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NONSTEROIDAL ANTI-INFLAMMATORY DRUG-INDUCED ENTERITIS: A CASE REPORT

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ABSTRACT

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are among the most frequently prescribed medications worldwide, particularly for the treatment of osteoarthritis, musculoskeletal pain, rheumatoid arthritis, and other inflammatory conditions. They act by inhibiting the activity of cyclooxygenase (COX) enzymes, resulting in the blockade of prostaglandin, prostacyclin, and thromboxane synthesis. This inhibition predisposes patients to adverse effects such as acute gastroduodenal mucosal injury, ulcers, esophagitis, enteritis, reactivation of inflammatory bowel disease, among others. NSAIDs exert deleterious effects throughout the gastrointestinal tract mucosa. Similar to the stomach, the intestine—especially the distal small intestine and colon—is susceptible to the harmful effects of NSAIDs. The ileocecal region is most commonly affected, where erosions, ulcers, strictures, perforations, and diaphragm-like lesions may occur, potentially leading to intestinal obstruction. We report the case of a 33-year-old male patient with chronic and abusive use of NSAIDs, admitted for investigation of abdominal distension and pain, nausea, vomiting, and diarrhea. After ruling out the most common causes of these symptoms, the diagnosis of NSAID-induced enteritis with substenosis formation was established. A review of the clinical and diagnostic aspects of NSAID-induced enteropathy is also presented.

Keywords: NSAIDs, Enteritis, Substenosis, Abdominal pain, Colonoscopy.

INTRODUCTION

Post-spinal Enteritis is defined as inflammation of the small intestinal mucosa and may lead to impaired absorptive function of the organ. The most common causes are infectious, mainly of viral, bacterial, and parasitic origin, but it can also result from ingestion of toxins in contaminated food. Less common causes include food allergy/intolerance, autoimmune diseases, inflammatory bowel disease, diabetes, hypothyroidism, alcohol abuse, and medication use.[1,3]

Among the drug classes with significant potential to induce enteritis are non-steroidal

anti-inflammatory drugs (NSAIDs). This group of medications acts by inhibiting the activity of cyclooxygenase enzymes, and through this mechanism, several adverse effects may occur, including potential damage to the gastrointestinal tract.[4,5]

The clinical presentation typically includes diarrhea, abdominal pain, nausea, and vomiting. More severe cases may progress with fever, weight loss, asthenia, muco-bloody diarrhea, melena, as well as symptoms related to malabsorption such as hypovitaminosis and electrolyte disturbances.[2,3,6] Despite NSAIDs being among the most widely prescribed medications worldwide and well known to be associated with adverse gastrointestinal effects, NSAID-induced enteritis remains a neglected and underdiagnosed condition. The aim of the present report is to describe the case of a young patient with prolonged and abusive NSAID intake, who developed enteritis and partial intestinal obstructions. We also review the clinical features and diagnostic aspects of this condition.

CASE REPORT

A 32-year-old male patient, with no previous comorbidities, social alcohol use but abstinent for the past two years, and a former smoker (16 pack-years, quit one month prior), had a history of right femoral fracture six years earlier due to a motor vehicle accident. Since then, he had been chronically and abusively using NSAIDs for pain control, reporting daily and excessive intake of diclofenac sodium 50 mg and ibuprofen 600 mg tablets. He also reported occasional use of minor analgesics (acetaminophen and dipyrone) and morphine derivatives (codeine). He denied the use of other medications. He had a previous episode of upper gastrointestinal bleeding three years earlier due to a gastric ulcer. There was no family history of neoplasia or inflammatory bowel disease.

The patient was admitted with a history of abdominal pain and distension for the past three years, worsened by food intake, associated with nausea, vomiting, and diarrhea—sometimes watery, sometimes pasty—of intermittent character, without blood, mucus, or pus, with significant worsening of symptoms one day before hospitalization. He denied fever, significant weight loss, new episodes of upper gastrointestinal bleeding, or respiratory or urinary complaints.

Laboratory tests revealed no electrolyte disturbances, renal dysfunction, or liver enzyme abnormalities. Findings included hypoalbuminemia, microcytic hypochromic anemia with anisocytosis, and iron and ferritin levels below the reference range. Oral lactose and fructose tolerance tests were positive. Anti-gliadin IgA and IgG antibodies were non-reactive. Fecal calprotectin was 40 (reference value < 200).

Upper gastrointestinal endoscopy showed distal erosive esophagitis (Los Angeles grade A), moderate enanthematous antral gastritis, and a healing pyloric ulcer (H2 SAKITA classification). Histopathological examination revealed mild non-granulomatous gastritis, moderate chronic duodenitis with crypt hyperplasia, villous-to-crypt ratio of 2:1, and multiple lymphoid follicles in the lamina propria.

