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# Rheumatologic Complications of Inflammatory Bowel Diseases

by Arthur Kavanaugh, Abha Goyal Singh

Rheumatologic manifestations are the most common extra-intestinal complications in patients with inflammatory bowel disease (IBD), and have been reported to occur among 6-46% of IBD patients. The immunopathophysiology may relate to aberrant lymphocyte trafficking from the inflamed gut into the articular synovium as well as extra-articular tissues, especially the entheses. There are multiple potential clinical presentations including peripheral arthritis, spinal or axial arthritis and enthesitis. Peripheral arthritis accompanied IBD may be oligo-articular or polyarticular, with the former occurring more early in the disease course, and sometimes transitioning to the latter. Much of data relevant to the treatment of peripheral arthritis related to IBD comes from the literature on the treatment of psoriatic arthritis (PsA) with peripheral arthritis. Treatment options include disease modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX), sulfasalazine, leflunomide and apremilast. Among biologic agents, tumor necrosis factor inhibitors (TNFi) have the longest and largest clinical data supporting their substantial efficacy. The most relevant data concerning the treatment of spinal, also called axial, arthropathies comes from studies of patients with ankylosing spondylitis (AS). While non-steroidal anti-inflammatory agents (NSAIDs) and specific cyclooxygenase 2 (COX2) inhibitors are effective in both peripheral and axial arthritis, their use in IBD must take into account their potential effects on the bowel. While DMARDs are ineffective for axial arthritis, TNFi are highly effective. IL-17 inhibitors, which have recently been shown effective in PsA and AS, would not be a good choice for IBD related arthritis as they can have a detrimental effect on bowel inflammation.

## INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, are chronic autoimmune diseases of the gastrointestinal tract that affect over 1.6 million Americans, with a rising global incidence and prevalence.<sup>1</sup> These diseases cause significant morbidity, with frequent hospitalizations, surgery, and use of corticosteroids and immunosuppressive medications. Annual direct and indirect healthcare costs of IBD are

estimated between \$14.6-31.6 billion, with over 50% attributable to hospitalization-related costs. Beyond gastrointestinal symptoms and complications, IBD is a systemic disease that is frequently accompanied by extraintestinal manifestations (EIM) involving virtually every organ in the body. Extraarticular manifestations can add to the detrimental impact that IBD has on affected patients in terms of pain, quality of life and functional status.

Among extraintestinal manifestations of IBD, those affecting the musculoskeletal system are among the most common, and have been reported in several series to affecting from 6 to 46% patients.<sup>2,3</sup> Indeed, from a rheumatology standpoint, IBD-associated arthritis, or 'enteropathic arthritis', has been considered to be

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within the family of conditions grouped under the title 'spondyloarthropathies' (SpA). Also included within this category are psoriatic arthritis (PsA), ankylosing spondylitis (AS) and reactive arthritis. There is growing understanding of the immunopathophysiology of these conditions, highlighting common alterations in the immune and inflammatory responses common to diseases with potentially diverse clinical manifestations. In addition, there are increasing therapeutic options for patients with SpA, with some agents more or less effective for specific manifestations. A number of agents used to treat SpA have also shown efficacy in IBD, highlighting some common aspects of immune dysregulation across these conditions.

### Epidemiology

Joint involvement is the most common extraintestinal manifestation of IBD, affecting up to 46% of patients.<sup>2,3</sup> In addition to non-inflammatory arthralgias without actual swollen joints, seen in 8-30% of patients, inflammatory arthritis of the spine (also called axial disease) or the peripheral joints have been clearly demonstrated. Early reports classified peripheral arthropathies into type I pauciarticular (four or fewer peripheral joints) or type II polyarticular (five or more peripheral joints involved). More recent work has shown that patients may present early with fewer joints involved and over time evolve into a polyarticular phenotype. In addition to peripheral arthritis, patients may have axial arthritis. Such patients typically present with inflammatory back pain, generally defined as pain that occurs in younger adults (e.g. less than 40 years of age), is worse in the morning, improves with use and responds clinically to non-steroidal anti-inflammatory drug (NSAID) therapy. Another area of inflammation common to SpA conditions is enthesitis. Entheses are areas where tendons, ligaments and joint capsules insert into bone. Inflammation at the entheses is not only common, but may be an early and perhaps etiopathogenically relevant aspect of SpA, including IBD related arthritis. While musculoskeletal involvement most often develops following the diagnosis of IBD, in a small subset of patients (<5%) articular symptoms may precede IBD. Risk factors for articular manifestations among IBD patients have been suggested to include a family history of IBD, appendectomy, cigarette smoking and the presence of other extraintestinal manifestations such as erythema nodosum or pyoderma gangrenosum.<sup>4</sup> Patients with extensive colitis (rather than proctitis) patients with

colonic Crohn's disease have been suggested to be more likely to develop articular EIMs.

