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TOPIC HIGHLIGHT

Walter Fries, MD, *Series Editor*

Gastrointestinal lesions associated with spondyloarthropathies

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Abstract

Subclinical gut inflammation has been described in up to two-thirds of patients with spondyloarthropathies (SpA). Arthritis represents an extra-intestinal manifestation of several gastrointestinal diseases, including inflammatory bowel disease (IBD), Whipple's disease, Behcet's disease, celiac disease, intestinal bypass surgery, parasitic infections of the gut and pseudomembranous colitis. Moreover about two-thirds of nonsteroidal anti-inflammatory drug users demonstrate intestinal inflammation. Arthritis may manifest as a peripheral or axial arthritis. The spondyloarthropathy family consists of the following entities: ankylosing spondylitis, undifferentiated spondyloarthritis, reactive arthritis, psoriatic arthritis, spondyloarthritis associated with IBD, juvenile onset spondyloarthritis. This topic reviews the major gastrointestinal manifestations that can occur in patients with SpA and in nonsteroidal anti-inflammatory drugs users.

Key words: Gastrointestinal diseases; Inflammation; Inflammatory bowel diseases; Crohn's disease; Arthritis; Spondylosis; Ankylosing spondylitis; Nonsteroidal anti-inflammatory drugs

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INTRODUCTION

Arthritis is a recognized extra-intestinal manifestation of several gastrointestinal diseases including inflammatory bowel disease (IBD). Arthritis occurs in 9%-53% of patients with IBD[1-3], and is more prevalent in patients with large bowel disease than in patients with small bowel involvement (42% *vs* 23%)[1]. It may manifest as a peripheral or axial arthritis. Peripheral arthritis includes two different patterns: a pauciarticular arthritis (type 1 arthropathy) striking large joints, which usually accompanies flares of IBD; and a polyarticular arthropathy (type 2 arthropathy) which involves the small joints and is less often associated with flares of IBD[4].

Subclinical gut inflammation has also been described in up to two-thirds of patients with spondyloarthropathies (SpA)[5-9]; histologic gut inflammation was found in SpA in 30%-60% of cases[9]. The observation that the extra-intestinal symptoms generally improve when the gastrointestinal disease is treated, suggests that the association between these two clinical entities is related. The mechanism by which this occurs is not fully understood[1,7].

This topic will review the major gastrointestinal manifestations which can occur in patients having SpA and other diseases with bowel and joint involvement, and in patients having nonsteroidal anti-inflammatory drugs (NSAIDs) related intestinal injuries.

It is useful to begin with a short review of the gastrointestinal function.

GASTROINTESTINAL FUNCTION

The human gastrointestinal tract is not a complete

barrier, being permeable to some macromolecules[10]. Permeability increases in pathologic conditions including IBD[4], celiac disease[11,12], and with the administration of NSAIDs[13,14]. When permeability is increased the gastrointestinal tract is exposed to bacterial and dietary antigens.

The epithelial lining of the gastrointestinal tract includes specialized cells (M cells) which permit transepithelial transport of foreign material from the lumen to mucosal lymphoid tissues; it is evident that some microorganisms use the M cell transport system as a means to infect the mucosa[10,15]. The human intestine harbours a complex microflora composed of aerobic and anaerobic bacteria. In normal individuals antigenic exposure results in tolerance rather than immunity, but this local tolerance is broken in inflamed intestinal tissue. Patients with active IBD lose tolerance to their own bacterial flora, whether this loss of tolerance is a cause or a consequence of the IBD is not known[16-18].

IBD represents a good model for the pathological events that may predispose a host to extraintestinal manifestations. Active IBD is characterized by the following features: (1) A breach of gastrointestinal wall integrity; (2) Increased permeability to macromolecules; (3) Increased exposure to microbial and dietary antigens; (4) Loss of tolerance to own bacterial flora; (5) Host susceptibility to the increased antigenic load. There is also data to suggest that patients with SpA often have subclinical inflammation that may progress to IBD[1].

SpA

The term SpA is used to refer to a family of diseases characterized by inflammation of axial joints, asymmetric oligoarthritis and enthesitis[19]. The SpA family consists of the following entities: ankylosing spondylitis (AS); undifferentiated spondyloarthritis; reactive arthritis (Reiter syndrome); psoriatic arthritis; spondyloarthritis associated with IBD; juvenile onset spondyloarthritis.

The prevalence of SpA in the Caucasian population is 0.5%-2%, with a significant variation worldwide[20].

