Multiple Colon Ulcers with Typical Small Intestinal Lesions Induced by Non-Steroidal Anti-Inflammatory Drugs

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Abstract

The diagnosis of NSAID-induced colon ulcers is difficult when the distribution or endoscopic findings are not typical. An 83-year-old woman was transferred to our hospital for hemorrhagic diarrhea. Colonoscopy showed multiple ulcers in the entire colon, particularly longitudinal ulcers in the transverse colon. These were unusual for NSAID-induced colopathy, although she had been on meloxicam. However, capsule endoscopy revealed multiple scars and erosions, characteristic of NSAIDs users. The final diagnosis was NSAID-induced enteropathy, and all lesions were in remission after meloxicam discontinuation. We herein emphasize the value of an endoscopic assessment of the entire digestive tract in the diagnosis of NSAID-induced mucosal lesions.

Key words: NSAID-induced ulcer, total colon, colonoscopy, capsule endoscopy


Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed drugs worldwide for their analgesic and anti-inflammatory properties. However, NSAIDs prescription may result in the induction of gastrointestinal toxicity. The adverse effects of NSAIDs on the upper gastrointestinal tract and small intestine are well established, and the prevalence of inflammatory lesions in the latter is 55-75% in healthy volunteers (1). Ulcerative lesions in the colon are less well described, although the prevalence of ileocolonic ulcers is 3.2% in chronic NSAIDs users (2). These lesions are predominantly distributed on the right side and, occasionally, elsewhere in the colon (1). When the clinical suspicion of NSAID-induced colopathy is raised, other causes that show a similar endoscopic appearance should be excluded, such as enteric infection, ischemic colitis, and inflammatory bowel disease.

We herein report a case of NSAID-induced ulcers extending throughout the entire colon, particularly longitudinal ulcers in the transverse colon. Additional findings revealed by capsule endoscopy were helpful for a prompt diagnosis. We also describe the case and emphasize the value of an endoscopic assessment of the entire digestive tract in the diagnosis of NSAID-induced mucosal lesions.

Case Report

An 83-year-old woman visited another hospital due to diarrhea, which had lasted for the past 5 days, and low-grade fever, which had lasted for the past 3 days. She had a history of shoulder pain and had been on meloxicam (10 mg daily) and lansoprazole (15 mg daily) therapy for 2 months. The patient had been taking zaltoprofen (160 mg daily) for 4 years until 6 months prior to the present episode. The blood tests showed mild anemia [hemoglobin (Hb), 8.7 g/dL] and inflammation [white blood cell (WBC) count, 8,400/μL and C-reactive protein (CRP), 16.81 mg/dL], and computed tomography (CT) of the abdomen did not show...
thickening of the digestive tract. On the fecal and blood culture analyses, pathogenic bacteria were not detected. The initial diagnosis was acute viral enteritis, and she was administered intravenous nutrition and lactic acid bacteria.

Four days after the first visit, the patient had bloody stool and experienced vital shock. Therefore, meloxicam was discontinued, a blood transfusion was performed because of gastrointestinal bleeding, and she was transferred to our hospital the next day. A physical examination revealed mild abdominal tenderness, and the laboratory tests showed an elevated WBC count of 6,350/μL, an Hb level of 11.3 g/dL, a CRP level of 13.3 mg/dL, and a procalcitonin level of 0.35 ng/mL. Pathogenic bacteria were not detected by the fecal and blood cultures. A contrast enhanced CT scan showed intestinal fluid and a slight thickening of the colonic wall without failure of the blood flow (Fig. 1). Therefore, the initial diagnosis was mucosal injury of the colon with bacterial translocation.

