum</td>
<td>Ulcerations in right colon</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>3</td>
<td>Upper-lip swelling and purple discoloration</td>
<td>Rectal skin tags and fissures</td>
<td>Granulomas of oral mucosa</td>
<td>Irregularities in the terminal ileum; ulcerations in the sigmoid colon</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>14</td>
<td>Right upper-lip swelling; angular cheilitis; aphthous ulcers; obesity</td>
<td>Perianal fissure; inguinal fistula; gluteal abscesses; pilonidal cyst</td>
<td>Dense mixed inflammatory infiltrate of oral mucosa</td>
<td>Esophagitis; gastritis; ileitis</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>4</td>
<td>Upper gingival edema; lip swelling</td>
<td>Perianal fissures</td>
<td>Granulomatous inflammation of oral mucosa</td>
<td>Upper and lower endoscopy normal</td>
</tr>
</tbody>
</table>

EGD indicates esophagogastroduodenoscopy; GI, gastrointestinal.
* Patients were reported previously in *J Pediatr Gastroenterol Nutr* 2003;37:150–154.
† Patient was reported previously in *J Am Acad Dermatol* 1992;27(5 pt 2):893–895.
infliximab and methotrexate were initiated, which led to almost complete resolution of the pyoderma gangrenosum.

RESULTS
In our series of children with silent IBD, mucocutaneous lesions appeared before gastrointestinal signs as the manifestation of Crohn’s disease (8 of 9) or ulcerative colitis (1 of 9). (Table 1 provides a summary of these cases.) Of the 9 patients, 8 were male, and the mean age was 8 years. Although patients with IBD tend not to be overweight, 2 of our patients were obese (patients 3 and 8). Six children presented with oral manifestations, 1 had genital lesions, and 2 had pyoderma gangrenosum. All patients were asked about gastrointestinal symptoms, fever, weight loss, and joint pain at presentation and denied any such symptoms. The majority of our patients (7 of 9) had perianal lesions at presentation; however, several of the perianal lesions were not discovered on initial evaluation but only became apparent during subsequent examinations. The time to diagnosis of IBD after development of the mucocutaneous findings ranged from 1 month to 42 months. In general, patients with oral and perianal lesions experienced a longer time until diagnosis compared with patients with lesions that presented elsewhere. One patient (patient 8) was diagnosed with Crohn’s disease on repeat endoscopy after the initial endoscopy that was performed ~1.5 years later.

TABLE 1. Case Presentations

<table>
<thead>
<tr>
<th>GI Biopsy</th>
<th>Other Findings</th>
<th>Diagnosis</th>
<th>Time to Diagnosis, mo</th>
<th>Treatment</th>
<th>Responded to Treatment?</th>
<th>Development of GI Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastritis, duodenitis; granuloma in the terminal ileum; granulomatous colitis</td>
<td>Microcytic anemia; hypoalbuminemia</td>
<td>Crohn’s disease</td>
<td>42</td>
<td>6-MP; metronidazole; infliximab</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Gastritis; granulomas in esophagus; granulomatous colitis</td>
<td>Hypoalbuminemia; ESR = 32 mm/h</td>
<td>Crohn’s disease</td>
<td>24</td>
<td>6-MP</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Gastritis, ileitis, and crypt destruction with giant-cell reaction in colon</td>
<td>ESR = 14 mm/h</td>
<td>Crohn’s disease</td>
<td>6</td>
<td>Intralosional steroids; infliximab; methotrexate</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Mild colitis with cryptitis and crypt abscesses</td>
<td>ESR = 12 mm/h</td>
<td>Ulcerative colitis</td>
<td>1</td>
<td>Intravenous steroids</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Chronic inflammation and granuloma</td>
<td>None</td>
<td>Crohn’s disease</td>
<td>6</td>
<td>Sulfasalazine</td>
<td>Yes</td>
<td>Diarrhea after therapy was discontinued 17 mo later</td>
</tr>
<tr>
<td>Gastritis and chronic colitis consistent with Crohn’s disease</td>
<td>Microcytic anemia; ESR = 26 mm/h</td>
<td>Crohn’s disease</td>
<td>3</td>
<td>Intralosional steroids; 6-MP; infliximab</td>
<td>Yes</td>
<td>Diarrhea, abdominal pain, and bloody stools 3 y after third infliximab infusion</td>
</tr>
<tr>
<td>Granulomatous infiltrate</td>
<td>ESR = 45 mm/h</td>
<td>Crohn’s disease</td>
<td>3</td>
<td>Prednisolone; metronidazole; 6-MP</td>
<td>Yes</td>
<td>One episode of bright-red blood per rectum before treatment instituted</td>
</tr>
<tr>
<td>Granulomas and focal granulomatous colitis</td>
<td>Microcytic anemia; hypoalbuminemia; ESR = 27 mm/h</td>
<td>Crohn’s disease</td>
<td>7 (oral); 20 (perianal)</td>
<td>Infliximab; methotrexate</td>
<td>Lost to follow-up</td>
<td>None: lost to follow-up</td>
</tr>
<tr>
<td>Chronic colitis of cecum and ascending colon</td>
<td>Hypoalbuminemia</td>
<td>Crohn’s disease</td>
<td>9 (oral); 18 (perianal)</td>
<td>Azathioprine</td>
<td>Medication recently instituted</td>
<td>None</td>
</tr>
</tbody>
</table>
prior was normal. In all patients followed after insti-
tuting therapy, the mucocutaneous lesions re-
sponded to therapy for their IBD.

