



## Nonsteroidal anti-inflammatory drug-induced colopathy: an uncommon cause of positive immunochemical faecal occult blood test in the program for colorectal cancer screening

Kolopatija izazvana nesteroidnim antiinflamatornim lekovima: redak uzrok pozitivnog imunohistohemijskog fekalnog testa na okultno krvarenje u programu skrininga kolorektalnog karcinoma

Brigita Smolović\*†, Ljiljana Vučković\*‡, Sanja Borozan§, Batrić Vukčević\*

University of Montenegro, \*Faculty of Medicine, Podgorica, Montenegro; Clinical Center of Montenegro, †Department of Gastroenterohepatology, ‡Department of Pathology, §Department of Endocrinology, Podgorica, Montenegro

### Abstract

**Introduction.** Nonsteroidal anti-inflammatory drug-induced colopathy is an uncommon condition associated with the long-term use of enteric-coated and slow-release nonsteroidal anti-inflammatory drugs. This paper presents a case of colopathy showing no symptoms or signs, discovered by a positive immunochemical faecal occult blood test. **Case report.** Performed within the framework of the National Program for Screening of Colorectal Cancer, the immunochemical faecal occult blood test was positive in a 56-year-old female patient. The colonoscopy revealed three lesions in the right colon: one erosion-ulceration and two concentric "diaphragm-like" strictures passable by the endoscope. The patient reported that she had been taking diclofenac 100 mg twice a day for the past seven years. After withdrawing the offending drug, the second colonoscopy indicated a marked improvement in the colonic mucosa while the "diaphragm-like" strictures persisted. **Conclusion.** The cases of nonsteroidal anti-inflammatory drug-induced colopathy are likely to become more frequent. It would be, therefore, advisable to consider the long-term use of such drugs as being a possible factor that leads to mucosal injury, particularly in the right colon, as well as being a rare reason for a positive immunochemical faecal occult blood test.

### Key words:

colorectal neoplasms; diagnosis; feces; occult blood; colonic diseases; anti-inflammatory agents; treatment outcome.

### Apstrakt

**Uvod.** Kolopatija izazvana nesteroidnim antiinflamatornim lekovima je retko stanje uslovljeno dugotrajnim uzimanjem entero-rezistentnih i sporo-oslobađajućih nesteroidnih antiinflamatornih lekova. U radu je prikazana kolopatija izazvana nesteroidnim antiinflamatornim lekovima, bez ispoljenih simptoma ili znakova, otkrivena pozitivnim imunohistohemijskim fekalnim testom na okultno krvarenje. **Prikaz bolesnika.** U okviru Nacionalnog programa skrininga kolorektalnog karcinoma, imunohistohemijski fekalni test na okultno krvarenje je bio pozitivan kod 56-godišnje bolesnice. Kolonoskopski su nađene tri lezije desnog kolona: erozija-ulceracija i dve koncentrične „dijafragmi-slične” strikture prolazne za endoskop. Detaljnom anamnezom utvrđeno je da je bolesnica uzimala diklofenak od 100 mg, dva puta dnevno, tokom poslednjih sedam godina. Nakon isključivanja diklofenaka, kontrolnom kolonoskopijom je ustanovljeno značajno poboljšanje sluznice kolona, uz zaostale „dijafragmi-slične” strikture. **Zaključak.** Učestalost kolopatije izazvane nesteroidnim antiinflamatornim lekovima će vrlo verovatno biti sve veća. Zbog toga bi bilo preporučljivo uzeti u obzir dugotrajnu upotrebu ovih lekova kao mogući faktor koji dovodi do oštećenja sluznice, posebno u desnom kolonu, ali i kao retki uzrok pozitivnog imunohemijskog fekalnog testa na okultno krvarenje.

### Ključne reči:

kolorektalne neoplazme; dijagnoza; stolica; okultna krv; kolon, bolesti; antiinflamatorici; lečenje ishoda.

