Isolated Ileal Erosions in Patients With Mildly Altered Bowel Habits

A Follow-up Study of 28 Patients

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Key Words: Crohn; Ileum; Erosion; Nonsteroidal anti-inflammatory drugs; NSAIDs; Aphthoid; Ulcer; Ileitis

Abstract

This study evaluated 28 patients to characterize the morphologic features associated with typical Crohn disease (CD). All patients had similar complaints, an endoscopically normal colon, and small isolated, aphthoid erosions in the terminal ileum. The mean length of follow-up was 5.8 years. Of 28 patients, 25 (89%) were female (mean age, 32.3 years). Four patients were ingesting nonsteroidal anti-inflammatory drugs. All 28 lesions were morphologically similar, with focal lamina propria edema, mild active inflammation, and crypt disarray. Most had a lymphoid aggregate within the region of edema. Erosion was identified histologically in 21 cases. Following colonoscopy, symptoms resolved in all 28 patients. Typical, full-blown CD developed in 8 patients (29%) after a mean interval of 3.6 years. CD lesions were morphologically identical to non-CD lesions. Most focal ileal erosions in patients with mildly altered bowel habits are idiopathic and clinically insignificant. They represent early CD in approximately 30% of patients. The interval between initial examination and typical CD can be long. Pathologists should remain diagnostically vigilant when examining ileal biopsy specimens obtained from patients with previous abnormal ileal biopsy findings, regardless of the interval. Persistent, mild morphologic abnormalities have a high likelihood of being CD.

Mildly altered bowel habits are common nonspecific complaints in patients who are examined by gastroenterologists. Looser than normal stools and increased frequency of defecation are the 2 most common symptoms noted by these patients. Colonoscopy usually demonstrates normal colonic and small bowel mucosa. Approximately 3% of such patients are found to have one to several small, isolated, aphthoid erosions in the distal terminal ileum. The significance of this finding, as the sole endoscopic abnormality in minimally symptomatic patients, is poorly defined. Although discrete erosions in areas of otherwise normal mucosa can precede typical, full-blown Crohn disease, the proportion of patients in whom typical Crohn disease eventually develops is unclear.

The present study evaluated 28 such patients to characterize the morphologic features of the lesion and study its relationship to Crohn disease.

Materials and Methods

I identified, from case files and conference logs, 28 patients who underwent colonoscopy for mild alterations in bowel habits from January 1, 1994, through December 30, 1998; had one to several isolated, small terminal ileum aphthous erosions as the sole endoscopic abnormality; and had follow-up information. The mean number of ileal biopsy tissue fragments procured per patient was 4.3 (range, 2-7). Focal erosion tissue fragment(s) and surrounding normal ileal mucosa biopsy specimens were submitted in separate containers in 20 cases (71%). Mucosal biopsy tissue fragments were formalin-fixed. Three slides, each with a ribbon of tissue sections separated by approximately 150 µm, were cut from each
tissue block and reviewed. All tissue blocks from all cases were available for further sectioning if needed.

Follow-up information was obtained until the last contact date or the date of definitive diagnosis of Crohn disease. The mean and median follow-up times for the 28 patients were 5.8 and 5.3 years, respectively (range, 1.5-9.3 years; SD, 2.1 years).

### Normal Ileum Control Group

The control group consisted of 100 right hemicolectomy resection-specimen, grossly normal, ileum slides from patients without inflammatory bowel disease who were younger than 55 years. The patients had postcecal, right colonic adenocarcinoma and underwent surgery during the period January 1, 2000, through December 30, 2004.

### Pathologic Features

The following features were evaluated in normal ileal mucosa sections and recorded as the number per centimeter of mucosa: (1) length of mucosa evaluated on each slide; (2) number of villous architectural distortion foci, defined as 2 or more adjacent flat and broad or fused villi unrelated to tangential sectioning; (3) number of isolated lymphoid aggregates, defined as discrete collections of lymphocytes and plasma cells, devoid of a central germinal center, that surrounded but did not push aside mucosal crypts; excluded regions of confluent Peyer patch lymphoid tissue; (4) number of foci of lamina propria edema, defined as foci in which the normally homogeneously distributed loose areolar connective tissue fibers of the lamina propria were attenuated in density and separated by oval to rounded clear spaces; (5) number of foci of active inflammation involving crypts or villi; and (6) number of focal erosions, defined as the absence of surface epithelium associated with fibrin and active inflammation.

