Rheumatological manifestations in inflammatory bowel disease

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Abstract

Rheumatological manifestations in inflammatory bowel disease (IBD) are frequent and include peripheral arthritis, axial involvement and peripheral enthesitis. Secondary osteoporosis and hypertrophic osteoarthropathy may also occur. Complications of IBD (e.g. septic arthritis) must be distinguished from sterile inflammation. Adverse effects of corticosteroid treatment, such as osteonecrosis, may also affect joints. Axial involvement ranges from low back pain to true ankylosing spondylitis. Human leukocyte antigen B27 is associated with axial involvement of IBD. Peripheral arthritis has been classified into two types. Type I is a pauciarticular, asymmetric usually non destructive arthritis affecting large joints and is usually associated with active bowel disease. Type II is a polyarthritis affecting small joints and tends to run a course independent of the bowel disease. Treatment of joint symptoms in IBD include sulphasalazine, azathioprine, methotrexate and glucocorticoids. Anti-tumor necrosis factor antibodies are effective in treating resistant or complicated Crohn's disease as well as peripheral arthritis and axial involvement.

Keywords

peripheral arthritis, sacroilitis, enthesitis, axial involvement

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Introduction

The idiopathic inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are systemic disorders that may be complicated by extraintestinal manifestations in up to 40% of patients, depending on the study population and definitions used [1-3]. Rheumatological manifestations in IBD are frequent and include peripheral arthritis, axial involvement, peripheral enthesitis, secondary osteoporosis, and secondary hypertrophic osteoarthropathy (HOA) (Table 1). Complications of IBD may also cause joint pain and must be distinguished from sterile inflammation. Bacterial infection of the sacroiliac or peripheral joints may occur due to fistulization or bacteremia. Adverse effects of treatment of IBD may also affect joints such as osteonecrosis due to corticosteroid use. IBD may be associated with relapsing polychondritis and cutaneous vasculitis. A relationship between the gut and arthritis was postulated in 1929 by Bargen who recognized arthritis as a complication of UC [4]. Hench in 1935 described a peripheral arthritis in patients with IBD and observed the tendency of arthritis to flare with exacerbations of the colitis and to subside with remission of the gut symptoms [5]. The introduction of the concept of spondyloarthropathies (SpA) by Wright and Moll generated further study of the relationship between arthritis and bowel inflammation [6]. IBD belong to SpA, sharing common features with other members of this family of disorders such as the asymmetric pattern of peripheral joint involvement, the occurrence of sacroilitis (SI) and spondylitis, the peripheral enthesopathy, the absence of rheumatoid factor, the association with human leukocyte antigen (HLA) B27, as well as extra-articular features, including uveitis, carditis, skin and mucous membrane lesions.

Table 1 Rheumatological manifestations in IBD

| 1. Peripheral arthritis |
| 2. Axial involvement (low back pain, SI, spondylitis, true AS) |
| 3. Enthesitis |
| 4. Secondary HOA |
| 5. Secondary osteoporosis |

IBD, inflammatory bowel diseases; SI, sacroilitis; AS, ankylosing spondylitis; HOA, hypertrophic osteoarthropathy
Epidemiologic features and genetic markers of rheumatological manifestations in IBD

The prevalence of UC ranges between 50 and 100 per 100,000 of the population. The disease seems to be more frequent in whites. The prevalence of CD has increased during the past few decades to about 75/100,000 of the population. Early epidemiologic studies on IBD-associated arthropathies from the 1960s, 70s and 80s include patients with classic ankylosing spondylitis (AS) or SI together with peripheral arthritis [7-15]. From these studies AS was present in 2-16% of patients mainly in CD. Asymptomatic and symptomatic SI was found in 12 to 20% of patients and peripheral arthritis in 11 to 20%. Association with HLA-B27 ranged from 3.9 to 18.9%. Studies on IBD populations using the European Spondyloarthropathy Study Group criteria [16] or the Amor Diagnostic Criteria for Spondyloarthropathy [17] showed various results [18-32]. More specifically, AS ranged from 1 to 45.1%, SI from 1.9 to 45.7%, peripheral arthritis from 2.8 to 30.6% and enthesopathy from 5.4 to 50% of patients. Most of these studies reported similar findings in CD and UC for peripheral and axial involvement. In addition, most studies agreed that ulcerative proctitis is rarely complicated by joint inflammation and that inflammatory joint disease occurs with increased frequency in CD patients with colitis or with more extensive bowel disease compared to those with ileal involvement. Furthermore, some patients develop one or more manifestations of SpA (e.g. enthesitis or/and dactylitis) without fulfilling the classification criteria.

Arthritis or axial symptoms may precede the gastrointestinal symptoms by lengthy periods of time, and the patients may be regarded as undifferentiated spondyloarthropathy until the IBD declares itself. The study of Mielants and Veyts has provided evidence that patients with undifferentiated SpA and even AS may have subclinical bowel inflammation that plays an important role in triggering and perpetuating joint inflammation [33]. A 20-year follow-up study of patients with IBD reported musculoskeletal features in 30% [34], HLA-B27 positive patients with CD have a high likelihood of progressing to frank AS. Conversely, the frequency of true IBD (UC or CD) in AS is below 4%. However, if the occurrence of subclinical bowel inflammation is considered, the prevalence of gut involvement in a group of patients with SpA increases to 60% [35].