The need for a standardized approach to classification led to the development of the European Spondyloarthropathy Study Group (ESSG) classification criteria for SpA. According to the ESSG criteria, for a patient to be classified as having SpA he has to show chronic inflammatory back pain before the age of 40 years, persistence for at least 3 mo or asymmetrical synovitis, predominantly of the lower limbs (Table 1). A patient is classified as having spondyloarthritis if he has one or both entry criteria plus one of the following additional criteria: positive family history, psoriasis, IBD, urethritis, cervicitis or acute diarrhea within 1 mo before arthritis, buttock pain alternating between buttocks, enthesopathy or plain film radiographic evidence of sacroiliitis.

The ESSG classification criteria for SpA have been validated in population studies and have a good sensitivity of 75% and a specificity of 87%[21].

An alternative to the ESSC classification criteria is that proposed by Amor and colleagues[22] and considers clinical and historical symptoms, radiologic findings, genetic background and response to treatment (Table 2). These classification criteria are more complicated due to the incorporation of common extra-articular manifestations of disease including gastrointestinal manifestation, but they give improved sensitivity (85%) and specificity (95%). Of these, each criterion is assigned a weight (one or two points) and the resulting points are summed. A patient is considered as having a spondyloarthritis if the sum of the criteria scores is at least six.

A high percentage of patients with SpA (90% of patients with AS and 70% of patients with undifferentiated spondyloarthritis) are HLA-B27 positive. However, this marker is not diagnostic of SpA because a significant percentage of the general population is also positive. In the presence of inflammatory back pain, a positive test for HLA-B27 increases the likelihood of SpA[23].

SpA are associated with several extra-articular manifestations, including acute anterior uveitis[24], genital and skin lesions[25] and inflammatory gut lesions[8].

Table 1 European Spondyloarthropathy Study Group (ESSG) classification criteria for spondyloarthritis

Inflammatory spinal pain, or synovitis (asymmetrical, predominantly in lower limbs), and any one of the following:
Positive family history
Psoriasis
Inflammatory bowel disease
Alternate buttock pain
Enthesopathy

Table 2 Amor classification criteria for spondyloarthropathy

Clinical symptoms or past history of
Lumbar or dorsal pain at night, or lumbar or dorsal morning stiffness = 1
Asymmetrical oligoarthritis = 2
Buttock pain (buttock pain = 1, alternating buttock pain = 2)
Sausage-like finger or toe = 2
Heel pain = 2
Iritis = 2
Non-gonococcal urethritis or cervicitis accompanying, or within 1 mo before, the onset of arthritis = 1
Acute diarrhoea accompanying, or within 1 mo before, the onset of arthritis = 1
Presence of history of psoriasis and/or balanitis and/or of inflammatory bowel disease (ulcerative colitis, Crohn's disease) = 2
Radiological findings
Sacroiliitis (grade > 2 if bilateral, grade > 3 if unilateral) = 3
Genetic background
Presence of HLA-B27 and/or family history of ankylosing spondylitis, reactive arthritis, uveitis, psoriasis or chronic inflammatory bowel disease = 2
Response to therapy
Definite improvement of musculoskeletal complaints with NSAIDs in less than 48 h or relapse of the pain in less than 48 h if NSAIDs discontinued = 2
A patient is considered as having a spondyloarthropathy if the sum of the scores is 6 or more

Table 3 Histologic types of gut inflammation in patients with SpA

Acute	Chronic
Architecture preserved	Architecture disturbed
PMN infiltration	Irregular, blunted and fused villi
Granulocytes, lymphocytes, plasma cells in lamina propria	Distortion crypts
	Basal lymphoid follicles
	Sarcoid-like granulomas

Two histologic types of gut inflammation in patients with SpA can be distinguished: acute and chronic inflammation (Table 3). This classification refers to the morphologic characteristics and not to the onset or duration of the disease.

The acute type mimics the acute bacterial enterocolitis: the mucosal architecture is well preserved, there is a polymorphonuclear infiltration of the ileal villi and crypts, and an increased number of inflammatory cells (granulocytes, lymphocytes and plasma cells) in the lamina propria.

Acute lesions are mainly seen in patients with reactive arthritis.

The chronic type is often indistinguishable from Crohn's disease (CD): the mucosal architecture is clearly disturbed, the villi are irregular, blunted and fused; the crypts are distorted and the lamina propria is edematous and infiltrated by mononuclear cells. In some cases aphthoid ulcers and sarcoid-like granulomas are present. Chronic lesions are more present in undifferentiated SpA and AS[9].

Similarities are present between the immune alterations in SpA and CD, suggesting that these are probably distinct phenotypes of a common immune-mediated disease, possibly being expressed in a genetically different host; in fact, the mutations of the CARD15/NOD2 gene that have been associated with CD have not been found in AS[26]. These similarities are: an increased expression of α-E-β-7 in T-cells from patients with SpA and in the intestinal lymphocytes of patients with CD; an increased expression of epithelial A-cadherin; an increased expression of CD 163 positive macrophages in CD and SpA; relative contribution of T-helper 1 cells; presence of IgA antibodies to Saccharomyces cerevisiae.