**DISCUSSION**

Although IBD typically presents with gastrointes-
tinal complaints, mucocutaneous lesions have been
reported to occur in 15% to 44% of cases and, when
present, can precede gastrointestinal symptoms.1,2,3,4
Gregory and Ho5 reviewed the mucocutaneous le-
sions of IBD and divided them into specific, reactive,
and miscellaneous categories (Table 2).

Although uncommon in children, pyoderma gan-
grenosum is a common mucocutaneous feature of
IBD. Typically, the early papulopustules or hemor-
rhagic bullae rapidly enlarge, become necrotic, and
ulcerate. The ulcerations have a characteristic viola-
ceous, undermined border (Fig 4). Lesions can occur
on any part of the body but are most frequently
located on the lower extremities. Pyoderma gangre-
nosum is characterized by pathergy (predilection for
lesions in areas of trauma); thus, aggressive debride-
ment must be avoided. Twenty percent of adult pa-
tients with pyoderma gangrenosum will have asso-
ciated IBD.6 It is associated more commonly with
ulcerative colitis than Crohn’s disease, occurring in
5% to 12% and 1% to 2% of patients, respectively.3,5,7
Pyoderma gangrenosum is uncommon in children,
with 4% of cases reported in children <15 years old.8
Although IBD is the most common underlying cause
of pyoderma gangrenosum in children, pyoderma
gangrenosum in children can be associated with sev-
eral other systemic disorders including immunode-
ficiencies (primary and HIV related), leukemia, hep-
itis, and arthritis.9,10 The occurrence of pyoderma
gangrenosum preceding gastrointestinal symptoms
in IBD has only been described in a few patients.6,8,11

Perianal lesions including skin tags, fistulas, fis-
sures, and abscesses are characteristic of Crohn’s
disease and occur during the course of IBD in 60% to
82% of patients; however, 25% to 30% of patients

**TABLE 2.** Mucocutaneous Lesions Associated With IBD5

<table>
<thead>
<tr>
<th>Specific</th>
<th>Reactive</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perianal fissures, fistulas, and skin tags</td>
<td>Erythema nodosum</td>
<td>Epidermolysis bullosa acquisita</td>
</tr>
<tr>
<td>Oral Crohn’s disease</td>
<td>Pyoderma gangrenosum</td>
<td>Clubbing</td>
</tr>
<tr>
<td>Metastatic Crohn’s disease</td>
<td>Aphthous ulcers</td>
<td>Vitiligo</td>
</tr>
<tr>
<td>Oral Crohn’s disease</td>
<td>Vesiculopustular eruption</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Metastatic Crohn’s disease</td>
<td>Pyoderma vegetans</td>
<td>Secondary amyloidosis</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>Necrotizing vasculitis</td>
<td>Alopecia areata</td>
</tr>
<tr>
<td>Aphthous ulcers</td>
<td>Cutaneous polyarteritis nodosa</td>
<td></td>
</tr>
<tr>
<td>Vesiculopustular eruption</td>
<td>Erythema multiforme</td>
<td></td>
</tr>
<tr>
<td>Pyoderma vegetans</td>
<td>Urticaria</td>
<td></td>
</tr>
<tr>
<td>Necrotizing vasculitis</td>
<td>Sweet’s syndrome</td>
<td></td>
</tr>
<tr>
<td>Cutaneous polyarteritis nodosa</td>
<td>Bowel-associated dermatosis-arthritis syndrome</td>
<td></td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

show perianal lesions before gastrointestinal com-
plaints.12,13 The majority of our patients with Crohn’s
disease (6 of 8), as well as our 1 patient with ulcer-
ative colitis, were noted to have perianal lesions be-
fore gastrointestinal symptoms. It is interesting to
note that the 2 patients with Crohn’s disease who did
not have perianal lesions had pyoderma gangreno-
sum as their initial finding. Of the patients with
perianal lesions, in only 2 (patients 8 and 9) was the
perianal lesion the presenting complaint. This sug-
gests that perianal lesions may often be present be-
fore gastrointestinal complaints but are less often
brought to the attention of the physician, especially
in adolescent boys.