Other studies aimed to clarify the frequency of symptomatic or asymptomatic SI. Steer et al found on computed tomography (CT) examination signs of SI in 31/134 of CD patients [36]. In another study carried out in 50 CD patients symptomatic for back pain, 28% fulfilled the modified New York criteria for AS on x-ray examination [37]. On the other hand, asymptomatic SI may be present in 10 to 50% of patients with IBD [38]. In a comparative study using conventional x-ray and CT, findings compatible with SI were found in 29% of CD patients with only 3% being symptomatic [39]. Magnetic resonance imaging (MRI) is the most sensitive method of detecting SI in IBD patients. In the literature there are also studies which describe musculoskeletal symptoms in IBD patients without using exact diagnostic criteria for IBD related SpA. Thus, racial differences in the prevalence of the extraintestinal including rheumatologic manifestations have been reported. A large study showed that African Americans with IBD were more likely to develop both uveitis and SI [40]. Another study described an increased incidence of arthritis and uveitis in African American patients with CD [41], although there are different results in the literature [42]. In addition, investigators from Spain reported extraintestinal manifestations almost in half (46%) of 157 patients with CD, while 22% had rheumatologic findings which were more frequent in patients with disease confined to the colon [43]. A study from Ukraine showed that 29.8% of 319 UC patients had joint manifestations. Arthritis correlated with extensive forms of UC and was more frequent in patients with left-sided UC and pancolitis. Arthralgia was a prevalent symptom in patients with distal UC [44]. The joint involvement in UC ranges between 20 and 35% in other studies [45-47]. A study from Japan found that 10.3% of CD patients had arthritis and 1.5% had spondylitis [48]. In a Greek cohort of CD patients 30% had arthritis/arthritis [49]. Another study from Canada reported a 4% prevalence of AS in IBD hospitalized patients, with male CD patients being more frequently affected than male UC patients [50]. However in a Brazilian study prevalence was 14.4% with no difference between CD and UC [51]. Finally, a study from Kuwait reported arthritis in 8.9% of UC patients while the overall prevalence of rheumatologic complaints was 31% [52]. Such racial differences in the prevalence of rheumatologic manifestations may be attributed to both immunologic and genetic factors. Peripheral arthritis occurring in IBD is not associated with HLA-B27. SI and especially spondylitis, however, are associated with HLA-B27 [40% and 60% respectively], but to a lesser degree than in uncomplicated AS [90%]. CD has been associated with mutation in the NOD2 [CARD15] gene on chromosome 16 [53]. This is of interest in the pathogenesis of CD because NOD2 plays an important role in innate immunity to pathogens and indirectly implicates microbial triggers in IBD. To date, studies have found no significant relationship between CARD15 and SpA. However, CARD15 mutations may be found more commonly among patients with CD complicated by SI [54], although this was not confirmed in a more recent series [55].

Clinical features of rheumatologic manifestations in IBD

Arthritis

Articular complications are the most common extraintestinal manifestations [56]. Arthritis is more likely to occur in patients with large-bowel disease and in patients with complications such as abscesses, pseudomembranous polyps, perianal disease, massive hemorrhage as well as in patients with erythema nodosum, stomatitis, uveitis and pyoderma gangrenosum. In addition, patients with CD and colonic
involvement are at higher risk of developing synovitis than those with isolated small bowel disease. Men and women are equally affected. Peripheral arthritis has been classified into two types [57]. Type I is a pauciarticular arthritis typically affecting fewer than five large (weight-bearing) joints. It is usually associated with active bowel disease and has an asymmetric pattern; a monoarthritis is not uncommon. Large and small joints are involved, predominantly those of the lower limbs (knees, ankles, and metatarsophalangeal joints). Arthritis of hips and shoulders is less frequent and tends to be associated with SI and spondylitis. Arthritis occurs early in the course of bowel disease. It is generally migratory and transient but recurrent, although it does not result in joint deformities [58, 59]. Five percent of IBD patients develop type I arthropathy. Joint symptoms may occur prior to the onset of bowel disease especially in CD. This can also remain absent, although ileocolonoscopic biopsy specimens taken from the terminal ileum reveal mild to severe inflammatory lesions indicating the presence of subclinical CD in these patients [60]. The timing of the first attack of arthritis seems to be independent of the duration of colitis in UC. In addition, a flare of the gut symptomatology mainly in UC is frequently accompanied by recurrence of peripheral arthritis. Surgical removal of the colon in UC has been reported to have a curative effect on the peripheral joint symptoms [60].

Type I peripheral arthritis is associated with the class II allele HLA-DRB1* O103 [56]. This allele is found in 35% of type I arthritis patients versus 3% of controls. If patients with recurrent arthritis are studied this association is found in 65% [2].

Type II is a polyarthritis mainly affecting the small joints. It rarely precedes the diagnosis of IBD. It tends to run a course independent of the bowel disease. Metacarpophalangeal joints are frequently involved and the differentiation of type II peripheral arthritis and rheumatoid arthritis is important and requires radiographic and immunologic correlation. Approximately half of the patients with IBD have migratory arthritis. Active synovitis may persist for months, and may recur repeatedly. Episodes of exacerbations and remissions may continue for years. Evolution to chronicity may occur together with radiographic erosive lesions [61]. Type II arthropathy affects 3 - 4% of patients with IBD. Type II peripheral arthritis is associated with HLA-B44* in 62% of patients versus 30% of controls [56]. It is also associated with uveitis but not with other extraintestinal manifestations.