Colonoscopy showed multiple well-circumscribed ulcers in the total colon, except the rectum; in particular, longitudinal ulcers in the transverse colon were observed (Fig. 2). A histological examination of the endoscopic biopsies from the right colon ulcer margins showed normal crypt architecture with moderate inflammatory infiltrates in the lamina propria. In the basal part of the crypts, a few apoptotic bodies were detected, and the nuclei of the epithelial cells were mildly enlarged (Fig. 2). The endoscopic biopsies from the ulcer margins of the transverse, descending, and sigmoid colon also revealed similar histological characteristics. Furthermore, granuloma, vasculitis, inclusion bodies, amyloid deposition, ghost-like appearance of epithelia, and thickening of the subepithelial collagen layer were not detected in the biopsy specimens of the ulcer margin. Pathogenic bacteria were not detected in the mucosal biopsy culture. Furthermore, the blood tests were negative for Entamoeba histolytica antibodies, and there was no elevation of virus IgM antibodies. This suggested that the multiple colon lesions represented NSAID-induced colopathy, and that the type of damage was colonic ulcers, although the extent of the disease and the endoscopic findings of the transverse colon were unusual. Therefore, following the assessment of small intestinal stenosis with patency capsule, the upper gastrointestinal tract and small intestine were examined by esophagogastroduodenoscopy and capsule endoscopy. The results revealed atrophic gastritis induced by Helicobacter pylori infection, hiatal hernia in the upper gastrointestinal tract, and mild stenosis with multiple ulcerative scars and mucosal erosions in the small intestine (Fig. 3). These findings are common in chronic NSAIDs users.

The abdominal pain diminished after meloxicam discontinuation and the commencement of enteral nutrition. The elevated CRP levels rapidly decreased (to 1.55 mg/dL) on the sixth day of admission, and the antibiotics were discontinued. Three weeks upon admission, the laboratory data showed CRP levels of 0.13 mg/dL, and the patient was discharged from our hospital. Four weeks after admission, all colon ulcers were in remission without stenosis (Fig. 4).

We concluded that the final diagnosis of all lesions in both the small intestine and colon was NSAID-induced enteropathy.

**Discussion**

The diagnosis of NSAID-induced colopathy is not always easy because other causes show similar endoscopic or histological findings and, occasionally, NSAIDs may exacerbate pre-existing colonic disease. Common endoscopic findings include erosion and ulcers, which should be diagnosed as soon as possible, particularly in cases with gastrointestinal bleeding or perforation. In the present case, the disease extent and endoscopic findings in the transverse colon were unusual for NSAID-induced colopathy. The enteric lesions revealed by capsule endoscopy have been useful in the early diagnosis and determination of treatment strategy. To the best of our knowledge, this is the first report where an endoscopic assessment of the total gastrointestinal tract in patients with NSAID-induced ulcers in the entire colon has been performed, according to a search in the PubMed database for the terms “NSAIDs,” “colon,” and “ulceration.”

NSAID-induced colopathy is diagnosed based on the following criteria: (1) presence of colonic lesions confirmed by colonoscopy; (2) administration of NSAIDs before colitis; (3) absence of other diseases, such as inflammatory bowel disease, amyloidosis, infectious colitis, and ischemic colitis; and (4) confirmation of improved ulcers by repeated colonoscopy after discontinuation of NSAIDs (3, 4). In the present case, colonoscopy showed multiple ulcerations in our patient receiving meloxicam, and other diseases were carefully excluded by the contrast enhanced CT scanning, culture tests with fecal and biopsy specimens, and a histological examination. All lesions were in remission after the discontinuation of NSAIDs, although antibiotics were used only for a short period. The CRP levels were high in the present case, and its possible explanation for this could be...
systemic inflammation induced by bacterial translocation after the NSAID-induced disruption of mucosal defense because the serum procalcitonin level was elevated. The CRP levels rapidly decreased after the administration of antibiotics, although its normalization required 3 weeks. Therefore, we concluded that the diagnosis was NSAID-induced en-
teropathy.

The endoscopic findings of NSAID-induced ulcers are characterized by well-circumscribed ulcers and thin diaphragm-like strictures, and these lesions are almost always observed in the right colon extending to the transverse colon (5-8). However, only three cases of NSAID-induced ulcers have been reported to extend to the entire colon (4, 6, 7) (Table). All drugs administered in those patients have been classified as compounds with approximately 5- and 50-fold selectivity for cyclooxygenase-2 (COX2) over cyclooxygenase-1 (COX1) (9).

