# Pathologic Quiz Case

## A 59-Year-Old Man With a 2-Week History of Right Iliac Fossa Pain

*Stanley Lipper, MD*

A 59-year-old white man presented with a complaint of mild right iliac fossa pain of 2 weeks' duration. His medical history was significant for a herniated lumbar disk that had been confirmed on magnetic resonance imaging and treated medically 2 years earlier. This was followed by a recent episode of mild lower backache preceding the onset of the right iliac fossa pain, for which the patient took naproxen sodium, 440 mg, at nighttime. A serendipitously scheduled surveillance colonoscopy showed a solitary 1 × 1.2-cm, oval, sharply delineated, whitish ulcer in the ascending colon, located 2 cm above the ileocecal valve on the opposite wall and involving a haustral crest (Figure 1, right margin). The rest of the large bowel appeared normal. The endoscopist noted that the ulcer edge ''felt soft'' to the biopsy forceps. A biopsy of the ulcer edge was taken. Hematoxylin-eosin–stained histologic sections were prepared from formalin-fixed, paraffin-embedded tissue.

Microscopic examination of the lesion showed superficial ulceration with a surface fibrinopurulent exudate (Figures 2 and 3). The underlying mucosa showed fibrosis of the lamina propria as well as evidence of mild glandular regenerative atypia (Figure 4).

**What is your diagnosis?**

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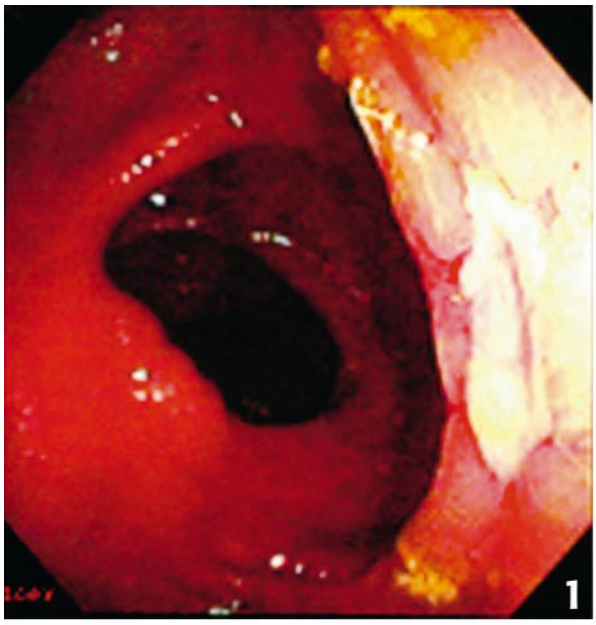

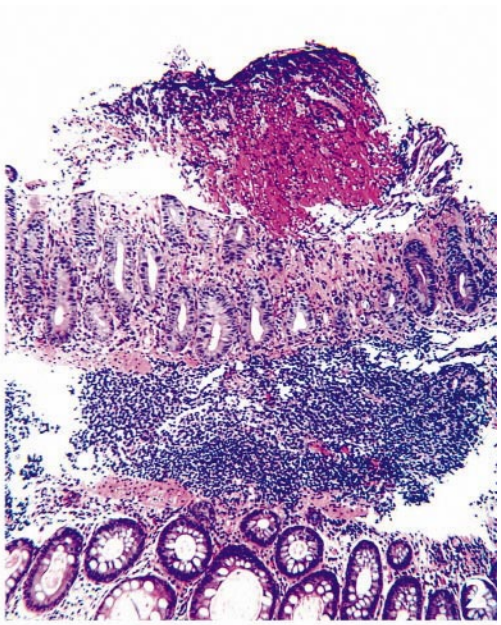

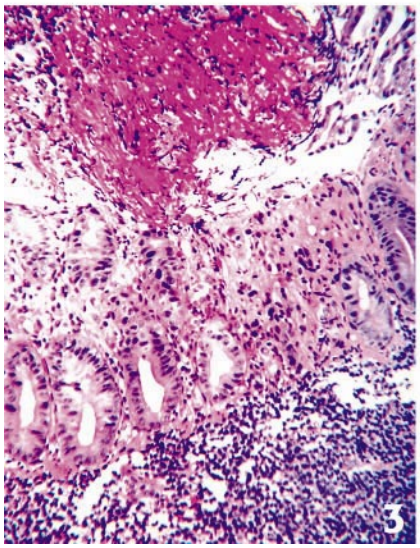

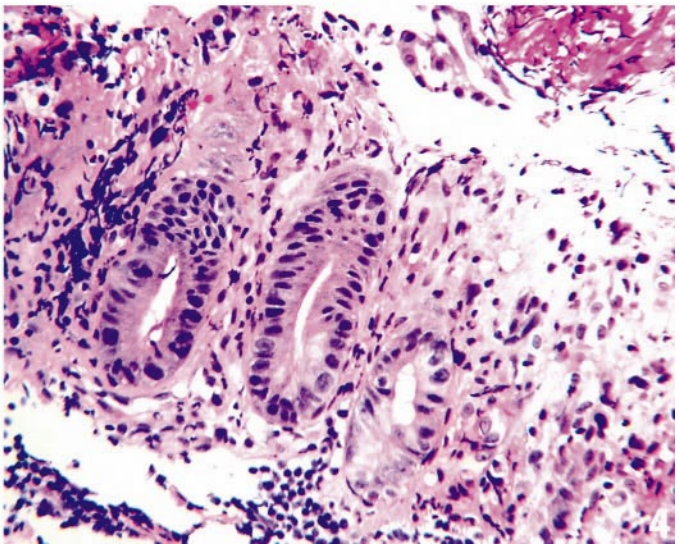

## Pathologic Diagnosis: Nonsteroidal Anti-inflammatory Drug–Induced Colonic Ulcer

The histologic features of superficial epithelial loss, inflammatory pseudomembranous exudate, mild regenerative atypia, and mucosal fibroplasia were consistent with a focal area of low-grade or chronic ischemia.