Spondylitis and SI

The spectrum of axial involvement ranges from inflammatory lower back pain with or without radiological evidence of SI, to asymptomatic SI and true AS characterized by the classical clinical [pain, spine stiffness] and radiologic features [squaring, syndesmophytes, bamboo spine]. The prevalence of axial involvement in patients with IBD is between 5 and 12% [62], but these percentages could be higher because of the existence of silent axial involvement [63] especially in SI. The male to female ratio is 3:1, comparable to AS. Axial involvement can precede the bowel disease by many years. The main complaints are inflammatory low back pain, buttock pain and chest pain. Inflammatory back pain is insidious in onset, usually before the age of 45 years, frequently monolateral and intermittent at onset, more intense at rest, associated with morning stiffness but relieved by movement, exacerbated by cough or sneezing, and accompanied by fatigue. The pain is persistent with duration of at least 3 months. The diagnosis of inflammatory back pain is reinforced when there is an improvement with exercise, awakening because of pain and the presence of alternating buttock pain [64]. Thoracic pain results from enthesitis of costovertebral, costosternal, manubriocostal articulations. It exacerbates with cough and deep inspirations and limits respiratory expansion with episodes of variable duration. Dactylitis can be seen in AS. It is characterized by the inflammatory swelling of one of more fingers [sausage fingers] or toes caused by tenosynovitis of the flexor tendons. The limitation of cervical spine mobility is a hallmark of progression of the disease to generalized ankylosis. In the presence of inflammatory back pain, the radiologic evaluation of the sacroiliac joints allows to make the diagnosis of SI [65]. In the absence of radiologic findings, MRI evaluation may lead to diagnosis and, thus, effective early treatment of axial spondyloarthritis [66]. The evidence of bone edema with T1 post-gadolinium and STIR (short tau inversion recovery) techniques is a sign of active inflammation in the sacroiliac joints and/or spine. The axial and spine symptoms are independent of exacerbation of bowel inflammation. Similarly, surgical therapy of UC or CD has no impact on the associated spondylitis. Consequently it has been suggested that peripheral arthritis is a manifestation of IBD, whereas the spondylitis is an associated disease.

Enthesopathy

Enthesopathy is a pathologic alteration at an entheses (a site of insertion of a tendon or ligament into bones). It manifests radiographically as ossification of entheses. In IBD, enthesopathies can occur at the heel (insertion of the Achilles tendon) or the plantar fascia) or at the knee (insertion of the patellar tendon). Inflammation at enthesis may cause erosive lesions which may lead to spur formation.

Osteoporosis

Osteoporosis is a silent condition characterized by reduced bone mass and microarchitectural changes leading to increased bone fragility and susceptibility to fracture. Osteoporosis is a complication of corticosteroid treatment in IBD.

HOA

HOA is a syndrome characterized by excessive proliferation of skin and bone at the distal parts of the extremities. Its
most prominent feature is a bulbous deformity of the tips of the digits, conventionally known as clubbing. In advanced stages, periostal proliferation of the tubular bones and synovial effusions become evident. UC and CD are two causes of secondary HOA. In patients with IBD the development of clubbing is usually a poor prognostic sign.

Diagnosis of rheumatologic manifestations in IBD

There is no pathognomonic finding to confirm the clinical suspicion of arthritis due to IBD. The diagnosis may be suspected in the proper clinical setting. Laboratory findings are determined by the activity of the IBD. Anemia is common in enteropathic SpA reflecting both the anemia of chronic disease and iron deficiency anemia due to gastrointestinal blood loss. Leukocytosis, a marked thrombocytosis with platelet counts higher than 700,000/mm³ is not uncommon. The erythrocyte sedimentation rate and C-reactive protein as well as other acute-phase reactants are elevated. Rheumatoid factor is absent and antinuclear antibodies are absent in most patients. The synovial fluid is not characteristic: mild to marked villous changes can be found with a white blood cells ranging from 1,500-50,000/mm³. Glucose levels are not reduced. Microbiologic cultures are negative [63]. Synovial membrane biopsies reveal nonspecific abnormalities including proliferation of synovial lining cells, increased vascularity and infiltration of mononuclear cells [67]. In cases of monoarthritis or oligoarthritis it is important to exclude septic arthritis performing a joint aspiration because its presentation may be atypical in patients with IBD who are receiving antiinflammatory or immunosuppressive treatment.

Radiographic findings

Radiographs of the spine and pelvis may show typical findings of AS and SI. The latter is typically bilateral, although a higher frequency of asymmetric SI and zygapophyseal joint ankylosis has been reported [68]. Peripheral joint involvement is generally not accompanied by radiographic changes, but erosive lesions mainly of the metatarsal joints, have been described. These lesions show some differences to rheumatoid lesions, for example an absence of osteoporosis and the absence of adjacent bone proliferation. Rarely, a destructive granulomatous synovitis may be seen in CD. Enthesopathies do not differ radiographically from those seen in other SpA.

Differential diagnosis

In patients with intestinal manifestations and arthritis the diagnosis of IBD excludes other diseases with similar symptoms: reactive arthritis (formerly Reiter syndrome), Whipple’s disease, Adamantiades-Behçet’s disease, intestinal bypass, gluten sensitive enteropathy and parasitic infections. Initially the clinical signs of SpA must be recognized and differentiated from those of rheumatoid arthritis and other connective tissue diseases. IBD is included in the differential diagnosis of SpA even when gut symptoms are mild. The presence of spondylitis in an HLA-B27 negative patient increases the risk of IBD. The differential diagnosis of joint pain in a patient with IBD is broad. It includes HOA [67], septic arthritis (common or opportunistic infections), osteonecrosis especially in patients treated with glucocorticoids and experience pain that is out of proportion to the degree of limitation of passive range of motion of the affected joint. Erythema nodosum may be difficult to distinguish from arthritis when lesions occur in a periarticular location. Inability to aspirate synovial fluid from a swollen and painful joint is a clue to the diagnosis.

