CHAPTER 98
Small-Intestinal Ulcerations

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Summary
The differential diagnoses of ulcers of the small bowel are well known. They include Crohn’s disease, non-steroidal anti-inflammatory drugs (NSAIDs), radiation, vasculitis, medication effects, some infections, and certain neoplasms (Table 98.1). Nonetheless, when faced with the finding of ulceration in the small bowel, it can be difficult to come up with a final diagnosis. Crohn’s disease is most common, but NSAID use is also frequently seen. How, then, does a physician make the diagnosis of Crohn’s disease based on the presence of ulcers seen only on endoscopy, capsule or otherwise?

In the past, we were confident in making the diagnosis in the clinical setting of pain and diarrhea in a young person in whom a small bowel series showed ileitis. We clearly should be able to do the same with endoscopic findings; that is, to combine the clinical scenario with the endoscopic, rather than the radiographic, findings. There can be other evidence to support a diagnosis of Crohn’s, including the family history of inflammatory bowel disease (IBD) and abnormal serologies of antineutrophil cytoplasmic antibodies (ANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA); though this is not the intended use of these blood tests. Endoscopic biopsy typically cannot differentiate a Crohn’s ulcer from an NSAID ulcer. Other testing, such as computed tomographic (CT) scanning, generally provides no additional information beyond what is supplied by endoscopy. Grading the severity of inflammatory findings on capsule endoscopy can provide more certainty in making a final diagnosis.

Case
A 45-year-old female presents with a history of obscure gastrointestinal (GI) bleeding. Her first episode was at 20 years of age. Since then, multiple episodes have occurred, occasionally requiring transfusion of packed red blood cells (RBCs). Evaluations, including colonoscopy, upper endoscopy, and bleeding scan, are unrevealing. Additionally, CT scan, Medda’s scan, and small bowel series are normal. Her history is otherwise remarkable, except for rare NSAID use and hypertension, for which she takes diuretics. Her past medical history is remarkable for dysautonomia and myasthenia gravis. She has also been on antibiotics for recurrent sinusitis. Her family history is unrevealing. Her maternal grandmother died of colon cancer at the age of 75 years. She has no personal history of malignancy. Her medications include antibiotics for chronic sinusitis, aspirin for headache, and occasional diuretics for hypertension. She also takes a multivitamin daily.

On physical examination, her vital signs are normal. She is in no apparent distress. Her abdomen is soft, non-tender, and non-distended. Her bowel sounds are normal. Her rectal examination is normal. Her laboratory values are unremarkable. Her white blood cell count is 7,500/mcL, her hemoglobin is 13.5 g/dL, and her platelet count is 250,000/mcL. Her albumin is 3.8 g/dL, and her creatinine is 0.8 mg/dL. Her electrolytes are normal. Her fasting glucose is 85 mg/dL, and her lipids are normal. Her lipid profile is normal. Her liver function tests are normal. Her C-reactive protein is 0.2 mg/dL. Her anti-nuclear antibody (ANA) is negative, as is her anti-smooth muscle antibody (ASMA). Her p-ANCA are negative. Other laboratory values are unremarkable.

Capsule Endoscopy
Capsule endoscopy is performed and discloses diffuse mucosal edema and erythema associated with scattered ulceration and luminal narrowing at the mid-ileum (Figure 98.1). These findings correlate to an activity score of 12/32. Serologies of ASCA and p-ANCA are negative. Other laboratory values are unremarkable.

Introduction
How are we to make the diagnosis of Crohn’s disease in our case study? There is no history of radiation therapy and no history of medication use, except the limited NSAID use described. Infections cause seem remote. The patient has no pain and no history of diarrhea, simply bleeding. This is known to occur in Crohn’s, but it is an unusual presentation. We can look for other evidence to support our diagnosis, including a family history of IBD (there is none) and serologies such as ANCA and ASCA (they are negative). These serologies help differentiate ulcerative colitis from Crohn’s, but are now being used by physicians to confirm a diagnosis of suspected Crohn’s disease. Unfortunately, using these serologies for this purpose is not supported by the literature [1]. ASCA is detected in 39–70% of patients with Crohn’s disease and in only 0–5% of healthy subjects [1, 2]. The sensitivity of ASCA in correctly identifying Crohn’s disease is 55%. ANCA is positive in 2–28% of Crohn’s patients and in 20–85% of ulcerative colitis patients. It also has a low sensitivity for diagnosing ulcerative colitis, at 56%.

Another way to diagnose Crohn’s disease is to make a tissue diagnosis. DBE is used to deeply intubate the small bowel from either the peroral or the transrectal approach [3]. Unfortunately, the hallmark finding of non-caseating granulomas is seen in a minority of cases [4]. Endoscopic biopsy cannot differentiate a Crohn’s ulcer from an NSAID ulcer, though it can exclude neoplastic change, if suspected. Other testing, such as CT scanning, generally provides no information beyond what is found with capsule endoscopy [5]. Enlarged lymph nodes can be seen in chronic inflammatory changes, but this finding may only fuel the thought that there is a neoplasm.

Capsule Endoscopy
Capsule endoscopy has provided us with the ability to detect mucosal inflammatory change of the small intestine often missed by other techniques. In a pooled data analysis, comparing capsule
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Table 98.1 Ulcerations in the small bowel.