Following the patient's discontinuation of the naproxen sodium, the right iliac fossa pain gradually subsided, and a repeat colonoscopy 3 months later showed no sign of a colon lesion. The patient remains symptom free 6 months later.

Naproxen sodium belongs to the nonsteroidal anti-inflammatory group of drugs (NSAIDs). Naproxen and other NSAIDs are a well-established cause of gastrointestinal tract injury.[1–3] This may occur even after short-term use.[1] The mechanism of NSAIDs injury is not definitively known. The stomach and duodenum bear the brunt of the injury.[1,3] In this case, 2 mechanisms are postulated to be responsible.[3,4] The first mechanism is the direct mucosal damaging effect of NSAIDs.[3] Back diffusion of gastric acid occurs with resultant peptic ulceration.[5] This is due to topical loss of cytoprotective and reparative mucosal epithelial prostaglandins as a result of inhibition by NSAIDs of the mucosal cyclooxygenase enzyme system responsible for their biosynthesis from arachidonic acid.[1,5] Mucosal damage may be exacerbated as a result of the local loss of prostaglandin-mediated mucus and bicarbonate secretions normally providing a barrier to back diffusion.[5] A similar topical effect may apply in the large bowel, since sustained-release NSAIDs tablets have been found within colonic diverticulae and in the abdominal cavity near a perforation.[6] Rectal lesions have been described in patients using NSAIDs suppositories, which provides evidence of direct mucosal damage.[7] Sustained-release and enteric-coated tablets reduce the incidence of gastroduodenal ulcerations but increase enterocolonic complications, possibly as a result of contact toxicity causing the uncoupling of mitochondrial adenosine triphosphate and the subsequent breakdown of intercellular junctions.[8] It has been suggested that topical cyclooxygenase enzyme inhibition favors the production of inflammatory leukotrienes in the colonic mucosa.[4,8] The second mechanism is an indirect mucosal damaging effect seen throughout the gastrointestinal tract due to systemic cyclooxygenase enzyme inhibition and a decrease in cytoprotective and reparative mucosal epithelial prostaglandin production.[4,8] Compelling evidence for a systemic pathway is provided by examples of gastric and colonic ulcerogenesis following the intramuscular administration of NSAIDs.[4]

Most accounts of NSAIDs-associated gastrointestinal tract disease have appeared in the clinical literature, with relatively little attention being given in the pathologic literature. Histologic descriptions of NSAIDs-associated colonic ulcers have generally been vague; however, focal mucosal fibrosis, similar to that observed in this case, has been reported.[1,2,4,8] This is suggestive of an ischemic etiology, although the clinical and endoscopic findings do not support a diagnosis of conventional ischemic colitis.[1,2,4] A vascular mechanism may indeed play a role in this localized mucosal fibroplasia. Prostaglandins synthesized within the mucosa not only exert a cytoprotective effect but also increase mucosal blood flow.[5] Their inhibition may therefore contribute to mucosal injury through a reduction in local mucosal blood flow. This hypothesis is supported by the association of NSAIDs with renal dysfunction and even acute renal failure attributable to a loss of vasodilatory control as a consequence of prostaglandin inhibition.[9]

It is becoming increasingly apparent that NSAIDs-induced lesions of the large intestine, although relatively uncommon, are a significant cause of abdominal pain, anemia due to colonic bleeding, diarrhea, ulceration, perforation, ulcerated and nonulcerated strictures, patchy erosive colitis, collagenous colitis, diffuse colitis, and even death.[2] The right side of the colon, especially the ileocecal region, is a favored site for both solitary and multiple ulcers.[4,7] Lesions may be localized to haustral crests.[6] Typically, the ulcers are sharply demarcated and surrounded by normal mucosa, and the remaining part of the colon is normal in appearance.[10] These ulcers heal rapidly after the cessation of NSAIDs therapy.[4,6,7] Some patients present initially with concentric, diaphragm-like strictures apparently resulting from stenotic healing of haustral ulcerations.[6–8] Such strictures may clinically mimic Crohn disease and colon carcinoma and probably result from the prolonged use of NSAIDs.[6]

Since the presence of a sizeable, single colon ulcer may suggest a colon carcinoma, it is easy to imagine a situation in which fragmented biopsy material showing regenerative glandular atypia and fibroplasia might lead to a mistaken diagnosis of colon cancer, a pitfall that can be avoided by close interaction with the endoscopist, acquaintance with the endoscopic appearance of the lesion, and, above all, obtainment of a history of NSAIDs use.[8]

Because NSAIDs are so frequently prescribed and extensively used as over-the-counter medication, there is a compelling need for a heightened awareness, among both clinicians and pathologists, of their association with a wide variety of colopathic changes. This awareness might help avoid inappropriate management, such as colon resection for suspected colon cancer and medical treatment for inflammatory bowel disease.[10] Except for cases of strictures and perforations, in which surgery may be indicated, the cessation of NSAIDs use is the only therapy required.[4,6–8]

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