### Results

#### Control Normal Ileal Mucosal Features

Lymphoid aggregates were present in 16 sections (16%). Of the sections, 13 had 1 lymphoid aggregate, 2 sections had 2 lymphoid aggregates, and 1 section had 3 aggregates.

#### Table II. Normal Ileal Mucosa (N = 100)

<table>
<thead>
<tr>
<th>Morphologic Feature</th>
<th>No. (%) of Specimens With Feature</th>
<th>Mean (Range) No. of Foci or Sections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoid aggregates</td>
<td>16 (16)</td>
<td>1.1 (1-3)</td>
</tr>
<tr>
<td>Active inflammation</td>
<td>11 (11)</td>
<td>1.6 (1-3)</td>
</tr>
<tr>
<td>Villous architectural distortion</td>
<td>9 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Erosions</td>
<td>0 (0)</td>
<td>0</td>
</tr>
</tbody>
</table>

Of the 100 sections, 11 (11%) had foci of active inflammation involving 1 or 2 adjacent crypt bases. Of these 11 sections, 5 had 1 focus of active inflammation, 5 had 2 foci, and 1 had 3 foci. None of the active inflammation foci were associated with villous architectural distortion, lamina propria edema, erosions, or hemorrhages.

#### Clinical and Endoscopic Findings

Of the 28 study patients, 25 (89%) were female. The mean and median patient ages at sentinel colonoscopy were 32.3 and 28 years, respectively (range, 17-46 years). All 28 patients had complaints of looser than normal stools and an increased defeation rate (mean, 2.9 stools per day; range, 2-5 stools per day). Fifteen patients also complained of occasional postprandial bloating and increased flatulence. None of the patients had abdominal pain, sharp cramps, constipation, bloody or mucus-rich stools, systemic or upper gastrointestinal symptoms, perianal abscesses, or fistulas. Celiac disease–related serum antibody titers were within the normal range in all 28 patients. Four patients were ingesting non-steroidal anti-inflammatory drugs (NSAIDs) at the time of the sentinel colonoscopy, either daily or as multiple doses per week. Information regarding the duration of NSAID ingestion before the sentinel endoscopy for these 4 patients was not available. Stool cultures and smears for ova and parasites were negative in all patients.

The colonic mucosa was endoscopically normal in all cases. In the terminal ileum, each case had one to several discrete, focal erosions within otherwise normal small bowel mucosa. The erosions were located 1 to 3 cm proximal to the ileocecal valve haustral contraction ring. None were located marginally or on a prominent mucosal fold. The ileal mucosa around and proximal to the ulcers was uniformly normal. No mucosal erythema or targetoid rings were present around the erosions. The aphthoid ulcers and the mucosa surrounding them were not raised or volcano-like projections. Each erosion was approximately 1 mm in dimension. One erosion was found in 10 cases (36%), and 18 cases (64%) had several closely clustered erosions.

#### Pathologic Findings

No erosion was seen histologically in the initial 3 slides cut from each block in 19 cases (68%). Serial sections completely through the tissue block were obtained in these 19 cases, which revealed a single focal erosion in 12 cases. No erosions were identified histologically in 7 cases (25%), despite the complete serial sectioning and targeted biopsies. In these 7 cases, there was one endoscopic erosion in 5 cases and several endoscopic erosions in 2 cases. The ileal lesion tissue fragments in these 7 cases were morphologically similar [Image 1](#), [Image 2](#), [Image 3](#), and [Image 4](#). Villi were architecturally normal or slightly irregular in size and shape. There was slight expansion...
of the lamina propria by patchy edema and a focal lymphoplasmacytic inflammation. Crypts within edematous regions were disarrayed slightly, with an irregular distribution and slight variation in size owing to the edema and lymphoid aggregate. All 7 lesions had sparse to mild active inflammation involving several crypts. A moderate number of eosinophils were present in the lamina propria; however, eosinophils did not infiltrate crypts and no eosinophilic microabscesses were seen. The density of goblet cells was not increased appreciably.

