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An uncommon entity in colorectal screening program
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 such a case of colopathy showing no symptoms or signs, which discovered by a positive immunochemical faecal occult blood test. **Case report.** Performed within the framework of the National Program for Screening of Colorectal Cancer, a immunochemical faecal occult blood test was positive in 56-years-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 daily for the past seven years. After withdrawal of the offending drug, the second colonoscopy indicated 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 therefore be advisable to take long-term use of such drugs into consideration as being a possible factor that leads to mucosal injury, particularly in the right colon, as well as their being a rare reason for a positive immunochemical faecal occult blood test.

**Key words:**
colopathy; colon diaphragm disease; "diaphragm-like" stricture; nonsteroidal anti-inflammatory drugs; immunochemical faecal occult blood test.

**Abstrakt.**

**Uvod.** Nesteroidnim antiinflamatornim lekovima povezana kolopatija je retko stanje uslovljeno dugotrajnim uzimanjem crevno-obloženih i sporo-oslobadajućih nesteroidnih antiinflamatornih lekova. Ovaj rad predstavlja nesteroidnim antiinflamatornim lekovima povezanu kolopatiju koja ne pokazuje simptome ili znake, a otkrivena je 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 pacijentkinje. Na kolonoskopiji su nađene tri lezije desnog kolona: erozija-ulceracija i dve koncentrične "diagragmi-slične" strikture prolazne za endoskop. Detaljnom anamnezom saznajemo da je pacijentkinja uzimala diklofenak od 100 mg dva puta dnevno tokom poslednjih sedam godina. Nakon isključivanja diklofenaka, kontrolna kolonoskopija je pokazala značajno poboljšanje služnice kolona, uz zaostale "diafragmi-slične" strikture. **Zaključak.** Pacijenti sa nesteroidnim antiinflamatornim lekovima povezanom kolopatijom će vrlo verovatno biti sve češći. Zbog toga bi bilo preporučljivo uzeti u obzir dugotrajnu upotrebu ovih lekova kao mogući faktor koji dovodi do ozlede služnice, posebno u desnom kolonu, ali kao i retkog uzroka pozitivnog imunoheminskog fekalnog testa na okultno krvarenje.
Introduction

To avoid possible upper gastrointestinal side effects of non-steroidal antiinflammatory drugs (NSAIDs), ‘slow’ or ‘modified release’ preparations have been increasingly coming into use, resulting in an higher incidence of colopathy, although it remained rare. Since NSAIDs have grown so widely prescribed and some available as over-the-counter drugs, an increased awareness of this largely underestimated clinical condition is necessary in order to reduce morbidity by prevention, promote early recognition and thereby mitigate further complications. We reported here the patient presented with NSAID-induced colopathy, without any symptoms or signs and 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 8.15x10⁹/L, the erythrocyte count was 5.04x10¹²/L, the hemoglobin level was 137g/L, and the mean corpuscular volume (MCV) was 82.3fL. 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 (Fig. 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 (Fig. 2). The patient then reported that she had been taking diclofenac 100 mg twice daily for the past seven years because she had chronic lower backache. This statement on her long-term diclofenac use, along with the endoscopic and histology finding, led to the diagnosis of NSAID-induced colopathy. The NSAIDs were discontinued and a colonoscopy was repeated eight weeks later. While the diaphragms persisted, the second colonoscopy showed a marked improvement in the colonic mucosa where there was tissue restitution in segments containing mucosal lesions (erosions-ulcerations) (Fig. 3). Balloon dilatation was decided not to be performed as the diaphragm strictures were passable by endoscope.

Discussion

Despite the extensive use of NSAIDs in the general population, NSAIDs-induced colopathy is the condition often goes unrecognized or misdiagnosed. Symptomatic patients usually present with chronic (median 3 months) and multiple symptoms, such as anaemia, rectal bleeding, abdominal pain, diarrhoea, obstruction, perforation and peritonitis.
In the case reported here, the patient had no symptoms or signs; she had only positive an 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 investigations of bowel symptoms or upon endoscopic examination. NSAID-induced colopathy usually involves the right colon due to a higher concentration of the enteric-coated and slow-release preparations of NSAIDs at this site. 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 bacterial breakdown in the distal ileum, herein the cecum acts as a reservoir. However, the duration of treatment is highly associated with the spectrum of endoscopic findings in NSAID-induced colopathy: 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. As a consequence, a multidisciplinary approach is important, and correlations with the anamnesis, clinical, and endoscopical data is 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. However, eosinophilia in the lamina propria, apoptosis of the epithelial cells, and penetration of lymphocytes into the superficial epithelium may indicate a NSAID injury.

Primary management of an NSAID colopathy is simple and includes withdrawal of the offending NSAID. All 13 patients who had uncomplicated ulceration and had no strictures in the cohort described by Kurahara et al. showed marked improvement on a repeat colonoscopy at 3–10 weeks after the withdrawal of the NSAIDs. This result is similar to the case reported here. While the ulcers are likely to resolve, strictures—already formed diaphragms—sometimes may persist in spite of cessation of the NSAID use. Balloon dilatation has been shown to be effective in the treatment of colonic and ileo-colonic strictures. Surgery is reserved for multiple strictures or complications. In the case presented here, balloon dilatation was not performed owing to the fact that the diaphragm strictures were passable by endoscope.

In 1965, Ser Austin Bradford Hill published nine viewpoints for determining causality: strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy. These viewpoints are regarded as criteria for identifying causality in clinical practice even beyond epidemiological studies. Despite the fact that NSAID-induced colopathy is a rare event (yielding a small number of reports in the literature), the systematic review by Munipalle et al. provided an optimistic basis for future research on the strength of association between NSAID use and colonic lesions. The existence of several case reports and case series (which have been referenced in this paper) account for the consistency of this association, while the plausibility and coherence can be estimated with the knowledge of NSAID metabolism, despite the fact that the pathophysiology of colopathy is not yet fully understood. In the case presented herein, 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 - which were 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. Kuttner Magalhaes et al. consider the presence of colonic inflammation, ulcers and diaphragm-like strictures to be pathognomonic for this disease 11. 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 6. Finally, the recovery of the eroded colonic mucosa after cessation of diclofenac acts as experimental evidence, in accordance with the suggestion that trial cessation of the NSAIDs should be implemented in the presence of colonic diaphragms 11.

One of the most frequent tools used in adverse drug reaction assessment is the Naranjo probability scale, featuring a list of weighted questions related to 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, as well as the drug dosage. The score ranges in four levels, from doubtful to definite adverse reaction. The Naranjo scale is frequently used owing to its simplicity and the fact that it is less time-consuming than other assessment tools 12. 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 due to the fact that 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 the detailed endoscopic and histological description of the disease). There were not any points on the questions regarding the repeated use of the drug, the use of a placebo, the toxic concentration of the drug, the influence of different drug dosage, and the presence of previous exposure and effects – owing to the fact that 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, a conclusion was reached 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. Also, it would therefore be advisable to take this entity into consideration as being a rare reason for a positive iFOBT.

References


Fig. 1 – Diaphragma disease on the first colonoscopy.

Fig. 2 – Mixed inflammatory infiltrates in the lamina propria, irregularity of the crypts, HE, 100x.
Fig. 3 – Discontinuation of the NSAID- a marked improvement in the colonic mucosa on the second colonoscopy.

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