Colonoscopy demonstrated deformity of the ileocecal valve with a scar lesion leading to stenosis, accompanied by local edema and enanthema. Histopathological examination showed moderate chronic erosive colitis associated with hyperplasia of lymphoid follicles in the lamina propria.

Enterotomography revealed diffuse distension of small bowel loops with formation of air-fluid levels, without evidence of obstructive factors by this method. No areas of mural thickening suggestive of inflammatory bowel disease were observed.

Retrograde enteroscopy demonstrated partial intestinal obstruction due to stenosis of the

ileocecal valve (FIGURES 1 and 2), which was endoscopically dilated without complications (FIGURES 3 and 4). It also revealed stenoses and aphthoid ulcers in the terminal ileum (FIGURES 5 and 6), from which biopsies were obtained. Histopathological examination of the ileum showed mononuclear lymphoplasmacytic inflammatory infiltrate in the lamina propria and hyperplastic follicles; preserved crypt-to-villous ratio; absence of ulceration or microabscesses; negative search for microorganisms (fungi and acid-fast bacilli); and no histological signs of malignancy.

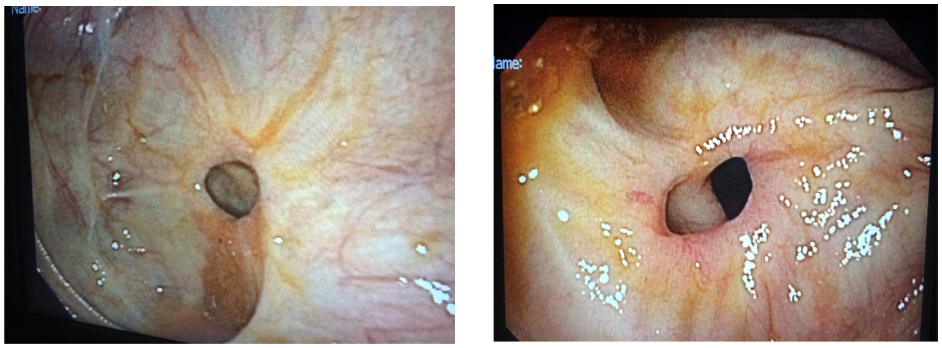

Figure 1 and 2. Ileocecal valve stricture observed on enteroscopy

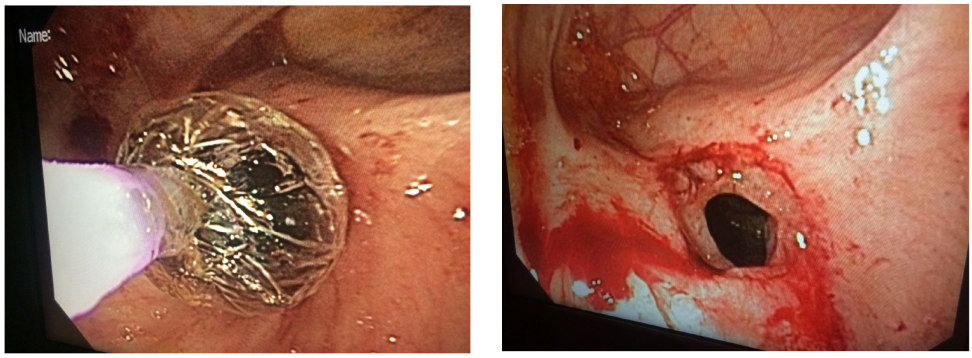

Figure 3 and 4. Endoscopic balloon dilation performed during enteroscopy.

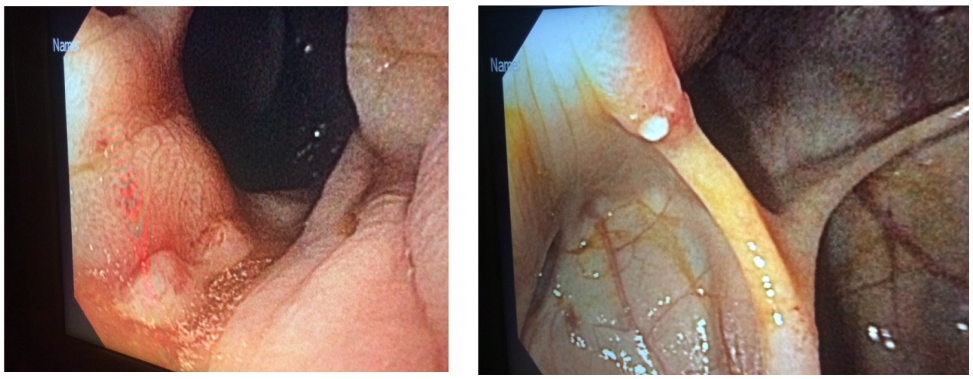

Figure 5 and 6. Strictures and aphthoid ulcers in the terminal ileum observed on enteroscopy.