As more effective therapies have become available for the treatment of peripheral arthritis, axial arthritis and enthesitis, early recognition has become even more important. Some signs and symptoms that could prompt consideration of inflammatory musculoskeletal involvement in an IBD patient include chronic (e.g. more than three months) back pain, peripheral joint pain and swelling, enthesial tenderness and dactylitis (swelling of an entire digit due to abundant arthritis and tenosynovitis).<sup>5</sup>

### Pathophysiology

Rheumatologic manifestations in patients with IBD have been hypothesized to be due to articular and peri-articular homing of activated intestinal lymphocytes; these data suggest the presence of a 'gut-joint axis'.<sup>6</sup> In patients with IBD, lymphocytes of various subtypes may access articular sites using multiple adhesion molecules and their counter receptors. In addition to aberrant lymphocyte homing, dysbiosis, or an alteration in the diversity of gut microbiota, may be another shared pathophysiological mechanism between IBD and IBD-associated arthritis.

### Clinical Presentation and Diagnosis

#### Peripheral Arthropathies

Peripheral arthritis in IBD typically presents as inflammatory arthritis, with joint pain and swelling. Traditionally, IBD-associated arthritis had been considered to be generally non-erosive and non-destructive; however, there is the possibility that these considerations were tautologic, and therefore this may not be an accurate distinction.<sup>3,4,5</sup>

Early reports classified peripheral arthropathies into so-called type I pauciarticular (four or fewer peripheral joints) or type II polyarticular (five or more peripheral joints involved) (Table 1). More recent work has shown that patients may present early with fewer joints involved and over time evolve into a polyarticular phenotype. The most important distinction is the number of joints involved. Patients with oligoarticular disease are more likely to have a more favorable prognosis over time. In contrast, those with polyarticular disease, either at onset or later in the disease course, are more likely to suffer impaired functional status and quality of life. IBD associated arthritis, as a SpA related condition,

**Table 1. Characteristics of Peripheral Arthropathies in Patients with IBD with Articular Extra-Intestinal Manifestations**

	Type 1 (Pauci-articular)	Type 2 (Polyarticular)
<b>Prevalence</b>	30-35%	20-25%
<b>Pattern</b>	<ul style="list-style-type: none"> <li>&gt; &lt; 5 JOINTS</li> <li>&gt; ASYMMETRIC</li> <li>&gt; MAINLY LARGE JOINTS (KNEE &gt; ANKLE &gt; WRIST &gt; ELBOW)</li> </ul>	<ul style="list-style-type: none"> <li>&gt; 5 JOINTS</li> <li>&gt; SYMMETRIC OR ASYMMETRIC</li> <li>&gt; MAINLY SMALL JOINTS (MCPS &gt; KNEE &gt; PIPS &gt; WRIST)</li> </ul>
<b>Relation to IBD</b>	Parallels IBD disease activity	Independent of IBD disease activity
<b>Natural History</b>	Self-limited episodes, generally <10 weeks	Persistent inflammation for months to years
<b>Association with Other EIMs</b>	High frequency of other EIMs (erythema nodosum, uveitis)	Uveitis

is distinct from rheumatoid arthritis that could also occur in IBD patients. Supporting this are the lack of correlation between IBD arthritis and antibodies to citric citrullinated peptides (anti-CCP).<sup>6</sup>

**Axial Arthritis**

Axial involvement is a common feature of IBD-associated arthritis. The prototypical symptom is inflammatory back pain; other features of ankylosing spondylitis have been clearly demonstrated in patients with arthritis associated with IBD.<sup>3,4,5</sup> These are more frequently observed in patients with Crohn’s disease (5-22%), as compared to ulcerative colitis (2-6%).