According to current knowledge, there is a clinical relationship between gut and joint inflammation in SpA, and the gut could have an important pathogenic role[9]: the prevalence of gut inflammation in AS is higher in patients with associated peripheral arthritis than in patients without arthritis[6]; chronic lesions in the gut are associated with more advanced radiologic signs of sacroiliitis and spondylitis and with more destructive peripheral arthritis[27]; remission of joint inflammation is usually associated with a disappearance of gut inflammation, whereas the persistence of locomotor inflammation is mostly associated with the persistence of gut inflammation[28-31].

Clinical, genetic, histopathologic and immunologic data suggest that SpA and CD probably should be considered as distinct phenotypes of a common immune-mediated inflammatory disease pathway rather than as separate disease entities[9].

Patients with peripheral arthritis and AS are often found to have endoscopic and histologic signs of small bowel inflammation, and a fraction of these patients go on to develop clinically overt CD. Moreover, some patients with SpA have a form of sub-clinical CD in which locomotor inflammation is the only clinical expression. In a prospective long-term study at first investigation about 6% of patients with SpA did not present any sign of CD, but demonstrated gut inflammation on biopsy. They developed CD 2 to 9 years later[32].

Ileal and colonic mucosal ulcerations in patients with SpA can be detected by endoscopy. Endoscopic lesions were found in 44% of patients with SpA versus 6% of patients with other inflammatory arthritis and the most common endoscopic diagnosis was early CD (26%)[5].

It has been highlighted that a capsule endoscopy can provide important information on upper gastrointestinal pathology in patients with SpA in which there is small bowel involvement. Eliakim *et al*[33] have compared the diagnostic yield of capsule endoscopy with that of ileo-colonoscopy in the finding of small bowel lesions in patients with SpA; significant small bowel findings (erythema, aphthous, erosions) were detected by capsule endoscopy in 30% and by ileo-colonoscopy in only 9% patients with SpA.

The association between SpA and clinical or subclinical intestinal association has rarely been described in children. Conti *et al*[34] investigated a group of 129 children for suspected IBD, 31 of whom had signs of axial and/or peripheral arthropathy, and after ileo-colonoscopy with biopsy, 7 children had classic IBD, 12 had indeterminate colitis, and 12 had lymphoid nodular hyperplasia of the distal ileum as the main feature. All were HLA-B27 negative. These patients may be a population at risk of developing a full IBD phenotype. SpA may be the initial manifestation of systemic disorders such as IBD.

Ankylosing spondylitis

AS is the most common disease among the SpA; it is a chronic inflammatory disease of the axial skeleton characterized by back pain and progressive rigidity of the spine. AS usually affects young adults and an association with the human leukocyte antigen HLA-B27 was observed. The association with HLA-B27 is weaker in IBD-associated AS than in idiopathic AS. Radiographic changes of the hips are present in roughly 10% of patients[35]. Other organs, such as eyes, lungs, gut and heart can be affected. Up to two-thirds of patients with AS have subclinical gut inflammations shown either by endoscopy or histology, between 5% and 10% of cases of AS are associated with IBD. Despite these observations, systematic screening of AS patients by ileo-colonoscopy is not indicated in the absence of gut symptomatology as only a small proportion of AS patients with subclinical gut inflammation will develop IBD in the future[2].

Reactive arthritis

Reactive arthritis may occur after an enteric infection due to *Salmonella*, *Shigella*, *Yersinia* or *Campylobacter species* with an incidence ranging from 2% to 33%. In particular an increased risk of arthritis is associated with a *Yersinia* infection and the presence of the HLA-B27 genotype. Joint symptoms develop within 2-3 wk of developing diarrhea and involve knee, ankle, wrist, and sacroiliac joints. To confirm the clinical suspicion of reactive arthritis it is useful to demonstrate a pathogenic organism by stool culture or a rise of antibody titres. Antibiotic treatment may be effective during the diarrheal phase but not when arthritis is present[8,27,36].

OTHER DISEASES WITH BOWEL AND JOINT INVOLVEMENT

In addition to ulcerative colitis and CD, other illnesses have intestinal involvement and arthritis as prominent clinical features. These include Whipple's disease, Behcet's disease, celiac disease, intestinal bypass arthritis, parasitic rheumatism, and pseudomembranous colitis. These disorders are also considered in the differential diagnosis of patients with suspected IBD and arthritis.

Whipple's disease

Whipple's disease is due to an infection with *Tropheryma Whippelii* and may cause diarrhea, malabsorption and weight loss. Systemic infection is often associated with joint manifestations, involving the knee, the ankle and the wrist and sometimes it is associated with spondylitis and sacroiliac joint involvement. In some patients the articular symptoms develop prior to symptomatic enteric involvement. A small bowel biopsy is usually diagnostic. Whipple's disease requires long term antibiotic therapy[37].