Pathogenesis of musculoskeletal manifestations of IBD

HLA-B27 is the major risk factor for AS and SpA associated with IBD. HLA-B27 transgenic rats develop a SpA. HLA-B27 is present in >90% of patients with AS while only 5 to 15% of the general population are HLA-B27 positive. Among the HLA class B molecules that determine the antigen binding cleft, HLA-B27 has a unique B pocket that likely influences the peptide repertoire. The subtypes of HLA-B27 (there are more than 30) differ in part only by single amino acids. Only a few HLA-B27 subtypes (e.g. HLA-B*2705, HLA-B*2702 or, HLA-B*2704 and HLA-B*2707) are associated with AS. There are 4 main theories on the pathogenesis of spondyloarthritides related to HLA-B27 (Table 2). The first is the arthritogenic peptide hypothesis. According to this HLA-B27 binds a unique set of antigenic peptides, bacterial or self, and these peptides are presented to CD8+ T cells giving rise to an HLA-B27-restricted cytotoxic T-cell response. The second theory is the self-association of the HLA-B27 molecule. A unique property of HLA-B27 is that its heavy chain can form homodimers in vitro that are dependent on disulfide binding through their cysteine-67 residues in the alpha-1 domain. These homodimers occur as a result of B27 misfolding within the endoplasmic reticulum. The accumulation of misfolded protein may result in a proinflammatory intracellular stress response. Alternatively, B27 homodimers can migrate to the cell surface where they either become antigenic themselves or present peptide to other inflammatory cells. The third theory refers to the alteration of intracellular handling of microbes due to HLA-B27. The HLA-B27 molecule leads to a less effective elimination of microbes, such as salmonella, in conjunction with an upregulated production of cytokines. The fourth hypothesis represents the recognition of HLA-B27 as an autoantigen. The HLA-B27 itself can be recognized by CD4+ T cells when presented by HLA class II (DR, DQ, DP) heterodimers as an autoantigen. This was also part of

[226x431]3. Glucose levels
[307x75]DP) heterodimers as an autoantigen. This was also part of
The molecular mimicry hypothesis, which supports that the homology of peptides from the HLA-B27 molecule shares striking sequence homology with that from bacterial sources [67]. However, non-major histocompatibility complex genetic effects appear to also have significant influence on disease severity [68-70].

The association between axial involvement and HLA-B27 in IBD patients is less conclusive because only 40-60% of patients with CD and AS present positivity for HLA-B27. The altered gut permeability could be a key factor in the development of SpA [71]. In addition, type 1 peripheral arthritis is associated with HLA-DRB1*0103, B*35 and B*27 [72] while no HLA-B27 nor DR-4 associations were observed for type 2 arthropathy. These data indicate that type 1 and 2 arthropathies are immunogenetically distinct entities and that type 1 is more similar to that of axial SpA. Apart from the genetic predisposition, the role of bacterial antigens seems to be important in the pathogenesis of peripheral arthritis.

A number of bacterial agents, including adherent, invasive E. coli and anaerobic rods of bacteroides and fusobacterium have been implicated in the etiopathogenesis of CD. Several studies have focused on an important “gut-synovium axis” [73,74]. Furthermore, cross-reactivity between gut bacteria and cartilage has been demonstrated in patients with CD [75].

The role of CARD15 in the process of presentation of intestinal bacteria by antigen-presenting cells remains unclear. CARD15 protein is expressed by monocytes, granulocytes, dendritic cells and epithelial cells. In vitro this protein induces the activation of the nuclear factor (NF) κB pathway after recognition of muramyl dipeptide and may help to protect the gut wall. Genetic mutation of CARD15 may lead to disturbed handling of bacterial products and hence inappropriate elimination. Cytokine production by antigen-presenting cells plays a critical role in directing adaptive immune responses. In addition, interaction between microorganisms and toll-like receptors (TLRs) on mucosal epithelial cells, monocytes, macrophages and dendritic cells induces the secretion of a variety of mediators like cytokines such as tumor necrosis factor (TNF) alpha and interleukin 6 by activation of NF-κB and triggers lymphocyte activation. Effector T cells need to migrate from inductive to effector sites. Intestinally activated T cells may enter the synovium, either through the presence of cognate antigens at both sites or by homing of lymphocytes primed by adhesion molecules [76,77]. The discovery of identical T-cells expansions in colon mucosa, synovium and blood support this hypothesis [78]. Thus, TLRs sit at the crossroads of innate and adaptive immunity, where microbial invasion is translated from nonspecific to antigen-specific inflammatory responses.

### Treatment of musculoskeletal manifestations in IBD

The aims of therapy in musculoskeletal manifestations of IBD are to reduce inflammation and to prevent disability or deformity. Rest and physical therapy are used as non-pharmacologic treatment. In patients with true AS, physical therapy is of great importance to maintain spinal mobility and to prevent deformities of the spine with subsequent respiratory compromise and disability. Breath exercises, spinal exercises and swimming should be preferred. Nonsteroidal antinflammatory drugs (NSAIDs) are usually prescribed to control peripheral arthritis, back pain and stiffness. Caution is necessary because these drugs may exacerbate IBD, particularly UC [79, 80]. NSAIDs-related adverse events may also mimic a flare of IBD and complicate management. Experience with the cyclooxygenase – 2 (Cox-2) selective inhibitors (such as celecoxib and rofecoxib, the latter is no longer available) in patients with IBD is limited. It is known that Cox-2 activity promotes epithelial proliferation and wound healing. Theoretically, Cox-2 inhibition could have deleterious effects in patients with IBD [81]. On the other hand, selective Cox-2 inhibitors ameliorate the severity of experimental colitis [82]. In a placebo – controlled trial the use of celecoxib in IBD patients for two weeks showed no significant difference in the rate of relapse of IBD [83]. Another study included 45 IBD patients with arthralgias treated with rofecoxib (12.5 mg/daily) ranging from three days to three months [84]. Arthralgia relief was reported by 71% of patients (complete relief in 18% and partial relief in 53%). However, 20% of IBD – 9 patients – versus 3% of control group (patients with dyspepsia) discontinued therapy due to gastrointestinal symptoms, which subsided after treatment was stopped. The rate of discontinuation was similar for those with CD or UC. Cox-2 selective agents may be better tolerated in the short term, but the withdrawal of rofecoxib and valdecoxib because of cardiovascular toxicity has raised concerns about their overall benefit.