Inflammatory back pain is characterized by insidious onset of back pain, lasting more than three months, associated with morning stiffness and improvement with exercise. Ankylosing spondylitis has been traditionally diagnosed based on a combination of inflammatory back pain symptoms, limitation of spinal flexion (Schober’s test) and reduced chest expansion and X-ray imaging showing bilateral sacroiliitis grade ≥2 or unilateral sacroiliitis grade 3–4. There appears to be a genetic association between ankylosing spondylitis and IBD. Approximately 5-10% patients with ankylosing spondylitis develop IBD, and up to 70% patients may have microscopic evidence of gut

inflammation; likewise, about 5-10% patients with IBD may develop ankylosing spondylitis.<sup>6</sup> The presence of an elevated C-reactive protein and serum and/or fecal calprotectin in patients with ankylosing spondylitis has been shown to have modest accuracy as a screening strategy to identify potential ankylosing spondylitis patients with gut inflammation. Most patients with ankylosing spondylitis are HLA-B27 positive. Patients with IBD and axial arthritis have a rate of HLA-B27 positivity far above the general population (~50%) but lower than those patients with AS. Regarding the diagnosis of axial inflammatory arthritis, magnetic resonance imaging (MRI) is often considered the gold standard. Changes on plain X-ray are more specific for the diagnosis of AS, but are less sensitive.

**Other Musculoskeletal Extraintestinal Manifestations of IBD**

Besides peripheral and axial arthropathies, enthesitis, tenosynovitis and dactylitis are commonly observed, particularly if highly sensitive imaging techniques such as ultrasound are utilized.<sup>5</sup>

**Rheumatic Complications in IBD**

While osteoporosis is not perhaps strictly an extraintestinal manifestation of IBD, it is indeed a

frequently observed complication, occurring in about 14–42% patients.<sup>3,4</sup> It is multifactorial, and related to a number of factors including intestinal malabsorption due to active disease or surgical resections, recurrent exposure to corticosteroids, and the local and systemic effects of chronic systemic inflammation. National guidelines suggest screening IBD patients with conventional risk factors for osteoporosis with dual energy X-ray absorptiometry.

## Treatment

Arthritis can be functionally limiting in patients with IBD, and hence warrants attention and treatment in symptomatic patients.

Much of the data relevant to the treatment of peripheral arthritis related to IBD comes from the literature on the treatment of psoriatic arthritis (PsA) with peripheral arthritis. Treatment options include disease modifying anti-rheumatic drugs (DMARDs), including methotrexate (MTX), sulfasalazine, leflunomide and apremilast. Among biologic agents, tumor necrosis factor inhibitors (TNFi) have the longest and largest clinical data supporting their substantial efficacy. The most relevant data concerning the treatment of spinal, also called axial, arthropathies comes from studies of patients with ankylosing spondylitis. While NSAIDs and specific cyclooxygenase 2 (COX2) inhibitors are effective in both peripheral and axial arthritis, their use in IBD must take into account their potential effects on the bowel. Short courses (less than two weeks) of NSAIDs, particularly, COX-2 inhibitors may be used in patients with IBD.<sup>7</sup> However, caution should be exercised since NSAIDs may exacerbate underlying IBD. In a large prospective cohort study of 791 patients with IBD in clinical remission at baseline, frequent use of NSAIDs  $\geq 5$  times per month was associated with 1.7 times higher risk of flare of Crohn's disease, but not of ulcerative colitis; less frequent use was not associated with risk of IBD exacerbation.<sup>8</sup> In a meta-analysis of 7 studies with 344 patients with IBD, about 14.4% patients treated with NSAIDs experienced exacerbation of gastrointestinal symptoms.<sup>9</sup>

While DMARDs are ineffective for axial arthritis, TNFi are highly effective. IL-17 inhibitors, which have recently been shown effective in PsA and AS, would not be a good choice for IBD related arthritis as they can have a detrimental effect on bowel inflammation. Given the considerable overlap in IBD and rheumatic diseases, the concept a multi-disciplinary approach in

a combined gastroenterology-rheumatology clinical has been explored. In a prospective study of 269 IBD patients with joint pain, Canigliaro and colleagues observed that a diagnosis of enteropathic arthritis was made in 50.5% of IBD patients with joint pain. These patients had peripheral arthropathies in 53%, axial arthropathies in 20.6% and both peripheral and axial arthropathies in 26.4% patients. These patients had higher prevalence of other EIMs and received more anti-TNF treatment compared with IBD patients without enteropathic arthritis.<sup>10</sup> The mean diagnostic delay of 5.2 years was revealed in these patients; however, with the creation of a combined clinic there was a considerable decline in diagnostic delay.

In summary, rheumatologic extraintestinal manifestations and complications are common in patients with inflammatory bowel disease, presenting as peripheral arthritis and/or axial arthritis. These may or may not be related to IBD disease activity, but can cause considerable impairment of quality of life. A high index of suspicion and early treatment may decrease healthcare burden. ■

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