The morphologic features of the 21 lesions in which an erosion was identified histologically also were similar Image 5, Image 6, Image 7, and Image 8. Active inflammation and fibrin overlaid a small region in which the surface epithelium was absent. Adjacent, intact surface epithelium had regenerative cytologic changes. The subjacent lamina propria was expanded by focal edema, active inflammation, and lymphoplasmacytic inflammation. Crypt architectural disarray was present owing to the inflammation and edema. Similar to the cases in which no erosion was identified morphologically, the density of lamina propria eosinophils was moderate and goblet cells did not appear to be increased. None of the biopsy specimens had mucous (pyloric) gland metaplasia.

The ileal mucosa around and distant from the focal erosions was normal in all 28 cases Image 9.

Clinical Course and Outcome

In 26 patients, abdominal computed tomography (CT) scans within 3 weeks of the sentinel colonoscopy appeared normal. The altered bowel habits resolved with a several-week course of loperamide or diphenoxylate in all 28 patients. NSAIDs were discontinued immediately in the 4 patients who were taking them. All 28 patients remained minimally symptomatic or asymptomatic during the follow-up period.

Typical Crohn disease developed in 8 (29%) of 28 patients after a prolonged interval Table 2. A single isolated ileal erosion was present endoscopically at the sentinel colonoscopy in 5 of these 8 patients. Of the 8 patients, 6 underwent another colonoscopy 0.9 to 1.7 months after the
sentinel colonoscopy. The small bowel and colonic mucosa were endoscopically normal in all 6 patients, and biopsy specimens from the region of the sentinel endoscopic erosions and random areas of the colon all were histologically normal.

The mean minimal or asymptomatic interval between the sentinel colonoscopy and typical Crohn disease symptoms was 3.6 years (range, 1.5-6.4 years). All 8 patients with Crohn disease had abdominal pain; mucus-rich, blood-tinged stools; irregular bowel function of intermittent constipation and diarrhea; and low-level systemic malaise. A definitive diagnosis of Crohn disease was made within 5 weeks after reexamination in the 8 patients. Colonoscopy performed after reexamination showed ileal disease in all 8 patients. Biopsy specimens from the involved region showed chronic Crohn ileitis with patchy activity in all 8 patients. In 5 cases, there also was cecal involvement, 2 of which also had patchy, mildly active chronic Crohn colitis in endoscopically normal, random biopsy specimens from more distal colon and rectum. In all 8 patients, an abdominal computed tomography scan was performed as part of the reexamination. A short segment of ileal wall thickening, consistent with early stricture, was present in 3 patients.

According to the Vienna Crohn disease classification system, 3 patients had stricturing-type Crohn disease and 5 had nonstricturing, nonpenetrating (inflammatory)-type Crohn disease. The disease in 1 of the latter 5 patients converted to stricturing-type disease during the subsequent 4 years, and the disease in 1 patient who had ileocecal disease at reexamination evolved into the penetrating-pattern of Crohn disease during 2 years.

In 20 patients, including the 4 who were ingesting NSAIDs, inflammatory bowel disease did not develop during the mean follow-up period of 6.6 years (range, 3.4-9.2 years). Of these patients, 17 underwent a follow-up colonoscopy after a mean interval of 2.8 years (range, 0.5-6.3 years). The ileum was devoid of erosions, and the colon was uniformly normal...
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in all 17 patients. Biopsy specimens obtained from the ileum in the region of the sentinel erosions and random areas of the colon were uniformly normal.