Despite concern about the potential for NSAIDs and Cox-2 selective agents to cause worsening bowel inflammation, rheumatologists, have used the above drugs successfully in patients with IBD. However, if symptoms or signs of IBD develop or worsen during the use of NSAIDs or Cox-2 selective treatment it is prudent to temporarily or permanently discontinue their use. Of the available NSAIDs, indomethacin and naproxen, have been used more, but anti-inflammatory doses of any NSAID or Cox-2 selective agent may be effective. Since the peripheral arthritis of IBD is generally non-destructive, therapy is primarily directed at symptomatic relief. NSAIDs or Cox-2 selective agents improve spinal pain and stiffness in AS although radiographic progression to bony

### Table 2 Major theories on the pathogenesis of SpA related to HLA-B27

| 1. The arthritogenic peptide theory |
| 2. Self-association of the HLA-B27 molecule |
| 3. Alteration of intracellular handling of microbes due to HLA-B27 |
| 4. The role of HLA-B27 as an autoantigen |

*SpA, spondyloarthopathies; HLA-B27, human leukocyte antigen B27*
ankylosis may occur.

Sulfasalazine, azathioprine, 6-mercaptopurine, methotrexate and glucocorticoids may be helpful for both bowel and joint inflammation. Intraarticular glucocorticoid injections can be used for flares of peripheral arthritis. Sulfasalazine has been effective in treating peripheral, but not axial arthritis in IBD patients. The initial dose is 500 mg twice daily with an increase in daily dose every two weeks until arthritis symptoms improve or a dose of 1000 mg three times daily is reached. Maintaining the maximum dose for up to 12 weeks is recommended before assessing efficacy.

Azathioprine and 6-mercaptopurine used for IBD may also have beneficial effects on joint disease. However, aminosalicylates (e.g. mesalamine), useful for controlling intestinal inflammation, appear to have no direct anti-inflammatory effect on the synovium [85].

Studies that address the efficacy of methotrexate in the peripheral arthritis of IBD are lacking. Many rheumatologists use methotrexate in patients with IBD and peripheral arthritis and the methotrexate may be preferred to azathioprine, but this is an empirical approach not backed by trial evidence [56]. Oral administered methotrexate is adequately absorbed, even in patients with active IBD. Subcutaneous injection of the drug may reduce gastrointestinal side effects.

Budesonide, a glucocorticoid with first-pass hepatic metabolism and fewer systemic side effects as a result has been used for CD flares, but there are no studies to date addressing the effect of this steroid on enteropathic arthritis.

Anti-TNF agents have had a major impact on the therapeutic approach to IBD and the associated musculoskeletal manifestations. The anti-TNF monoclonal antibodies (infliximab, adalimumab) are effective in IBD particularly CD and they are useful in patients with axial involvement and peripheral arthritis [86-88]. Etanercept can control the arthritis associated with CD while having no effect on the bowel disease itself [89]. Patients with IBD and true AS who have an inadequate response to conventional treatment are candidates for anti-TNFα treatment. Infliximab, adalimumab, etanercept and golimumab (human monoclonal antibody, 50 mg once per month subcutaneously) can be used in patients with AS, although golimumab has not been approved for CD.

Certolizumab pegol is a pegylated humanized antibody, Fab fragment of TNFα monoclonal antibody. Certolizumab binds to and selectively neutralizes human TNFα activity. Since it is not a complete antibody (lacks Fc region) it does not induce complement activation, antibody dependent cell-mediated cytotoxicity or apoptosis. Pegylation of certolizumab allows for delayed elimination and therefore an extended half life. Certolizumab pegol received approval from the United States Food and Drug Administration in 2008 for treatment and maintenance of response in adults with moderate to severe CD who had an inadequate response to conventional therapy. The drug is also approved in Switzerland but it has not been approved by the European Medicines Agency and is therefore not widely available in Europe. The recommended dosing for induction is 400 mg subcutaneously at weeks 0, 2, and 4 and then every four weeks for maintenance of response.

Studies evaluating the efficacy of infliximab, adalimumab and certolizumab have generally shown similar results but no studies have directly compared them. Preliminary data suggest that certolizumab pegol can be effective in patients who responded to infliximab and lost response or became intolerant to it [90-92]. Safety and precautions are similar to all anti-TNFα agents. All patients should have a skin test for tuberculosis prior to initiation of the anti-TNFα therapy and should be evaluated for latent infection.

Conclusions

- Rheumatological manifestations of IBD are frequent and may be present in one third of patients.
- Axial involvement ranges from inflammatory lower back pain to SI or true AS while enthesopathies can also occur.
- HLA-B27 is associated with axial involvement of IBD.
- The role of HLA-B27 in the pathogenesis of axial disease or AS in IBD has been supported by various theories.
- Peripheral arthritis has been classified into two types. Type I is a pauciarticular, asymmetric usually non destructive arthritis affecting large joints and it is usually associated with active bowel disease. Type II is a polyarthitis affecting small joints and tends to run an independent of the bowel disease course.
- Sulfasalazine, azathioprine, methotrexate and glucocorticoids have been used to treat IBD and joint symptoms.
- Anti-TNFα antibodies are effective in patients with resistant or complicated CD as well as for both axial and peripheral arthritis.

References

1. Ricart E, Panaccione R, Loftus EV Jr, et al. Autoimmune disorders and extraintestinal manifestations in first-degree familial and sporadic inflammatory bowel disease: a case-control study. Inflamm Bowel Dis 2004;10:207-214.
2. Greenstein AJ, Janowitz HD, Sachar DB. The extra-intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. Medicine (Baltimore) 1976;55:401-412.
3. Bernstein CN, Wajda A, Blanchard JE. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. Gastroenterology 2005;129:827-836.
4. Bargen JA. Complications and sequelae of chronic ulcerative colitis. Ann Intern Med 1929;3:335.
5. Hench PS. Acute and chronic arthritis. In: Whipple GH (ed). Nelson’s looseleaf of surgery I. Thomas Nelson Sons: New York 1935;104.
6. Wright V. Seronegative polyarthritis: a unified concept. Arthritis Rheum 1978;21:619-633.
7. Acheson Ed. An association between ulcerative colitis, regional enteritis, and ankylosing spondylitis. Q J Med 1960;29:489-499.
8. Ansell BM, Wigley RA. Arthritic manifestation in regional enteritis. Ann Rheum Dis 1964;23:64-72.
9. Haslock I. Arthritis and Crohn’s disease. A family study. Ann Rheum Dis 1973;32:479-486.