## Introduction

To avoid possible upper gastrointestinal side effects of non-steroidal anti-inflammatory drugs (NSAIDs), 'slow' or 'modified-release' preparations have been used increasingly, thus resulting in a higher incidence of colopathy, even though it remained rare<sup>1</sup>. Since NSAIDs have become so widely prescribed and some even available as over-the-counter drugs, increased awareness of this largely underestimated clinical condition is necessary in order to reduce morbidity by prevention, promote early recognition<sup>2</sup> and, thereby, mitigate further complications. The patient reported here was present with NSAID-induced colopathy, showing no symptoms or signs, with only a positive immunochemical faecal occult blood test (iFOBT).

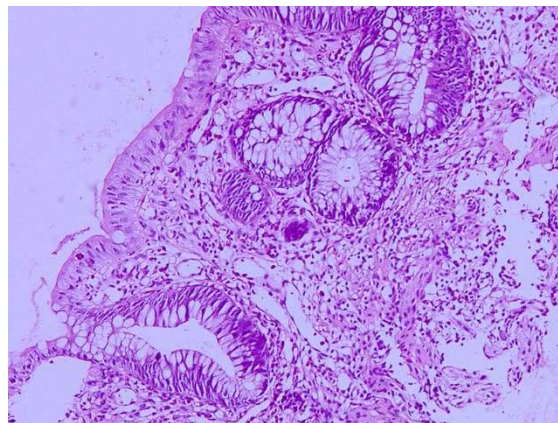
## Case report

A 56-year-old female was referred to a gastroenterologist due to a positive iFOBT: 477.173 ng/mL (reference value 0–99) performed in the National Colorectal Cancer screening program for the average-risk population. Physical examination and laboratory findings were

unremarkable. The leukocyte count was  $8.15 \times 10^9/L$ , the erythrocyte count was  $5.04 \times 10^{12}/L$ , the hemoglobin level was 137 g/L, and the mean corpuscular volume (MCV) was 82.3 fL. The colonoscopy revealed three lesions in the right colon: one erosion-ulceration and two concentric 'diaphragm-like' strictures with a mucosal lesion passable by the endoscope (Figure 1). The histopathological examination showed erosions of the mucosa, reactive changes in the epithelial cells, irregularity of the crypts, and mixed inflammatory infiltrates of lymphocytes, plasma cells, and eosinophilia in the lamina propria (Figure 2). The patient then reported that she had been taking diclofenac 100 mg twice a day for the past seven years because she had chronic lower backache. This statement on her long-term diclofenac use, along with the endoscopic and histological findings, led to the diagnosis of NSAID-induced colopathy. The NSAID was discontinued, and a colonoscopy was repeated eight weeks later. While the 'diaphragm-like' strictures persisted, the second colonoscopy showed a marked improvement in the colonic mucosa, with tissue restitution in segments containing mucosal lesions (erosions-ulcerations) (Figure 3). It was decided not to perform the balloon dilatation as the diaphragm strictures were passable by the endoscope.



**Fig. 1 – Diaphragm disease on the first colonoscopy.**



**Fig. 2 – Mixed inflammatory infiltrates in the lamina propria, irregularity of the crypts (hematoxylin & eosin staining, 100×).**



**Fig. 3 – Discontinuation of the non-steroidal antiinflammantory drug: a marked improvement in the colonic mucosa on the second colonoscopy.**

## Discussion

Despite the extensive use of NSAIDs in the general population, NSAIDs-induced colopathy is a condition that often goes unrecognized or even misdiagnosed<sup>3</sup>. Symptomatic patients are usually present with chronic (median 3 months) and multiple symptoms<sup>1</sup>, such as anaemia, rectal bleeding, abdominal pain, diarrhoea, obstruction, perforation, and peritonitis<sup>4,5</sup>.

In the case reported here, the patient had no symptoms or signs; she only had a positive iFOBT, accompanied by a history of taking diclofenac for seven years. In support of this finding, the literature data does indicate the majority of cases to be asymptomatic, with a diagnosis made incidentally during the investigations of bowel symptoms or upon endoscopic examination<sup>4,5</sup>.

