

BOWEL LESIONS IN ANKYLOSING SPONDYLITIS. IS IT THE DISEASE OR THE TREATMENT?

M. Rimbasi, MD; Madalina Marinescu, MD; M.R. Voiosu, MD, PhD

“Carol Davila” University of Medicine and Pharmacy; Clinic of Internal Medicine, Gastroenterology Department, Colentina Clinical Hospital, Bucharest, Romania

ABSTRACT

Ankylosing spondylitis (AS) is one form of spondyloarthritis (SpA), a group which also includes psoriatic arthritis, Reiter's syndrome, enteropathic arthritis, Behçet's disease and juvenile idiopathic arthritis (see table 1 for diagnostic criteria) (1). The target organs are not only the joint, the axial skeleton and the entheses, but also among others, the gut.

Key words: Ankylosing spondylitis, spondyloarthritis, Reiter's syndrome

ILIITIS OF SPONDYLOARTHROPATHY OR SUBCLINICAL CROHN'S DISEASE?

Macroscopic signs of gut inflammation are reported in 29% to 49% of ankylosing spondylitis (AS) patients, whereas histologic inflammatory lesions are found in 25% to 62% (1-4). The lesions are histologically different and two types of inflammation, acute and chronic, could be distinguished – the classification of the inflammatory lesions is a morphologic interpretation and is not related to the duration of the disease (5). In AS, chronic lesions (39-52%) are significantly more frequent than acute lesions (10-15%) (3), especially in patients with a family history of SpA, AS, or Crohn's disease (CD) (6).

The chronic form closely resembles ileal CD (disturbed mucosal architecture; irregular, blunted, and fused villi; distorted crypts; lamina propria infiltrated by mononuclear cells), as it is characterized by the same prevalence of granulomas (7),

and ileitis associated with ankylosing spondylitis cannot be distinguished easily from CD, either macroscopically or microscopically (8) (figures 1 and 2). Moreover, ileocolonoscopy findings seem to have prognostic importance, as the presence of gut inflammation is related to a more severe clinical and radiological expression of the rheumatologic condition, and an important proportion of these patients with an initial subclinical chronic gut inflammation develop clinical-overt inflammatory bowel disease (IBD) (6).

Furthermore, there are similarities between the immune alterations in spondyloarthritis and CD (upregulation of the E-cadherin/catenin glycoprotein complex, expression of the alphaE/beta7 integrin, increase in the number of CD68+ macrophages in the bowel mucosa, increased CARD15 gene polymorphisms carrier frequency) (9), and patients with both diseases are significantly more closely related than controls (10), leading some to suggest that these are distinct clinical

Table 1. The Modified New York Criteria for Ankylosing Spondylitis (2)

Criteria components
1. Low back pain of at least 3 months' duration that improved by exercise and was not relieved by rest
2. Limited lumbar spinal motion in sagittal (sideways) and frontal (forward and backward) planes
3. Chest expansion decreased relative to normal values for sex and age
4. Bilateral sacroiliitis grade 2-4 or unilateral sacroiliitis grade 3 or 4*

*Grades are 0, normal; 1, possible; 2, minimal; 3, moderate; 4, completely fused (ankylosed).

Definite ankylosing spondylitis if criterion 4 and any one of the other criteria is fulfilled

Address for correspondence:

Mihai Rimbasi, MD, Gastroenterology Department Clinic of Internal Medicine, Colentina Clinical Hospital, 19-21 Stefan cel Mare Blvd, Zip Code 020125, Bucharest, Romania
email address: mrimbas@gmail.com



Figure 1. Video capsule endoscopy examination of a 45-year-old female patient with ankylosing spondylitis and no NSAID intake showing an aphthoid ulceration in the mid ileum (arrows).



Figure 2. Ileocolonoscopy examination in a 24-year-old female with Crohn's disease. Note the almost identical aspect of the aphthoid ulceration in the terminal ileum (arrow).



Figure 3. Video capsule endoscopy examination of a 57-year-old male patient with a NSAID-induced erythematous ulcerated small area in the proximal ileum (arrows).

phenotypes of a common immune mediated disease, possibly being expressed in a genetically different host.

In an extensive prospective study of the clinical evolution of spondyloarthritis, 123 patients who previously underwent an ileocolonoscopy were reviewed clinically after 2 to 9 years (11). In total, 7.7% of the AS patients who did not present with any clinical sign of gut abnormality developed inflammatory bowel disease during the disease course, in comparison with 0.05% of the population when randomly screened. All of these patients initially presented subclinical inflammatory gut lesions, and all but one had the features of chronic inflammation. These findings were responsible for the consideration that at the start these patients may have suffered from “subclinical CD” (12).

