**Hypothesis:** Small-bowel diaphragm disease is an important source of gastrointestinal tract bleeding and subacute intestinal obstruction that may require surgical intervention.

**Design:** Case series.

**Setting:** Tertiary-care academic medical center.

**Patients:** Seven consecutive patients with histologically confirmed enteropathy induced by use of nonsteroidal anti-inflammatory drugs received treatment at our institution from February 2001 to February 2004.

**Interventions:** Laparotomy with small-bowel resection.

**Main Outcome Measures:** Initial symptoms and signs, findings at diagnostic workup, type of medication and duration of use, operation performed, and intraoperative findings were evaluated.

**Results:** Patients were identified who had symptoms of subacute intestinal obstruction or signs of gastrointestinal tract bleeding and were determined to have used nonsteroidal anti-inflammatory drugs for differing periods. All 7 patients underwent extensive nondiagnostic radiologic and endoscopic examinations. The diagnosis of diaphragm disease was ultimately made at either video capsule endoscopy or laparotomy. Randomly distributed diaphragms throughout the jejunum and ileum necessitated resection in all cases. No patient has had a documented recurrence, although follow-up is short (range, 0-20 months).

**Conclusions:** Nonsteroidal anti-inflammatory drugs are clearly linked to pathologic findings of diaphragm disease in both the upper and lower gastrointestinal tracts. Although rarely reported in the surgical literature, small-bowel diaphragm disease may be more common than thought and can manifest as gastrointestinal tract bleeding or obstruction. Diagnosis is difficult and may require laparotomy and small-bowel resection.

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**Methods**

A retrospective review of records identified patients with histologically confirmed NSAID-induced small-bowel enteropathy treated at our institution during a 3-year period (February 2001-February 2004). The study was approved by the Mayo Foundation Institutional Review Board.

**Results**

Seven patients (4 women and 3 men) were identified. Their mean age was 68 years (age range, 54-77 years). All 7 patients had been taking NSAIDs for varying durations (range, 4-30 years). One patient (patient 1) adamantly denied taking any NSAIDs other than celecoxib, 5 patients were taking aspirin, and 4 patients had also been taking cyclooxygenase-2 (COX-2) inhibitors as part of their treatment regimen.
When first seen, all 7 patients had either subacute obstructive symptoms or occult GI tract blood loss. An extensive preoperative endoscopic and radiologic workup revealed no diagnostic findings except in patient 6, in whom angiographic findings were positive. The diagnosis of DD was confirmed in the other 6 patients at capsule endoscopy when the video capsule was retained in the obstructed bowel, necessitating operative extraction (Figure 1). The diaphragms were randomly distributed throughout the ileum and jejunum. In patients with multiple lesions, the DD lesions seemed to be located somewhat close together along the small bowel. There were no instances of multiple lesions in both the proximal and the distal small bowel. One patient (patient 5) also had a Meckel diverticulum. In this patient, the retained video capsule was located within the diverticulum because of near-obstructing diaphragms just distal to it (Figure 2). On average, 9 diaphragms (range, 2-18) were identified in each patient by means of intraoperative palpation and enteroscopy, and were confirmed at pathologic examination.

Resection had been performed in all 7 patients; in addition, patient 2 had undergone strictureplasty. Patient 5 began taking celecoxib instead of a combination of diclofenac sodium and misoprostol, but the other 6 patients all discontinued NSAIDs as part of their course of treatment. Although follow-up was short (range, 0-20 months), no recurrence of DD was documented. In patients 1, 2, and 3, there was complete resolution of symptoms. Patient 4 continued to require blood transfusions and has reported intermittent nausea, but both conditions are related to another documented gastric pathologic condition. Patient 5, who was initially anemic postoperatively, has a stable hemoglobin level and has required no further blood transfusions. The last 2 patients in this series, patients 6 and 7 were treated recently, but symptoms have resolved and uneventful recovery continues.