NSAID-induced colopathy usually involves the right colon due to a higher concentration of the enteric-coated and slow-release preparations of NSAIDs on this site<sup>6</sup>. The mechanism of NSAID-induced colopathy is still unclear. Since most NSAIDs undergo enterohepatic circulation, the proximal colon is directly exposed to the intact drug following a bacterial breakdown in the distal ileum, and herein the cecum acts as a reservoir<sup>2,7</sup>.

However, the duration of treatment is highly associated with the spectrum of endoscopic findings in NSAID-induced colopathy<sup>8</sup>: 51% of patients are reported to have either one or two lesions, while multiple diaphragms are seen in 33%. In our patient, the colonoscopy revealed two concentric "diaphragm-like" strictures passable by the endoscope, accompanied by mucosal lesions.

A histological diagnosis of NSAID colopathy can prove to be difficult. Consequently, a multidisciplinary approach is important, and correlations with the anamnesis, clinical and endoscopic data are crucial. There are no specific histopathological features of NSAID colopathy; most report non-specific inflammation with mixed inflammatory infiltrates (in some cases with lymphocyte dominance), erosions of the mucosa, and fibrosis of the lamina propria<sup>7</sup>. However, eosinophilia in the lamina propria, apoptosis of the epithelial cells, and penetration of lymphocytes into the superficial epithelium may indicate an NSAID injury.

Primary management of an NSAID colopathy is simple and includes the withdrawal of the offending NSAID. All 13 patients who had uncomplicated ulceration and had no strictures in the cohort described by Kurahara et al.<sup>5</sup> showed marked improvement on a repeated colonoscopy 3–10 weeks after withdrawing the NSAIDs. These results are similar to the case reported here. While the ulcers are likely to resolve, the strictures - already formed diaphragms - may sometimes persist despite the cessation of the NSAID use. Balloon dilatation proved to be effective in treating colonic and ileocolonic strictures, and surgery is reserved for multiple strictures or complications<sup>8,9</sup>. In the case presented here, balloon dilatation was not performed since the diaphragm strictures were passable by the endoscope.

In 1965, Ser Austin Bradford Hill published nine viewpoints for determining causality: the strength of association, consistency, specificity, temporality, biological

gradient, plausibility, coherence, experiment, and analogy. These viewpoints are regarded as the criteria for identifying causality in clinical practice even beyond epidemiological studies<sup>10</sup>. Although NSAID-induced colopathy is a rare event (yielding a small number of reports in literature), the systematic review by Munipalle et al.<sup>1</sup> provided an optimistic foundation for future research on the strength of association between the NSAID use and colonic lesions. The existence of several case reports and case series (which have been referenced in this paper) accounts for the consistency of this association. Still, the plausibility and coherence can be estimated with the knowledge of NSAID metabolism, even though the pathophysiology of colopathy is not yet fully understood. In the case presented here, the essential criterion of temporality is satisfied through the NSAID exposure occurring before the positive iFOBT. The lack of other causes of colonic lesions (such as inflammatory bowel disease, ischemic colitis, or vasculitis – assessed with endoscopy and histopathological examination), as well as other causes of positive iFOBT, result in the specificity of this adverse effect as the cause of colopathy. Küttner Magalhães et al.<sup>11</sup> consider the presence of colonic inflammation, ulcers, and diaphragm-like strictures to be pathognomonic for this disease. The amount of diclofenac that the patient had used, as well as the duration of the drug use, account for the biological gradient (the presence of a dose-response relationship) and the temporality, as previously stated by Aftab et al.<sup>7</sup>. Finally, the recovery of the eroded colonic mucosa after cessation of diclofenac acts as experimental evidence, under the suggestion that trial cessation of the NSAIDs should be implemented in the presence of colonic diaphragms<sup>1</sup>.