WHAT ABOUT NSAIDS?

Most patients with ankylosing spondylitis are treated with NSAIDs, and the bowel is a potential site for a variety of NSAID-induced injuries including erosions, ulcers or strictures, lesions that are usually asymptomatic (13, 14) (figure 3). Small bowel lesions are reported in patients taking NSAIDs in between 8.4 (for ulcers) and 55% (for mucosal breaks) of cases, versus 0.6-7%, res-

pectively, in nonusers (15-17), and the use of COX-2 selective agents does not seem to be protective (18).

Moreover, the use of enteric-coated, sustained-release, or slow-release NSAIDs may have shifted the damage to the distal small intestine and colon, in the attempt to decrease gastroduodenal side effects (19).

Findings on capsule endoscopy (20), double-balloon enteroscopy (21), and/or ileocolonoscopy may lend support to the diagnosis of NSAID-induced injury, although there is nothing endoscopically specific about NSAID-induced erosions, ulcers, or colitis. Histology is also nonspecific (8, 22).

Starting from the fact that it has been convincingly shown that NSAIDs increase gut permeability and thereby may exacerbate gut inflammation, and even reactivate quiescent IBD (23, 24), one question arises: what is the actual participation of NSAIDs to the bowel lesions?

Extensive ileocolonoscopy studies have however been carried out in patients with ankylosing spondylitis, all of whom were on or had received conventional NSAIDs long term (25). Many of these patients had macro- and microscopic ileitis with a variable proportion of patients having concurrent cecal or colonic inflammation (4), but there is a striking similarity of the macroscopic and microscopic features of these lesions to those found in mice subjected to long term COX-2 inhibition or absence (26, 27), just as if NSAIDs have played a role in the generation of those lesions.

CONCLUSION

There are many similarities between the bowel lesions from spondyloarthritis and Crohn's disease, including genetical background, pathogenesis, microscopic and macroscopic picture. Some go even further and suggest that this inflammation may represent subclinical Crohn's disease in patients with ankylosing spondylitis (7) and those patients with this chronic form of ileal inflammation have a more severe expression of their rheumatologic condition.

It seems also possible that part of the spondyloarthropathic small bowel involvement represents iatrogenic COX-2 driven damage as described in animals (28). And if so, then the most worrying aspect is that the severity and prognosis of the disease are in part dependent on the histopathologic features of this inflammation, but taking into consideration the complex treatment strategies in patients with SpAs, it is probably very hard to prove it in specially designed controlled trials.

ACKNOWLEDGEMENT

This work (“Bowel Lesions in Ankylosing Spondylitis. Is It the Disease or the Treatment?”) was supported through the research grant no. 320/2007, ClinicalTrials.gov Identifier: NCT00768950, entitled “The Characterization of Small Bowel and Colonic Involvement in Patients With Seronegative Spondyloarthritides”, financed by the Romanian Ministry of Education and Research – Executive Unit for Financing Higher Education and Scientific University Research (MEdC – UEFISCSU).