Small bowel follow-through X-ray showed dilation and mucosal thickening of distal jejunal and ileal loops. The distal portion of the ileum was not visualized, with only a small amount of contrast passing into the right colon. No clear evidence of obstructive processes or caliber reduction of bowel loops was seen (FIGURES 7, 8, 9, and 10).

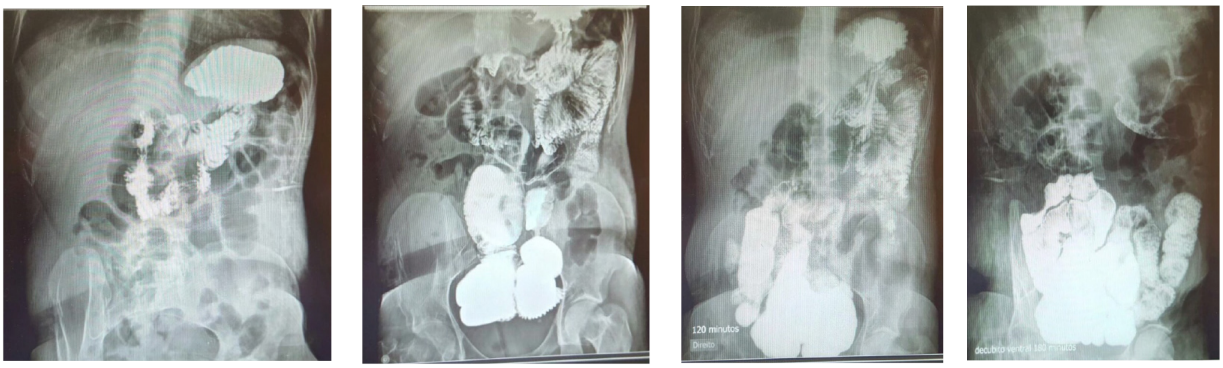

Figure 7, 8, 9 and 10 - Small bowel follow-through X-ray showing dilation and mucosal thickening of distal jejunal and ileal loops.

Based on the low fecal calprotectin level, histopathological findings, and imaging results, inflammatory bowel disease (Crohn's disease) was excluded, and the diagnostic hypothesis of NSAID-induced enteritis was suggested.

After undergoing endoscopic balloon dilation during enteroscopy, the patient presented with significant clinical improvement and was discharged on mesalazine therapy, with recommendations for continued outpatient follow-up.

DISCUSSION

NSAIDs are among the most widely prescribed medications worldwide, mainly for the treatment of osteoarthritis, musculoskeletal pain, rheumatoid arthritis, and other inflammatory conditions. However, they have adverse effects that can affect the entire gastrointestinal tract mucosa, compromising its functions such as absorption and digestion.[1-5]

The small intestine, particularly the distal segments, as well as the colon, are susceptible to the various deleterious effects of NSAIDs. In the ileocecal region, a wide range of NSAID-induced lesions may occur, such as erosions, ulcers, strictures, perforations, and diaphragm-like lesions, which may lead to intestinal obstruction.[4,6] When the colonic mucosa is affected, NSAID-related colitis may mimic inflammatory bowel disease, exacerbate pre-existing colitis, or complicate diverticular disease. Although intestinal injury related to NSAID use is common, the proportion of patients who develop significant clinical signs and symptoms of enteropathy remains relatively small. Approximately two-thirds of NSAID users show some degree of intestinal inflammation.[5-7]

NSAIDs act by inhibiting the activity of cyclooxygenase (COX) enzymes, resulting in blockade of prostaglandin, prostacyclin, and thromboxane synthesis. COX-1 plays a role in maintaining gastroduodenal mucosal integrity, vascular homeostasis, platelet aggregation, and modulation of renal plasma flow. COX-2 is generally undetectable in most tissues, but

its expression increases during inflammatory processes. It is constitutively expressed in the brain, kidney, and bone, and is of major importance in modulating glomerular blood flow and fluid–electrolyte balance.[3-5]

Prostaglandins have vasodilatory action and are associated with physiological effects in the renal, cardiovascular, and gastrointestinal systems. Therefore, NSAIDs that non-selectively block cyclooxygenases predispose patients to adverse effects such as acute gastroduodenal mucosal lesions, ulcers, esophagitis, enteritis, reactivation of inflammatory bowel disease, diverticulitis and diverticular perforation, colonic ulcers, as well as renal (dose-dependent) and hepatic injury.[3-5]