Behcet's disease

Behcet's disease is characterized by oral and genital ulceration, iritis and occasionally by central nervous system involvement; oligoarticular, asymmetric arthralgia and arthritis may develop in 50% of patients involving the knee, the ankle, the wrist and the elbow. Mucosal ulceration of the small bowel is a frequent manifestation of Behcet's disease and may cause nausea, diarrhea, abdominal pain and distension. It is often difficult to distinguish from IBD[38,39].

Celiac disease

Celiac disease may be associated with arthritis in some patients; articular involvement was peripheral in 10%, axial in 8% and combined in 9%. The arthritis is typically non erosive and can be either oligo-or-polyarticular. Joint symptoms may precede gastrointestinal manifestations and respond to a gluten-free diet[11,12].

Intestinal bypass surgery

Intestinal bypass surgery is a surgical technique used for the treatment of obesity in the past. Arthritis affecting knee, wrist, ankle, shoulder and finger joints was recognized as a postoperative complication of this technique. Polyarthralgia and sometimes arthritis has been reported to occur weeks or years following surgery in 8% to 36% of patients[2,36].

Parasitic infections

Parasitic infections of the gut due to *Strongyloides stercoralis*, *Taenia saginata*, *Endolimax nana* and *Dracunculus medinensis* have been associated with a form of reactive arthritis[36].

Pseudomembranous colitis

Arthritis associated with pseudomembranous colitis has been described following antibiotic therapy, often affecting the large joints of the lower extremity. In a report of four patients, arthritis developed 9-35 d after the onset of diarrhea[36].

NSAIDS RELATED INTESTINAL INIURY

The distal small bowel and colon are susceptible to the dangerous effects of NSAIDs; although the proportion of patients who develop clinically important NSAID-induced enteropathy or colopathy is small, the intestinal injuries induced by NSAIDs, including erosions, ulcers, strictures and perforations, are common[13]. About two-thirds of NSAID users demonstrate intestinal inflammation[13,14,40]. In a case control study, patients with small or large bowel perforation or bleeding were more than twice as likely to be NSAID users[41]. In an autopsy study nonspecific small intestinal ulceration was much more common in those who had taken NSAIDs (8.4% *vs* 0.6%)[42]. A randomized, controlled trial revealed more mucosal breaks in a group of patients who used NSAIDs plus omeprazole compared with a group of patients who used COX-2 inhibitors. This study suggests relative protection of the COX-2 inhibitors compared with non-selective NSAIDs plus omeprazole against small bowel injury[43]. By contrast a non-randomized cohort study found similar rates and types of small bowel injury with long-term use of COX-2 selective agents versus NSAIDs[44].

Most NSAID-induced injuries are subclinical and go unrecognized. When present, symptoms and signs are nonspecific and may include: anaemia, bleeding from ulcers, hypoalbuminemia, intermittent or complete bowel obstruction from broad-based or diaphragm-like strictures, watery or bloody diarrhea and acute abdomen. The typical patient is one taking a NSAID for a rheumatic condition and the duration of NSAID use to time of diagnosis is widely variable (days to years)[41].

A pathognomonic lesion of NSAID injury is the diaphragm-like stricture, which is likely to be due to a scarring reaction secondary to ulcerative injury. These lesions are thin, concentric, diaphragm-like septa which are usually multiple in the mid-intestine but may be also present in the ileum and colon. Histologically, they are characterized by sub-mucosal fibrosis with normal overlying epithelium, apart from the tip of diaphragm,

which may be ulcerated; the mucosa between diaphragms is normal[14,45].

Capsule endoscopy, double-balloon enteroscopy and colonoscopy may help in the diagnosis of NSAID-induced injury, although there is nothing endoscopically specific about NSAID-induced gut lesions[46,47]. Histology is also nonspecific; the differential diagnosis should include: Campylobacter, Yersinia, Cytomegalovirus, TB infections, IBD, ischemia, radiation enteritis, vasculitides and other drugs. The NSAIDs-induced lesions generally improve upon withdrawal of the drug.

CONCLUSION

An important role of the gut in the pathogenesis of SpA and for an overlap between SpA and CD is supposed. It is not clear if SpA and CD should be considered as distinct phenotypes of common immune-mediated inflammatory disease pathways or separate disease entities. Systematic screening of SpA patients by ileo-colonoscopy is not indicated in the absence of gut symptomatology but these patients may be a population at risk of developing a full IBD phenotype. It is important to know that there are other diseases with bowel and joint involvement like Whipple's disease, celiac disease and so on and that two-thirds of NSAID users demonstrate intestinal nonspecific inflammation.

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