REFERENCES

- Dougados M, Hochemberg MC** – Why is the concept of spondyloarthropathies important? *Best Pract Res Clin Rheumatol* 2002;16: 495–505.
- Braun J, Sieper J** – Building consensus on nomenclature and disease classification for ankylosing spondylitis: results and discussion of a questionnaire prepared for the International Workshop on New Treatment Strategies in Ankylosing Spondylitis, Berlin Germany, 18–19 January 2002. *Ann Rheum Dis* 2002;61:61–67.
- Lee YH, Ji JD, Kim JS, et al** – Ileocolonoscopy and histological studies in Korean patients with ankylosing spondylitis. *Scand J Rheumatol* 1997;26:473–476.
- Leirisalo-Repo H, Turunen U, Stenman S, et al** – High frequency of silent inflammatory bowel disease in spondylarthropathy. *Arthritis Rheum* 1994;37:23–31.
- Cuvelier C, Barbatis C, Mielants H, et al** – Histopathology of intestinal inflammation related to reactive arthritis. *Gut* 1987;28:394–401.
- Mielants H, Veys EM, Goemaere S, et al** – Gut inflammation in the spondylarthropathies: Clinical, radiologic, biologic and genetic features in relation to the type of histology: A prospective study. *J Rheumatol* 1991;18:1542–1551.
- Smale S, Natt RS, Orchard TR et al** – Inflammatory bowel disease and spondyloarthropathy. *Arthritis Rheum* 2001;44:2728–2736.
- Adebayo D, Popat R, Thjodleifsson B, et al** – Granulomatous ileitis in a patient with ankylosing spondylitis. *Nat Clin Pract Gastroenterol Hepatol* 2007;6:347–51.
- Mielants H, De Keyser F.** – Bowel inflammation in rheumatic diseases: trigger or consequence. *Annals of the Rheumatic Diseases* 2005;64(Suppl 3):70.
- Thjodleifsson B, Bjarnason I, Thorvaldsson S et al** – A genealogical study in Iceland demonstrates a common genetic background for inflammatory bowel disease and ankylosing spondylitis. *Gastroenterology* 2005;128 (Suppl 2):A137–A137.
- Mielants H, Veys EM, De Vos M, et al** – The evolution of spondylarthropathies in relation to gut histology: I. Prospective study of the clinical spondylarthropathy. *J Rheumatol* 1995;22:2266–2272.
- Mielants H, Veys EM, Cuvelier C, et al** – The evolution of spondylarthropathies in relation to gut histology: Part III. Prospective study of the clinical evolution of spondylarthropathies in relation to the evolution of gut histology. *J Rheumatol* 1995;22:2279–2284.
- Adebayo D, Bjarnason I** – Is NSAID-enteropathy clinically more important than NSAID-gastropathy? *Postgrad Med J* 2006;82: 186–191.
- Kwo PY, Tremaine WJ** – Nonsteroidal anti-inflammatory drug-induced enteropathy: Case discussion and review of the literature. *Mayo Clin Proc* 1995; 70:55–61.
- Allison MC, Howatson AG, Torrance CJ, et al** – Gastrointestinal damage associated with the use of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1992; 327:749.
- Matsumoto T, Kudo T, Esaki M, et al** – Prevalence of non-steroidal anti-inflammatory drug-induced enteropathy determined by double-balloon endoscopy: a Japanese multicenter study. *Scand J Gastroenterol* 2008; 43:490–496.
- Hawkey CJ, Ell C, Simon B, et al** – Less small-bowel injury with lumiracoxib compared with naproxen plus omeprazole. *Clin Gastroenterol Hepatol* 2008; 6:536–544.
- Maiden L, Thjodleifsson B, Seigal A, et al** – Long-Term effects of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 selective agents on the small bowel: A cross-sectional capsule enteroscopy study. *Clin Gastroenterol Hepatol* 2007; 5:1040–1045.
- Bjarnason I, Hayllar J, MacPherson AJ, Russell AS** – Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans. *Gastroenterology* 1993; 104:1832–1847.
- Graham DY, Opekun AR, Willingham FF, Qureshi WA** – Visible small-intestinal mucosal injury in chronic NSAID users. *Clin Gastroenterol Hepatol* 2005; 3:55–59.
- Hayashi Y, Yamamoto H, Kita H, et al** – Non-steroidal anti-inflammatory drug-induced small bowel injuries identified by double-balloon endoscopy. *World J Gastroenterol* 2005; 11:4861–4864.
- Kwo PY, Tremaine WJ** – Nonsteroidal anti-inflammatory drug-induced enteropathy: Case discussion and review of the literature. *Mayo Clin Proc* 1995; 70:55–61.
- Sigthorsson G, Tibble J, Hayllar J, et al** – Intestinal permeability and inflammation in patients on NSAIDs. *Gut* 1998; 43:506–511.
- Kaufman HL, Taubin HL** – Nonsteroidal antiinflammatory drugs activate quiescent inflammatory bowel disease. *Ann Intern Med* 1987;107:513–515.
- De Vos M, Cuvelier C, Mielants H, et al** – Ileocolonoscopy in seronegative spondylarthropathy. *Gastroenterology* 1989;96:339–344.
- Sigthorsson G, Simpson RJ, Walley M, et al** – COX-1 and 2, intestinal integrity and pathogenesis of NSAID-enteropathy in mice. *Gastroenterology* 2002;122:1913–1923.
- Anthony A, Dhillon AP, Sim R, et al** – Ulceration, fibrosis and diaphragm-like lesions in the caecum of rats treated with indomethacin. *Aliment Pharmacol Ther* 1994;8:417–424.
- Bjarnason I, Takeuchi K, Simpson R** – NSAIDs: the Emperor's new dogma? *Gut* 2003;52:1376–1378.