Although not as well documented, oral lesions
associated with IBD are relatively common, occur-
ing in 6% to 20% of patients.14 When present, they
are the presenting sign/symptom in approximately
one half of cases.1,4,15-17 In addition, more recent

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**Fig 4.** Patient 3: 2 × 2-cm ulcer with indurated viola-
ceous borders on the right lower extremity.
reviews have found an increased prevalence of various oral lesions in IBD, particularly in children. Barnard and Walker-Smith found that 80% of pediatric patients with Crohn’s disease and 41% of children with ulcerative colitis had oral lesions in their series of patients. In reviews by Pittock et al and Plauth et al, 48% and 66% of patients with Crohn’s disease, respectively, were found to have oral manifestations, with an increased prevalence in children.

A variety of specific and nonspecific oral lesions can occur (Table 3). Differences in the percentage of patients with IBD described with oral lesions may relate to specific versus nonspecific oral findings reported. Aphthous ulcers are considered by many to be nonspecific, as they can be seen in up to 20% of the general population; however, aphthae are usually more extensive and persistent when associated with IBD. The descriptive term “orofacial granulomatosis” has been used for any granulomatous process of unknown etiology involving the oral cavity, which includes disorders previously described as granulomatous cheilitis and partial Melkersson-Rosenthal syndrome. Orofacial granulomatosis is a common manifestation in children with IBD and is typified by recurrent or persistent swelling of the lips, cheeks, gingiva, or oral mucosa with characteristic noncaseating granulomas on histologic examination. Many patients with orofacial granulomatosis do eventually develop gastrointestinal disease consistent with Crohn’s disease. Cobblestoning refers to nodular granulomatous swellings that result in a cobblestone appearance of the oral mucosa, particularly on the labial and buccal mucosa. Along with mucosal tags, cobblestoning is highly suggestive of Crohn’s disease. Pyostomatitis vegetans, on the other hand, is more characteristic of ulcerative colitis. It is characterized by multiple pustules, erosions, and ulcers on a diffuse erythematous background with vegetations or folding of the gingival and buccal mucosa. Deep, linear ulcers surmounted by hyperplastic folds occur in the gingival sulci and are also specific for IBD.

Genital findings associated with IBD are also more common in Crohn’s disease and in children. Genital involvement includes vulvar swelling, skin tags, pustules, abscesses, fistulas, fissures, ulcerations, and vaginal discharge. Penile and scrotal lesions are less common and include subcoronal ulcers as well as penile and scrotal edema. Twenty-five percent of genital Crohn’s disease presents before gastrointestinal complaints.

Although there are few cases reported in the pediatric literature, mucocutaneous lesions presenting as the initial sign of IBD is relatively common and can be an important clue in making the diagnosis of IBD before the development of gastrointestinal symptoms. We have identified 9 pediatric patients with asymptomatic IBD presenting with mucocutaneous lesions. The majority of these patients had oral and/or perianal lesions. Because oral disease, in general, is uncommon in children, we believe that IBD is a common etiology for persistent oral lesions in the pediatric population. Children and adolescents with unexplained oral mucous membrane lesions such as lip/mucosal swelling, gingival hyperplasia, cobblestoning of the oral mucosa, or deep linear ulcerations should have a good history taken regarding gastrointestinal symptoms, fever, and weight loss as well as an examination of the rectal and genital mucosa to seek other mucocutaneous clues of IBD that may not be mentioned to the physician. We would also recommend additional work-up including complete blood count, iron levels, ESR, albumin, occult blood in the stool, and serial endoscopies with biopsies to aid in the diagnosis if suspicions are high.

### TABLE 3. Oral Lesions in IBD

<table>
<thead>
<tr>
<th>Specific</th>
<th>Nonspecific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orofacial granulomatosis (granulomatous cheilitis)</td>
<td>Aphthous ulcers, Angular cheilitis, Labial/facial edema, Gingivitis, Gingival erythema/edema</td>
</tr>
</tbody>
</table>

### REFERENCES


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