Discussion

Mildly altered bowel habits are a common initial symptom in patients seen by gastroenterologists. Most of these patients are found to have no underlying pathologic process. Mildly altered bowel habits also can be the initial symptoms of Crohn disease. Early, mild Crohn disease lesions display a range of endoscopic appearances from isolated ileal erosions surrounded by endoscopically normal-appearing mucosa to fully developed “classic” aphthoid ulcers. The diagnosis of Crohn disease often is straightforward when the endoscopic appearances of the lesions are those of fully developed, typical, early Crohn disease. However, when the endoscopic features are less well developed, the lesions are more nonspecific in regard to their etiology. To avoid overdiagnosis of Crohn disease, authors have emphasized the importance of a combined endoscopic-histologic diagnosis in early Crohn disease. Patients undergoing evaluation for mildly altered bowel habits occasionally are found to have one to several isolated ileal erosions in an otherwise normal ileal mucosa. The diagnostic significance of nonspecific isolated ileal erosions is poorly defined. To this end, this study evaluated 28 such cases. During follow-up, the lesions were found to be idiopathic and clinically insignificant in 16 cases (57%), early Crohn disease in 8 (29%), and related to NSAID use in 4 (14%).
The morphologic features of isolated ileal erosions in all 28 cases were similar and substantially overlapped with the range of changes seen in early, mild Crohn disease reported by other authors. Grossly or endoscopically seen erosions that ranged from pinpoint to approximately 3 mm were first termed *aphthoid ulcers* by Brooke in 1953 owing to their resemblance to the oral ulcers of aphthous stomatitis. Microscopically, these lesions consist of a small surface erosion situated directly over or positioned at the periphery of a lymphoid aggregate. Active inflammation admixed with fibrin often is present within the erosion and in the adjacent lamina propria. Crypts within the inflammatory focus usually contain active inflammation and have some injury changes to the epithelium. The villi and lamina propria immediately around the inflammatory focus are edematous. With the widespread use of high-resolution magnification endoscopy, the so-called preaphthoid lesion in nonulcerated mucosa was recognized; it consists morphologically of focal active inflammation with increased eosinophils relative to the adjacent lamina propria, patchy edema, increased intraepithelial

### Table 2
Outcome for 28 Patients With Isolated Ileal Erosions

<table>
<thead>
<tr>
<th>Feature</th>
<th>No. (%) of Cases</th>
<th>No. of Endoscopic Erosions</th>
<th>Histologic Erosion</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. with factor</td>
<td>28 (100)</td>
<td>18 (64)</td>
<td>10 (36)</td>
</tr>
<tr>
<td>Crohn disease present at follow-up</td>
<td></td>
<td>7 (25)</td>
<td>21 (75)</td>
</tr>
<tr>
<td>No</td>
<td>20 (71)</td>
<td>13 (72)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>Yes</td>
<td>8 (29)</td>
<td>5 (28)</td>
<td>3 (30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 (71)</td>
<td>15 (71)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 (29)</td>
<td>6 (29)</td>
</tr>
</tbody>
</table>

**Image 8** Higher magnification of Image 7. **A**, There is a small erosion of the mucosa between the lymphoid follicles (H&E, ×120). **B**, The surface epithelium has regenerative changes, and there is active inflammation in the superficial lamina propria and the surface epithelium adjacent to the erosion (H&E, ×320).

**Image 9** Normal ileal mucosa adjacent to an ileal erosion. Villi are architecturally normal, and the lamina propria is devoid of patchy edema or focal lymphoplasmacytic infiltrates (H&E, ×120).
lymphocytes, focal variation in villous width and length, and flattening of surface enterocytes overlying the inflammatory focus.\textsuperscript{13,16,17,20-23}