NSAID-related injury can also be local. At the mucosal level, the mechanisms of damage include inhibition of protective prostaglandins, alterations in blood flow, and increased intestinal permeability. Mucosal damage may lead to inflammation and ulceration, followed by reparative fibrosis and stricture formation. Proton pump inhibitor (PPI)-induced gastric acid suppression is unlikely to protect against NSAID-induced small bowel injury. In attempts to reduce gastroduodenal adverse effects, the use of enteric-coated, sustained-release, or slow-release NSAIDs may have shifted the site of injury to the distal small intestine and colon, since after ingestion or biliary excretion a high local drug concentration is required to increase intestinal permeability, which appears to be a prerequisite for NSAID-induced enteropathy.[6-12] This increase in mucosal permeability may be associated with bacterial overgrowth and is more frequently linked to NSAIDs that undergo enterohepatic circulation, as drug secretion into bile leads to repeated exposure of the intestinal mucosa to the toxic compound.[4-8]

The clinical presentation of most NSAID-induced lesions is commonly subclinical and often unrecognized. When present, signs and symptoms are nonspecific and may include: iron-deficiency anemia and/or bleeding from ulcers; hypoalbuminemia or malabsorption due to enteropathy; intermittent or complete intestinal obstruction; watery or bloody diarrhea; and acute abdomen due to perforation or obstruction. In chronic disease, alternating constipation and diarrhea may occur; abdominal pain may be intermittent; food intolerances may develop; and additional symptoms may arise from malabsorption, such as hypovitaminosis, hypokalemia, hypocalcemia, and their consequences. The typical patient is one using NSAIDs for a rheumatologic condition, such as osteoarthritis or rheumatoid arthritis. The relationship between NSAID use and diagnosis may range from a few days to several years.[6-9]

Intestinal diaphragms are considered pathognomonic lesions of NSAID-related injury. They are strictures (Figure 1), probably resulting from a cicatricial reaction secondary to ulcerative lesions. These lesions consist of thin, concentric septa, leading to the formation of a diaphragm with a narrowed lumen (Figure 2). They are usually multiple, most often found in the mid-small intestine, but have also been described in the ileum and colon. Histologically, they are characterized by submucosal fibrosis with normal overlying epithelium, and in some cases ulceration may be found at the diaphragm tip. The mucosa between diaphragms is normal. They are causes of subacute obstruction, but on abdominal radiographs they are difficult to visualize, appearing as exaggerated circular constrictions. During laparotomy, the surgeon should be alerted to this possibility, since the external appearance of the intestine may seem normal and the lesion is difficult to palpate. For this

reason, intraoperative enteroscopy becomes important.[9-12]

The diagnosis of NSAID-induced enteropathy is based on clinical presentation, laboratory tests, imaging, and histopathology, while also excluding more common causes of enteritis.

Imaging modalities such as capsule endoscopy, enteroscopy, and colonoscopy may support the diagnosis of NSAID-induced lesions, such as erosions, ulcers (Figure 4), or colitis. However, there are no pathognomonic findings on these examinations, nor is histology specific. Therefore, the differential diagnosis should include infectious etiologies (e.g., Campylobacter, Yersinia, cytomegalovirus, tuberculosis), irritable bowel syndrome, ischemia, radiation enteritis, vasculitis, and other drug-induced injuries (e.g., potassium chloride tablets).[3-9]

NSAID-induced lesions—except strictures and diaphragms—generally improve or resolve completely after drug discontinuation. Endoscopic findings such as a "cobblestone" appearance, longitudinal ulcers, or inflammatory polyps, as well as histological findings of granulomas, crypt abscesses, or crypt distortion, should suggest Crohn's disease rather than NSAID-induced injury. Similarly, the presence of vasculitis on biopsy would favor a collagen vascular disease.[8-12]

The mainstay of treatment for NSAID-induced enteritis is discontinuation of the offending drug. In non-stenotic ileocecal lesions, withdrawal of NSAIDs usually results in considerable clinical improvement. A follow-up colonoscopy six to eight weeks later should confirm partial or complete resolution of ulcerations, enteritis, or colitis. If disease persistence or worsening is observed, Crohn's disease or other etiologies must be considered.[10-13]

Obstructive symptoms due to strictures do not improve solely with drug discontinuation. Strictures or diaphragms accessible to endoscopy may be managed with balloon dilation (Figure 5) or electrocision (Figure 6). However, diaphragm-type strictures tend to be multiple and frequently require intestinal segment resection. Surgery is also indicated for other NSAID-induced complications, such as significant hemorrhage or perforation, and when malignant neoplasia cannot be reliably excluded.[8-16]

CONCLUSION

NSAIDs are among the most widely prescribed medications worldwide; therefore, the consequences of their use must be well recognized. However, NSAID-induced enteritis remains a neglected and underdiagnosed condition. It should be considered in patients using NSAIDs who present with abdominal pain associated with signs and symptoms of partial intestinal obstruction, with or without diarrhea.

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EDITORIAL AND REVIEW

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