NSAID-induced mucosal colonic injury appears to occur because of at least three reasons: reduced blood flow, epithelial damage, and neutrophil adherence (10, 11). The suppression of COX1 and COX2 activity is essential for the formation of these lesions. The most likely mechanism is the inhibition of colonic prostaglandin predominantly derived from COX2 due to exogenous prostaglandin, which can prevent experimental colonic injury in rats (12). Moreover, prostaglandins in endothelial cells by COX2 are involved in ulcer healing through the regulation of angiogenesis (13). Celecoxib, a COX2-specific inhibitor, has not been shown to reduce the incidence of colonic or small bowel disease compared with NSAIDs, although its use leads to a reduction in the incidence of upper gastrointestinal disease (14). This suggests that the high selectivity of COX-2 inhibition is associated with the extent and exacerbation of colopathy (as shown in Table).

Capsule endoscopy studies have demonstrated that NSAIDs used by healthy volunteers raised the incidence of intestinal damage by 55-75%. The sensitivity allowed for the detection of small intestinal lesions, such as red spots, erosions, ulcers, and ulcer scars (1). In addition, another observational study suggested that small intestinal ulcers in NSAID-induced enteropathy occurred in multiplicity either simultaneously or metachronously and improved rapidly after drug discontinuation (15). In the present case, capsule endoscopy showed mild stenosis with multiple ulcerative scars in the small intestine, in addition to erosion. The finding of stenosis may suggest that past administration of zaltoprofen repeatedly induced small intestinal injury. Patency capsules have been reported to allow patients to safely undergo a capsule endoscopy, despite the clinical and radiographic evidence of small bowel stenosis in Crohn’s disease (16). In the present case, the use of a patency capsule was safe and helpful for the assessment of stenosis of the small intestine.

The most important treatment of NSAID-induced enteropathy is the discontinuation of NSAIDs use. Proton pump inhibitors have no preventive or therapeutic effects. Misoprostol and rebamipide have also been shown to reduce the incidence of NSAID-induced small intestinal injury in both a rodent model and clinical studies (17, 18). In the present case, these drugs were not administered because their therapeutic effects on mucosal injury had not yet been established, particularly in the colon. Thus, there remains a strong clinical need for effective anti-inflammatory drugs with improved safety profiles.

Table. Characteristics of Reported Cases of NSAIDs-induced Ulcers Extended to Total Colon.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Gender</th>
<th>Indication</th>
<th>Simultaneous disorder</th>
<th>Drug</th>
<th>Duration</th>
</tr>
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<tbody>
<tr>
<td>4</td>
<td>69</td>
<td>F</td>
<td>RA</td>
<td>Renal failure</td>
<td>Loxoprofen</td>
<td>5 year</td>
</tr>
<tr>
<td>6</td>
<td>56</td>
<td>M</td>
<td>tonsillitis</td>
<td>none</td>
<td>Dicrofenac</td>
<td>19 days</td>
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<tr>
<td>Mefenamic acid</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>F</td>
<td>arthritis</td>
<td>none</td>
<td>Dicrofenac</td>
<td>1 year</td>
</tr>
<tr>
<td>Our case</td>
<td>83</td>
<td>F</td>
<td>Omarthralgia</td>
<td>Osteoporosis</td>
<td>Meroxicam</td>
<td>2 months</td>
</tr>
</tbody>
</table>

Figure 4. Colonoscopic findings 4 weeks after the discontinuation of meloxicam. All ulcers in the colon were in a remission state (a), and stenosis was not detected in the transverse colon (b).
In conclusion, we herein reported an unusual case with multiple ulcers in the entire colon with a final diagnosis of NSAID-induced mucosal injury. The present case showed that NSAIDs can affect the entire gastrointestinal system and that an endoscopic assessment of the entire digestive tract is important for the early diagnosis and determination of treatment strategies.

The authors state that they have no Conflict of Interest (COI).

References