One of the most frequent tools used in adverse drug reaction assessment is the Naranjo probability scale. The scale features a list of weighted questions related to the following: the presence of previous reports on a specific reaction, the temporal relationship between the drug and the effect, alternative causes for the event, previous reactions to the same drug, and the drug dosage. The score ranges in four levels, from doubtful to definite adverse reaction. The Naranjo scale is frequently used for its simplicity and the fact that it is less time-consuming than other assessment tools<sup>12</sup>. The case presented herein scored positive on the questions related to the previous reports (1 point), the temporal sequence between the drug and the effect (2 points), the improvement of the symptoms after discontinuation of the drug (1 point), the lack of other alternative causes of this effect (2 points; a decision was made for this answer to be positive since the endoscopic and histological examination failed to identify any other causes of colonic lesions), and the presence of objective evidence of the effect (1 point, with a detailed endoscopic and histological description of the disease). There were no points on questions regarding the repeated use of the drug, the use of a placebo, the toxic concentration of the drug, the influence of different drug dosages, and the presence of previous exposure and effects – because these criteria were not applicable in this case. The

total score was 7, amounting to a probable adverse reaction to the drug.

Given these facts, it was concluded that diclofenac was the causative agent of colopathy in this patient. Future research should aim at understanding the pathophysiology of this adverse effect, as well as to describe its true prevalence.

## Conclusion

Due to the increased use of enteric-coated and slow-release NSAIDs, cases of NSAIDs-induced colopathy are likely to become more frequent. Therefore, it would be advisable to consider this entity as a rare reason for a positive iFOBT.

## R E F E R E N C E S

1. *Munipalle PC, Garud T, Light D.* Diaphragmatic disease of the colon: systematic review. *Colorectal Dis* 2013; 15(9): 1063–9.
2. *Tonolini M.* Acute nonsteroidal anti-inflammatory drug-induced colitis. *J Emerg Trauma Shock* 2013; 6(4): 301–3.
3. *Margolius DM, Cataldo TE.* Nonsteroidal anti-inflammatory drug colopathy mimicking malignant masses of the colon: a report of three cases and review of the literature. *Am Surg* 2010; 76(11): 1282–6.
4. *Masannat AY, Harron M, Harinath G.* Nonsteroidal anti-inflammatory drugs-associated colopathy. *ANZ J Surg* 2010;80(1–2): 96–9.
5. *Kurahara K, Matsumoto T, Iida M, Honda K, Yao T, Fujishima M.* Clinical and endoscopic features of nonsteroidal anti-inflammatory drug-induced colonic ulcerations. *Am J Gastroenterol* 2001; 96(2): 473–80.
6. *Mokhtare M, Valizadeh SM, Emadian O.* Lower gastrointestinal bleeding due to Non-steroid Anti-inflammatory Drug-induced Colopathy Case Report and Literature Review. *Middle East J Dig Dis* 2013; 5(2): 107–11.
7. *Aftab AR, Donnellan F, Zeb F, Kevans D, Cullen G, Courtney G.* NSAID-induced colopathy. A case series. *J Gastrointestin Liver Dis* 2010; 19(1): 89–91.
8. *Püspök A, Kiener HP, Oberhuber G.* Clinical, endoscopic, and histologic spectrum of nonsteroidal anti-inflammatory drug-induced lesions in the colon. *Dis Colon Rectum* 2000; 43(5): 685–91.
9. *El Hajj I, Hawchar M, Sbarara A.* NSAID-induced colopathy: case report and review of the literature. *J Med Liban* 2009; 57(4): 274–6.
10. *Fedak KM, Bernal A, Capshaw ZA, Gross S.* Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerg Themes Epidemiol* 2015; 12: 14.
11. *Küttner Magalhães R, Ferreira JM, Pedroto I.* Nonsteroidal anti-inflammatory drug (NSAID)-induced colopathy with diaphragm-like strictures. *J Gastrointestin Liver Dis* 2014; 23(1): 9.
12. *Belbekar MN, Taur SR, Munshi RP.* A study of agreement between the Naranjo algorithm and WHO-UMC criteria for causality assessment of adverse drug reactions. *Indian J Pharmacol* 2014; 46(1): 117–20.

Received on October 4, 2018.  
Revised on January 3, 2019.  
Accepted on January 11, 2019.  
Online First January, 2019.