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10. Wright V, Watkinson G. Sacro-ilitis and ulcerative colitis. Br Med J 1965;2:675-680.

11. Wright V, Watkinson G. The arthritis of ulcerative colitis. Br Med J 1965;2:670-675.

12. Rankin GB, Watts HD, Melynck CS, Kelley ML Jr. National Cooperative Crohn's Disease Study: extraintestinal manifestations and perianal complications. Gastroenterology 1979;77:914-920.

13. Münch H, Purrmann J, Reis HE, et al. Clinical features of inflammatory joint and spine manifestations in Crohn's disease. Hepatogastroenterology 1986;33:123-127.

14. Dekker-Saejs BJ, Meuwissen SG, Van Den Berg-Loonen EM, De Haas WH, Agenant D, Tytgat GN. Ankylosing spondylitis and inflammatory bowel disease. II. Prevalence of peripheral arthritis, sacroiliitis, and ankylosing spondylitis in patients suffering from inflammatory bowel disease. Ann Rheum Dis 1978;37:33-35.

15. Salvarani C, Fries W. Clinical features and epidemiology of spondyloarthritides associated with inflammatory bowel disease. World J Gastroenterol 2009;15:2449-2455.

16. Dougados M, van der Linden S, Juhlin R, et al. The prevalence of enteropathic spondyloarthropathy. J Rheumatol 1991;18:373-377.

17. Protzer U, Duchmann R, Höhler T, et al. [Very early diagnosis of chondrolysis phases in arthrosis]. Rev Rhum Mal Osteoartic 1990;57:253-254.

18. Scarp R, del Puente A, D'Arienzo A, et al. The arthritis of ulcerative colitis: clinical and genetic aspects. J Rheumatol 1992;19:373-377.

19. Proctor U, Duchmann R, Höhler T, et al. [Enteropathic spondyloarthritis in chronic inflammatory bowel disease: prevalence, manifestation pattern and HLA association]. Med Klin (Munich) 1996;91:330-335.

20. Veloso FT, Carvalho J, Magro F. Immune-related systemic manifestations of inflammatory bowel disease. A prospective study of 792 patients. J Clin Gastroenterol 1996;23:29-34.

21. Suh CH, Lee CH, Lee J, et al. Arthritic manifestations of inflammatory bowel disease. J Korean Med Sci 1998;13:39-43.

22. de Vlam K, Mielants H, Cuvelier C, De Keyser F, Veys EM, De Vos M. Spondyloarthropathy is underestimated in inflammatory bowel disease: prevalence and HLA association. J Rheumatol 2001;28:2860-2865.

23. Queiro R, Maiz O, Intxausti J, et al. Subclinical sacroiliitis in inflammatory bowel disease: a clinical and follow-up study. Clin Rheumatol 2000;19:445-449.

24. Christodoulou DK, Katsohanis KH, Kitsanou M, Stergiopoulou C, Hatziis J, Tsianos EV. Frequency of extraintestinal manifestations in patients with inflammatory bowel disease in Northwest Greece and review of the literature. Dig Liver Dis 2002;34:781-786.

25. Palm O, Moom B, Jahnsen J, Gran JT. The prevalence and incidence of peripheral arthritis in patients with inflammatory bowel disease, a prospective population-based study (the IBSEN study). Rheumatology (Oxford) 2001;40:1256-1261.

26. Mendola JL, Lana R, Taxonera C, Alba C, Izquierdo S, Díaz-Rubio M. [Extraintestinal manifestations in inflammatory bowel disease: differences between Crohn's disease and ulcerative colitis]. Med Clin (Barc) 2005;125:297-300.

27. Peeters H, Vander Cruyssen B, Mielants H, et al. Clinical and genetic factors associated with sacroiliitis in Crohn's disease. J Gastroenterol Hepatol 2008;23:132-137.

28. Rodriguez VE, Costas PJ, Vazquez M, et al. Prevalence of spondyloarthropathy in Puerto Rican patients with inflammatory bowel disease. Etnn Dis 2008;18(2 suppl 2):225-229.

29. Lanna CC, Ferrari Mde L, Rocha SL, Nascimento E, de Carvalho MA, da Cunha AA. A cross-sectional study of 130 Brazilian patients with Crohn's disease and ulcerative colitis: analysis of articular and ophthalmologic manifestations. Clin Rheumatol 2008;27:503-509.

30. Orchard TR, Wordsworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. Gut 1998;42:387-391.

31. Salvarani C, Vlachonikolis IG, van der Heijde DM, et al. Musculoskeletal manifestations in a population-based cohort of inflammatory bowel disease patients. Scand J Gastroenterol 2001;36:1307-1313.

32. Türkçapar N, Özyüncü N, İdilman R, Ensari A, Soylu K, Ozden A. Macro-amylosaemia in a patient with selective IgA deficiency and antiphospholipid antibodies. Turk J Gastroenterol 2006;17:140-143.

33. Mielants H, Veys EM, Cuvelier C, De Vos M, Botelberge L. HLA-B27 related arthritis and bowel inflammation. Part 2. Ileocolonoscopy and bowel histology in patients with HLA-B27 related arthritis. J Rheumatol 1985;12:294-298.

34. Veloso FT, Fraga J, Saleiro JV. Macroglobulinemia and small intestinal disease. A case report with review of the literature. J Clin Gastroenterol 1988;10:546-550.