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age, y</th>
<th>NSAID Use</th>
<th>Indication</th>
<th>Symptoms</th>
<th>Workup*</th>
<th>Location</th>
<th>No. of Diaphragms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/72</td>
<td>Celecoxib</td>
<td>4</td>
<td>OA</td>
<td>Obstruction and anemia</td>
<td>EGD, colonoscopy, enteroclysis, arteriogram, and bleeding seen on the tagged RBC scan</td>
<td>Jejunum</td>
</tr>
<tr>
<td>2/F/54</td>
<td>Aspirin</td>
<td>30</td>
<td>SLE and arthropathy</td>
<td>Obstruction and bleeding</td>
<td>EGD, colonoscopy, CT, and arteriogram</td>
<td>Jejunum and ileum</td>
</tr>
<tr>
<td>3/M/77</td>
<td>Aspirin</td>
<td>23</td>
<td>CAD</td>
<td>Obstruction and bleeding</td>
<td>EGD, colonoscopy, SBFT, enteroclysis, and arteriogram</td>
<td>Ileum</td>
</tr>
<tr>
<td>4/F/56</td>
<td>Naproxen</td>
<td>20</td>
<td>RA</td>
<td>Obstruction and bleeding</td>
<td>EGD, colonoscopy, enteroscopy, and SBFT</td>
<td>Jejunum</td>
</tr>
<tr>
<td>5/F/66</td>
<td>Aspirin</td>
<td>15</td>
<td>OA and ankylosing spondylitis</td>
<td>Obstruction and bleeding</td>
<td>EGD, colonoscopy, UGI tract series, and SBFT</td>
<td>Ileum</td>
</tr>
<tr>
<td>6/M/76</td>
<td>Aspirin and rofecoxib</td>
<td>25</td>
<td>OA and CAD</td>
<td>Bleeding</td>
<td>EGD, colonoscopy, SBFT, enteroclysis, bleeding seen on the tagged RBC scan, and angiography</td>
<td>Jejunum</td>
</tr>
<tr>
<td>7/M/73</td>
<td>Aspirin and piroxicam</td>
<td>17</td>
<td>CAD</td>
<td>Obstruction and bleeding</td>
<td>EGD, colonoscopy, SBFT</td>
<td>Jejunum and ileum</td>
</tr>
</tbody>
</table>

Abbreviations: CAD, coronary artery disease; CT, computed tomography; EGD, esophagogastroduodenoscopy; OA, osteoarthritis; RA, rheumatoid arthritis; RBC, red blood cell; SBFT, small-bowel follow-through; SLE, systemic lupus erythematosus; UGI, upper gastrointestinal.

*All findings were negative except for angiography in patient 6, which demonstrated positive findings. The conditions of all patients except patient 6 were diagnosed using capsule endoscopy. Patient 6 underwent laparotomy. With the exception of patient 2, who underwent a resection and strictureplasty, all of the remaining patients underwent only a resection.

†Patient 1 was previously described in Yousfi et al.6

Figure 1. Longitudinal pathologic section of small-bowel specimen contains a distal diaphragm almost totally obstructing the bowel and a retained video capsule endoscope proximally.
The reported overall prevalence of DD ranges from 8.4% to 66%. Pinpointing the exact prevalence is precluded by the vague symptoms of this disorder, which impede diagnosis. Bjarnason used nonspecific radionuclide scanning to identify a 66% prevalence in patients who had been taking NSAIDs for longer than 6 months, whereas Allison et al reported a 13.5% ulceration rate in autopsy specimens from patients who had been taking NSAIDs for longer than 6 months. Allison et al also found a 6.3% ulceration rate in patients who had been taking NSAIDs for less than 6 months, for an overall prevalence of 8.4% compared with control subjects (0.6%). However, no relationship was found between small-bowel ulceration and gastroduodenal ulceration.

Another unknown factor is how long it takes for DD to develop in a patient who is taking NSAIDs. In general, DD has been associated with high doses taken daily. However, some patients with DD had been taking NSAIDs for less than 4 weeks. In an attempt to decrease the detrimental effects of NSAIDs on the gastroduodenal mucosa, researchers have developed enteric-coated and timed-release medications. However, sustained direct contact of NSAIDs with small-bowel mucosa and prolonged use of NSAIDs are both thought to contribute to an increase in small-bowel ulceration and gastroduodenal ulceration.

The mechanism of action of NSAIDs on the upper GI tract is related mainly to inhibition of the COX pathway. The inhibition of prostaglandin synthesis contributes to both the beneficial and toxic effects of NSAIDs. Inhibition of the first COX isoform is thought to be responsible for erosive effects in the GI tract, whereas inhibition of the second COX isoform (COX-2) is related to maintaining mucosal protection. More recent data indicate that this mechanism is overly simplistic. Both isoforms are constitutive and inducible, and COX-2 may also have a role in mucosal defense. Nonsteroidal anti-inflammatory drugs also may modulate COX-independent signal transduction pathways, such as nuclear factor-kB and peroxisome proliferator-activated receptor γ, which may contribute to the anti-inflammatory activity of these medications. Other proposed mechanisms include the production of increased intestinal permeability and the uncoupling of mitochondrial oxidative phosphorylation. These mechanisms may work alone or in combination to facilitate invasion by toxins and bacteria. Moreover, they decrease leukocyte migration and adhesion that aid the clearance of these toxins. The enterohepatic circulation of NSAIDs and their concentration in bile have also been shown to correlate with mucosal injury. The pathogenesis of DD may be related to a combination of these factors, but why some patients are more susceptible than others is unknown.

Clinical manifestations of DD include obstructive symptoms, abdominal pain, nausea, vomiting, diarrhea, iron-deficiency anemia, GI tract blood loss, and protein-losing enteropathy. The diagnosis should be considered in patients taking NSAIDs who have obscure obstructive symptoms or GI tract blood loss. Standard endoscopy can be used to rule out more common causes of GI tract blood loss.