In the present study, lesions that on follow-up proved to be idiopathic and clinically insignificant were morphologically similar to lesions that eventually proved to be early Crohn disease and to those caused by NSAIDs. It was not possible to distinguish the subset of lesions that were early Crohn disease. Most of the patients with isolated nonspecific ileal erosion in this study (57\%) had idiopathic and clinically insignificant lesions.\textsuperscript{24} This result is similar to those of earlier studies that collectively report that in 44\% to 48\% of patients with isolated ileal disease, typical Crohn disease eventually develops.\textsuperscript{13,25} The distal ileal mucosa may be prone to mild mechanical injury and ischemia as it is pulled forward and squeezed by repetitive haustral contractions and constrictions of the ileocecal valve. These results highlight the point made by other authors that isolated ileal erosions and focal active inflammation with edema are not, as an isolated finding, specific for Crohn disease. They can occur in acute infectious enteritis and Behçet disease, be associated with ankylosing and nonankylosing spondylitis, and result from NSAID medications.\textsuperscript{11,26-31} In light of these findings, the optimal diagnostic approach in this situation may be a histologic descriptive diagnosis and a comment noting that similar lesions are most often idiopathic and found to be clinically insignificant and, less often, early Crohn disease or caused by NSAIDs.

These cases raise the issue of the appropriate diagnostic approach in this situation. There are no formal guidelines about whether similar lesions should be classified by pathologists as nonspecific or as “suggestive of Crohn disease.” One option is to use the diagnosis of “isolated ileal erosion” and add a comment stating “this lesion is idiopathic in most patients; however, in approximately one third, the disease will eventuate into typical Crohn disease, often after a prolonged interval.”

No histologic erosion was identified in 7 cases. The discrepancy between endoscopically seen aphthoid ulcers and histologically confirmed erosions has been noted by previous authors.\textsuperscript{13} In an early study of 109 patients with Crohn disease, 21\% had no histologic abnormalities seen on biopsy despite the endoscopic appearance of ileitis.\textsuperscript{32} In a more recent study of colonic cleansing preparatory agents in which 14 patients had several to numerous “prep”-induced, endoscopic aphthoid-like ulcers, only 1 patient (7\%) had histologic surface erosions.\textsuperscript{33} Although an apparent cause for this discrepancy was not apparent in the present study, the focality of the histologic erosion in some of the serially sectioned cases raises the possibility that it was cut through and lost when the surface of the block was initially faced-off.

Of the control normal ileal mucosa resection sections, 11\% had isolated foci of minimal active inflammation in the lamina propria that did not form crypt abscesses. This result is similar to the 7.8\% incidence of slight nonspecific active ileitis reported by others.\textsuperscript{3} These results suggest that focal, minimal, active ileal inflammation as an isolated morphologic finding should be considered physiologic rather than pathologic. It is important to note that none of the normal control sections had patchy lymphoplasmacytic inflammation, edema, villous shape irregularities, or crypt disarray in association with the active inflammation.
Of the 8 patients with Crohn disease in the present study, 7 had lengthy intervals (mean, 3.6 years) between their sentinel colonoscopy and the diagnosis of Crohn disease, during which they were minimally symptomatic or asymptomatic. This interval between initial symptoms and diagnosis is similar to that reported by other authors. Patients with early, minimally active Crohn disease can be asymptomatic, and disease progression to a state of sufficient structural damage to produce detectable clinical signs and symptoms of complicated Crohn disease can take years. Approximately 15% of patients with Crohn disease have a prolonged prodromal phase of low-level, periodic, irritable bowel disease—like signs and symptoms. Of the 8 patients with Crohn disease in the present study, 7 had similar manifestations: low-level irritable bowel disease symptoms and a slow rate of disease progression. These 7 patients serve to remind pathologists to remain diagnostically vigilant when examining ileal biopsy specimens obtained from patients with previous abnormal ileal biopsy findings, even if the interval between colonoscopic procedures is several years.

For most patients with Crohn disease, a prolonged minimal or asymptomatic period is not disease remission. Studies with follow-up periods of more than 20 years have found that Crohn disease is not a stable disease in most patients, regardless of its initial manner of presentation. In most patients, the disease eventually progresses and develops a strictureing or a perforating complication. The rate of developing complicated Crohn disease is uniform during the follow-up period in these studies, suggesting that the intensity of the Crohn disease inflammatory process and the systemic reaction to it varies among individuals.

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