35. Mielants H, Veys EM. The gut in the spondyloarthropathies. J Rheumatol 1990;17:7-10.

36. Steer S, Jones H, Hibbert J, et al. Low back pain, sacroiliitis, and the relationship with HLA-B27 in Crohn's disease. J Rheumatol 2003;30:518-522.

37. Podwiadek M, Punzi L, Stramare R, et al. The prevalence of radiographic sacroiliitis in patients affected by inflammatory bowel disease with inflammatory low back pain. Reumatismo 2004;56:110-113.

38. Mielants H. Reflections on the link between intestinal permeability and inflammatory joint disease. Clin Exp Rheumatol 1990;8:523-524.

39. Scott WW Jr, Fishman EK, Kuhlmans JE, et al. Computed tomography evaluation of the sacroilac joints in Crohn disease. Radiologic/clinical correlation. Skeletal Radiol 1990;19:207-210.

40. Nguyen GC, Torres EA, Regueiro M, et al. Inflammatory bowel disease characteristics among African Americans, Hispanics, and non-Hispanic Whites: characterization of a large North American cohort. Am J Gastroenterol 2006;101:1012-1023.

41. Basu D, Lopez I, Kulkarni A, Sellin JH. Impact of race and ethnicity on inflammatory bowel disease. Am J Gastroenterol 2005;100:2254-2261.

42. Mahid SS, Mulhall AM, Gholson RD, Eichenberger MR, Galandiuk S. Inflammatory bowel disease and African Americans: a systematic review. Inflamm Bowel Dis 2008;14:960-967.

43. Repiso A, Alcántara M, Muñoz-Rosas C, et al. Extraintestinal manifestations of Crohn's disease: prevalence and related factors. Rev Esp Enferm Dig 2006;98:510-517.

44. Dorofevey AE, Vasiленko IV, Rassokhina OA. Joint extraintestinal manifestations in ulcerative colitis. Dig Dis 2009;27:502-510.

45. De Vos M. Review article: joint involvement in inflammatory bowel disease. Aliment Pharmacol Ther 2004;20:36-42.

46. Rothfuss KS, Stange EF, Herrlinger KR. Extraintestinal manifestations and complications in inflammatory bowel diseases. World J Gastroenterol 2006;12:4819-4831.

47. Danese S, Semeraro S, Papa A, et al. Extraintestinal manifestations in inflammatory bowel disease. World J Gastroenterol 2005;11:7227-7236.

48. Maeda K, Okada M, Yao Y, et al. Intestinal and extraintestinal complications of Crohn's disease: predictors and cumulative probability of complications. J Gastroenterol 1994;29:577-582.

49. Triantafillidis JK, Emmanouilidis A, Manousos O, Nicolakis D, Kogevinas M. Clinical patterns of Crohn's disease in Greece: a follow-up study of 153 cases. Digestion 2000;61:121-128.

50. Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal manifestations in inflammatory bowel disease: a population-based study. Am J Gastroenterol 2001;96:1116-1122.

51. Souza MH, Troncon LE, Rodrigues CM, et al. Trends in the occurrence (1980-1999) and clinical features of Crohn's disease and ulcerative colitis in a university hospital in southeastern Brazil. J Gastroenterol Hepatol 2006;21:179-184.
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Brazil. Arg Gastroenterol 2002;39:98-105.

52. Al-Shamali MA, Kaloumi M, Patty I, Hasan F, Khajah A, Al-Nakib B. Ulcerative colitis in Kuwait: a review of 90 cases. Digestion 2003;67:218-224.

53. Economidou M, Filis G, Tianou Z, et al. Crohn's disease incidence evolution in North-western Greece is not associated with alteration of NOD2/CARD15 variants. World J Gastroenterol 2007;13:5116-5120.

54. Peeters H, Vander Cruyssen B, Laukens D, et al. Radiological sacroiliitis, a hallmark of spondylitis, is linked with CARD15 gene polymorphisms in patients with Crohn's disease. Ann Rheum Dis 2004;63:1131-1134.

55. Peeters H, Vander Cruyssen B, Mielants H, et al. Clinical and genetic factors associated with sacroiliitis in Crohn's disease. J Gastroenterol Hepatol 2008;23:132-137.

56. Williams H, Walker D, Orchard TR, Extraintestinal manifestations of inflammatory bowel disease. Curr Gastroenterol Rep 2008;10:597-605.

57. Travis SP, Stange EF, Léman M, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: current management. Gut 2006;55(Suppl 1):i16-135.

58. Wordsworth P. Arthritis and inflammatory bowel disease. Curr Rheumatol Rep 2000;2:87-88.

59. Fomberstein B, Yerra N, Pitchumoni CS. Rheumatological complications of GI disorders. Clin Gastroenterol Hepatol 2001;44:2728-2736.

60. Smale S, Natt RS, Orchard TR, Russell AS, Bjarnason I. Inflammatory bowel disease and spondylarthropathy. Arthritis Rheum 2001;44:2728-2736.

61. Moll JM. Inflammatory bowel disease. Clin Rheum Dis 1985;11:87-111.

62. Leirisalo-Repo M, Turunen U, Stenman S, Helenius P, Seppälä HJ. M-cells are damaged and increased in number in inflamed human ileal mucosa. Histopathology 1994;24:417-426.

63. Salmi M, Natt RS, Orchard TR, Russell AS, Bjarnason I. Crohn's disease associated with spondyloarthropathy: effect on the colon mucosa and the synovium of a patient with enterogetic spondylarthropathy. Gastroenterology 2000;119:1745-1755.

64. Braun J, Sieper J. Early diagnosis of spondyloarthritis. Arthritis Rheum 2005;52:87-88.

65. Bennett PH. Wood PHN population studies of the rheumatic diseases Amsterdam. Excerpta Medical Fountion 1968;456-457.

66. Braun J, Sieper J. Early diagnosis of spondyloarthritis. Nat Clin Pract Rheumatol 2006;2:536-545.

67. Klippel JH, Stone JH, Crofford LJ, White PH. Primer on the rheumatic diseases (13th edition). Springer: New York 2008;204-205.