Radiographic studies with contrast media are notoriously inaccurate for the diagnosis of DD. They either do not show the diaphragms or show them so indistinctly that they are misinterpreted as exaggerated plicae circulares. Push enteroscopy is also frequently uninformative because of its technical and logistical limitations. Certain radionuclide scans have documented malabsorption or blood loss, but none has yet demonstrated a cause of obstruction. Because of the low yield of standard radiologic and endoscopic methods, surgical intervention has often been necessary to make the definitive diagnosis of DD. The advent of capsule enteroscopy and virtual enterography may facilitate preoperative evaluation of the small bowel.

Because DD is so difficult to identify, the diagnosis is frequently made after an extensive and painstaking workup that yields normal findings. Most often, documented DD of the small bowel has been treated with resection. Discontinuation of the offending NSAID is a mainstay of empirical treatment. Little information exists about the natural course of DD after discontinuation of NSAIDs. To our knowledge, there is only one published report of a patient with known ileal ulcers and diaphragms who had resolution of bleeding and abdominal pain after discontinuing piroxicam treatment and taking a high dose of prostaglandin E1, a derivative of scurcalate, and sulfasalazine. Lang et al have reported a symptom recurrence rate as high as 50% after resection for DD. This high rate may be caused by progression of the disease, with or without cessation of NSAIDs, or by the inability to definitively establish the extent of disease even when surgical procedures are used.

During laparotomy, the diaphragms are often imperceptible by their external appearance; thus, palpation and intraoperative enteroscopy are essential. Laparoscopy was attempted in the first few patients, but the lack of definitive external clues limited our ability to correctly identify lesions. A diaphragm may be apparent only by a slight decrease in extraluminal diameter, by serosal discoloration, or by increased thickness evident at palpation. Intraluminally, the lesions occur as random, thin, concentric fi-
brotic ridges interspersed between sections of normal bowel, and the size of any luminal occlusion varies from that of a pinhole to normal diameter (Figure 3). The first 5 patients underwent both palpation and intraoperative enteroscopy. All palpated lesions were tagged with a silk suture before enteroscopy. All questionable tagged lesions were found to have DD, and no lesions were missed in the small bowel that was considered normal. Because intraoperative endoscopy can lead to its own set of difficulties (eg, larger incisions, mesenteric tears, small-bowel inflation), only palpation was used in the last 2 patients. All tagged lesions revealed DD, and the patients are doing well. The combination of palpation and intraoperative endoscopy is recommended in at least the first few patients.

Definitive surgical treatment options include small-bowel resection or strictureplasty. As in patients with Crohn disease–induced small-bowel strictures, strictureplasty can be used whether there are only a few strictures or multiple strictures throughout the entire small bowel (not found in our patient population). Most patients underwent resection because multiple lesions (on average, 9) were located within a short length of small bowel. In addition, DD does not seem to be a chronic or recurrent problem, like Crohn disease, which requires a length of small bowel to be optimized.

The diaphragms are characterized histologically by submucosal fibrosis and a chaotic arrangement of smooth muscle fibers, vascular elements, and neural elements (Figure 4). They resemble neuromuscular and vascular hamartomas and are most likely part of the same group of pathologic processes related to NSAID-induced injury. Microscopically diagnosed neuromuscular and vascular hamartomas might actually be related to NSAID-induced enteropathy.

The use of NSAIDs has often been linked to ulcerations and strictures in both the upper and lower GI tracts. Although rare, DD may also occur, resulting in GI tract bleeding and subacute obstruction. The pathogenesis of DD, although not entirely apparent, is almost certainly multifactorial. More study is needed to elucidate the mechanism of injury, the natural history of the disease, the possibility of effective medical therapy, and the development of improved diagnostic methods. As the use of NSAIDs and awareness of their possible adverse effects continue to increase, the diagnosis of DD will likely become more common. The surgeon should be aware of this pathologic process and should consider DD in the differential diagnosis when trying to identify the cause of GI tract bleeding or subacute intestinal obstruction.

Treatment of small-bowel DD complicated by GI tract bleeding or obstruction includes cessation of all NSAIDs, including COX-2 inhibitors, and strong consideration of surgical resection. Identifying the location of diaphragms often requires laparotomy with intraoperative palpation and enteroscopy.

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REFERENCES


Figure 3. View from a video capsule endoscope shows a small-bowel diaphragm induced by use of nonsteroidal anti-inflammatory agents.

Figure 4. Microscopic cross section of mucosal diaphragm shows submucosal fibrosis, chaotic smooth muscle fibers, vascular elements, and neural elements (hematoxylin-eosin, original magnification ×20).


Announcement

Online Submission and Peer Review System to Be Available in January 2006. The Archives of Surgery editorial office will be introducing an online manuscript submission and peer review system developed by eJournalPress that will serve the needs of authors, reviewers, and editors. The new system is scheduled to go live on January 16. See http://archsurg.ama-assn.org for more detailed information.