<table>
<thead>
<tr>
<th>Crohn's disease</th>
<th>Ulcerative jejuno-ilietis</th>
<th>Zollinger–Ellison syndrome (ZES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections: mycobacterium, spirochete and histoplasmosis</td>
<td>Medications: potassium, non-steroidal anti-inflammatory drugs (NSAIDs)</td>
<td>Vasculitis: polyarteritis nodosa, Churg–Strauss disease, rheumatoid arthritis, systemic lupus erythematosis (SLE), Behcet's disease, Wegener's granulomatosis, cryoglobulinemia, Henoch–Schönlein purpura</td>
</tr>
<tr>
<td>Radiation enteritis</td>
<td>Meckel's diverticulum</td>
<td>Duplication cyst</td>
</tr>
<tr>
<td>Graft-versus-host disease (GVHD)</td>
<td>Neoplasms: adenocarcinoma, carcinoid, lymphoma</td>
<td></td>
</tr>
</tbody>
</table>

Endoscopy with ileocolonoscopy, push enteroscopy, and small bowel series, capsule endoscopy had a miss rate for ulcers of only 0.5% [6]. A meta-analysis of studies comparing capsule endoscopy to other imaging modalities of the small bowel for IBD established that capsule endoscopy has an incremental diagnostic yield of 25–40% over other modalities, including CT enterography, small bowel series, and ileocolonoscopy [7]. One report described finding small bowel ulcers in 22 patients in whom no ulcers could be identified by any other means [8]. Yet, turning the ability to detect ulcerations into a diagnosis has been difficult. The most common clinical scenario is the opposite of that in the case study: it typically involves applying capsule endoscopy in patients with symptoms of Crohn's disease in an effort to find ulcerations. Suspicion of Crohn's disease was previously defined at the discretion of the treating physician, and was usually considered when a patient had either abdominal pain or persistent diarrhea. Yields of capsule endoscopy are low when performed in patients with abdominal pain alone [9] or in patients with abdominal pain and diarrhea alone [10].

The presence of inflammatory changes in the small bowel can not only be seen in a variety of disease states, but can also be noted in normal individuals. Goldstein conducted a trial comparing the effects of naproxen, celecoxib, and placebo in the small bowel [14]. Before randomization, all volunteers were forbidden NSAIDs for a period of 2 weeks. Goldstein reported that 10.6% of the healthy volunteers had mucosal breaks after this run-in period. The study did not measure these ulcers, and since these cases were excluded, we do

Figure 98.1 Mucosal edema, luminal narrowing, and ulceration at capsule endoscopy.

Figure 98.2 Criteria for suspected Crohn's disease. Source: Mergener 2007 [13]. Reproduced with permission of Georg Thieme.
not know their number or severity. Thus, ulcers in the small bowel may be normal. How does one make a diagnosis? These differing clinical scenarios show the complexity of trying to make a diagnosis based on an endoscopic image alone. Are the ulcers seen on the capsule study in the case example a normal finding, secondary to the patient’s occasional NSAID use, or do they represent Crohn’s disease? Though a few small ulcers may be normal or may be secondary to NSAID use, most experts would agree that numerous large ulcers can only mean Crohn’s disease. This is much like our feelings toward ileitis seen on a small bowel series. These changes are quite pronounced and could never be felt to be normal or secondary to NSAID use. The necessity of grading the severity of inflammatory change noted on capsule exams raises the need for a scoring index. An index has been created and validated, and is presently part of standard capsule software (Figure 98.3) [15]. This index evaluates three parameters: villous edema, ulceration, and stenosis. The severity of these changes is assessed by the number, size, and extent of the findings. Scores <135 designate normal or clinically insignificant mucosal inflammatory change, a score between 135 and 790 is considered mild, and a score ≥790 is considered moderate to severe. The positive predictive value (PPV) for the score has been reported to be 86.2% [16]. Other scoring indices have been devised. The Niv score or CEDAI (capsule endoscopy Crohn’s disease activity index) involves dividing the small bowel into proximal and distal segments according to transit time and then rating each segment on the basis of three parameters: inflammation, extent of disease, and presence of strictures. Studies have shown good correlation among different readers [17]. It is recognized that neither scoring index can at present differentiate the causes of inflammatory change in the small intestine. However, the Lewis score for the individual in the case study is 1232. This is well above the cutoff for moderate to severe inflammatory change of 790. This markedly elevated number strongly suggests that this patient has Crohn’s disease.

A new idea in the interpretation of capsule images suggests that progressive changes as the capsule moves distally is pathognomonic for Crohn’s. The concept is that the number and size of mucosal breaks increases in the distal small bowel and that the activity score should increase in subsequent tertiles.

Case Continued

The patient is started on 6-mercaptopurine 50 mg by mouth daily and mesalamine 500 mg by mouth four times daily. The capsule study is repeated 1 month later, revealing findings similar to the initial study 9 months prior. Finally, 7 months after treatment initiation, and 16 months after the initial capsule examination, a third capsule exam reveals complete mucosal healing. Neither the previously affected segments nor other locations within the small bowel reveal ulcers, erythema, or edema. The Lewis score of this examination is zero. Currently, the patient remains free of symptoms.
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Take Home Points

- A diagnosis of Crohn’s disease cannot be based solely by the appearance of ulcers. Circumferential and linear ulcers can be seen in both Crohn’s and non-steroidal anti-inflammatory drug (NSAID) enteropathy.
- The diagnosis of a small bowel ulcer seen on endoscopy has to be made in conjunction with clinical factors.
- The mucosal activity index, part of standard small bowel capsule software, can be used to suggest a diagnosis.

References