68. Hamersma J, Cardon LR, Bradbury L, et al. Is disease severity in ankylosing spondylitis genetically determined? Arthritis Rheum 2001;44:1396-1400.

69. Brown MA. Non-major-histocompatibility-complex genetics of ankylosing spondylitis. Best Pract Res Clin Rheumatol 2006;20:61-621.

70. Brown MA, Brophy S, Bradbury L, et al. Identification of major loci controlling clinical manifestations of ankylosing spondylitis. Arthritis Rheum 2003;48:2234-2239.

71. Fornaciari G, Salvanari C, Beltrami M, Macchioni P, Stockbrügger RW, Russel MG. Musculoskeletal manifestations in inflammatory bowel disease. Can J Gastroenterol 2001;15:399-403.

72. Orchard TR, Thiayagaraja S, Welsh KI, Wordsworth BP, Hill Gaston JS, Jewell DP. Clinical phenotype is related to HLA genotype in the peripheral arthropathies of inflammatory bowel disease. Gastroenterology 2000;118:274-278.

73. Curvelier CA, Quatacker J, Mielants H, De Vos M, Veys E, Roels HJ. M-cells are damaged and increased in number in inflamed human ileal mucosa. Histopathology 1994;24:417-426.

74. Salmi M, Andrew DP, Butcher EC, Jalkanen S. Dual binding capacity of mucosal immunoblasts to mucosal and synovial endothelium in humans: dissection of the molecular mechanisms. J Exp Med 1995;181:137-149.

75. Van den Broek ME, Van der Putte LB, Van den Berg WB. Crohn's disease associated with arthritis: a possible role for cross-reactivity between gut bacteria and cartilage in the pathogenesis of arthritis. Arthritis Rheum 1988;31:1077-1079.

76. Elewaat D, De Keyser F, Van Den Bosch F, et al. Enrichment of T cells carrying beta7 integrins in inflamed synovial tissue from patients with early spondyloarthropathy, compared to rheumatoid arthritis. J Rheumatol 1998;25:1932-1937.

77. Salmi M, Jalkanen S. Human leukocyte subpopulations from inflamed gut bind to joint vasculature using distinct sets of adhesion molecules. J Immunol 2001;166:4650-4657.

78. May E, Märker-Hermann E, Wittig BM, Zeitz M, Meyer zum Büschenfelde KH, Dachmann R. Identical T-cell expansions in the colon mucosa and the synovium of a patient with enterogetic spondylarthropathy. Gastroenterology 2000;119:1745-1755.

79. Kaufman HL, Fischer AH, Carroll M, Becker JM. Colonic ulceration associated with nonsteroidal anti-inflammatory drugs. Report of three cases. Dis Colon Rectum 1996;39:705-710.

80. Kaufmann HJ, Taubin HL. Nonsteroidal anti-inflammatory drugs activate quiescent inflammatory bowel disease. Ann Intern Med 1987;107:513-516.

81. O'Brien J. Nonsteroidal anti-inflammatory drugs in patients with inflammatory bowel disease. Am J Gastroenterol 2000;95:1859-1861.

82. Smale S, Natt RS, Orchard TR, Russell AS, Bjarnason I. Inflammatory bowel disease and spondylarthropathy. Arthritis Rheum 2001;44:2728-2736.

83. Sandborn WJ, Stenson WE, Brynksow J, et al. Safety of celecoxib in patients with ulcerative colitis in remission: a randomized, placebo-controlled, pilot study. Clin Gastroenterol Hepatol 2006;4:203-211.

84. Biancone L, Tosti C, Geremia A, et al. Rofecoxib and early relapse of inflammatory bowel disease: an open-label trial. Aliment Pharmacol Ther 2004;19:755-764.

85. De Keyser F, Van Damme N, De Vos M, Mielants H; Veys EM. Opportunities for immune modulation in the spondyloarthropathies with special reference to gut inflammation. Inflamm Res 2000;49:47-54.

86. Van den Bosch F, Kruthol E, De Vos M, De Keyser F, Mielants H. Crohn's disease associated with spondylarthropathy: effect of TNF-alpha blockade with infliximab on articular symptoms. Lancet 2000;356:1821-1822.

87. Generini S, Giacomelli R, Fedi R, et al. Infliximab in spondyloarthropathy associated with Crohn's disease: an open study on the efficacy of inducing and maintaining remission of musculoskeletal and gut manifestations. Ann Rheum Dis 2004;63:1664-1669.

88. Rispo A, Scarpa R, Di Girolamo E, et al. Infliximab for the treatment of extra-intestinal manifestations of Crohn's disease. Scand J Rheumatol 2005;34:387-391.

89. Marzo-Ortega H, McGonagle D, O'Connor P, Emery P. Efficacy of etanercept for treatment of Crohn's related spondyloarthritis but not colitis. Ann Rheum Dis 2003;62:74-76.

90. Hanauer SB, Panes J, Colombel JF, Bloomfield R, Schreiber S, Sandborn WJ. Clinical trial: impact of prior infliximab therapy on the clinical response to certolizumab pegol maintenance therapy for Crohn's disease. Aliment Pharmacol Ther 2010;32:384-393.

91. Sandborn WJ, Abreu MT, D'Haens G, et al. Certolizumab pegol in patients with moderate to severe Crohn's disease and secondary failure to infliximab. Clin Gastroenterol Hepatol 2010;8:688-695.

92. Allez M, Vermeire S, Mozicconacci N, et al. The efficacy and safety of a third anti-TNF monoclonal antibody in Crohn's disease after failure of two other anti-TNF antibodies. Aliment Pharmacol Ther 2010;31:92-101.