Inflammatory bowel disease associated arthropathy

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Abstract Arthritis is the most common extraintestinal manifestation of inflammatory bowel disease (IBD) and can have a significant impact on morbidity and quality of life. IBD-associated arthropathy is considered a subtype of seronegative spondyloarthropathy, with axial, peripheral, or a combination of both joint manifestations. Peripheral arthritis is generally non-erosive and the oligoarticular variant particularly may correlate with intestinal disease activity. Axial arthritis may include inflammatory back pain, sacroiliitis, or ankylosing spondylitis, and is less likely to correlate with gastrointestinal symptoms. While there have been advances in identifying predisposing genetic factors and in elucidating pathophysiology of inflammatory bowel disease, the mechanisms surrounding the development of arthritis in IBD remain unclear. Treatment of inflammatory bowel disease is not always sufficient for control of arthritis. While treatment with biologic agents is promising, there remains a great need for larger, randomized studies to address optimal therapy of IBD associated arthropathy.

Keywords Inflammatory bowel disease · IBD · Arthritis · Ulcerative colitis · Crohn's disease · Extraintestinal manifestations · DMARDS · Biologics

Introduction

Inflammatory bowel disease (IBD) is an inflammatory disorder of the gastrointestinal (GI) tract that is both chronic and relapsing; it encompasses both Crohn's disease

(CD) and ulcerative colitis (UC). In addition to affecting the GI tract, IBD has several extra-intestinal manifestations (EIM), including arthritis, ocular involvement, dermatologic manifestations, pulmonary manifestations, biliary tree complications, anemia, and thromboembolism.

Arthritis is a common EIM in IBD, occurring in approximately 30% of IBD patients [1, 2]. Arthropathy has significant effects on morbidity and quality of life in patients with IBD. Here we review the epidemiology, pathophysiology, clinical manifestations, and treatment of arthropathy associated with IBD.

Methods

A literature search of PUBMED restricted to English language publications was conducted using the search terms “arthritis,” “arthropathy,” and “extraintestinal,” in combination with “inflammatory bowel disease.” Similar separate searches were done with “Crohn's Disease” and “Ulcerative Colitis” in place of inflammatory bowel disease to ensure that no articles were missed. Each article was then reviewed for quality and clinical relevance.

Definitions and clinical manifestations

Arthropathy associated with IBD can involve both peripheral and axial joints. IBD associated arthropathy is considered a type of seronegative spondyloarthropathy (SpA). Spondyloarthropathies (which also include Ankylosing Spondylitis (AS), Psoriatic Arthritis, Reactive Arthritis, and Undifferentiated SpA), are characterized by axial and peripheral joint disease with inflammatory features and classically a negative rheumatoid factor.

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Spondyloarthropathies share a common genetic predisposition, including HLA-B27 association. Extraarticular manifestations such as skin manifestations, dactylitis, enthesopathy, and eye disease can also be seen. IBD-associated arthritis is more akin to AS than to the other subtypes of SpA in that it is more likely to be symmetric and continuous, whereas reactive arthritis or psoriatic arthritis can be asymmetric or have non-continuous lesions within the spine. The European Spondyloarthropathy Study Group criteria (ESSG) are most commonly used for classification of SpA [3].

Orchard et al. [4] defined two categories of IBD patients with peripheral arthritis. Type 1 is a pauci/oligo-articular arthritis with swelling and pain of five or fewer joints, particularly affecting large joints in the lower extremities. Type 1 arthritis tends to be acute and self-limiting, and correlates with IBD activity. Joint symptoms can occur prior to the diagnosis of IBD. Type 2 peripheral arthritis has a more polyarticular (affecting greater than five joints), symmetrical distribution, affecting upper limbs predominantly (MCPs commonly affected). Type 2 peripheral arthritis may be chronic and is less likely to parallel the IBD activity. In both types, peripheral arthritis tends to be non-deforming and non-erosive. The possibility of an alternative diagnosis, such as Rheumatoid Arthritis or PsA should be considered in IBD patients who develop erosive arthritis.

Axial arthropathy in IBD can involve isolated sacroiliitis (frequently asymptomatic), inflammatory back pain (IBP), and AS. As the terms AS, sacroiliitis and IBP have some overlap, the distinctions can be confusion. AS required the presence of sacroiliitis on imaging in addition to either back pain and stiffness for greater than 3 months that does not improve with rest but does improve with exercise, or limitation of motion in both the sagittal and frontal planes, or limitation of chest wall expansion after correcting for age and gender. Sacroiliitis is defined as inflammation of the sacroiliac joint, and can be asymptomatic or painful. Inflammatory back pain is a clinical diagnosis, and does not require imaging. The Calin criteria can be used to differentiate IBP from mechanical back pain, and are fulfilled if at least 4/5 are present: (1) age of onset <40, (2) duration >3 months, (3) insidious onset, (4) morning stiffness, and (5) improvement with exercise [5]. New IBP criteria developed by the Assessment of SpondyloArthritis International Society (ASAS) in 2009 may have better specificity than the Calin criteria [6].

IBD associated AS is considered a separate entity from isolated AS, with less frequent association with male gender and HLA-B27. The 1984 modified NY classification criteria for AS consist of inflammatory back pain with findings of radiologic sacroiliitis (grade 2 bilaterally or grade 3 unilaterally) [7]. Of note, asymptomatic sacroiliitis can be seen in 32% of patients with IBD [8], and is of

unclear significance. Patients with axial involvement often complain of back pain which is associated with morning stiffness and improves with exercise. Axial symptoms typically do not correlate with intestinal activity. Axial involvement can occur in isolation or in combination with peripheral arthritis.

Other musculoskeletal manifestations in IBD include enthesitis (inflammation at tendon insertion site), dactylitis (sausage like swelling of digit), and arthralgia (joint pain with lack of inflammation). Complications of IBD and its treatment such as septic arthritis or osteonecrosis should also be considered in the differential of joint pain occurring in the IBD patient, particularly in the setting of mono or oligoarticular arthritis.

Lastly, many patients will note diffuse pain that is due to an underlying myofascial pain syndrome. This is seen in other inflammatory disorders as well, for example in 4% to 17% of affected patients with RA or AS [9–11]. Fibromyalgia or chronic widespread pain has been reported in approximately 10% to 30% of patients with IBD [12, 13].

Epidemiology

Nearly 4 million individuals worldwide are affected with inflammatory bowel disease and approximately 1.4 million of these cases occur in the United States [14]. In the U.S. the prevalence of CD and UC among adults is 201 and 238 per 100,000, respectively [15]. Arthropathy is the most common EIM seen in IBD, with reported overall prevalences of 17–39% (Table 1). Major retrospective and prospective studies from the literature are summarized in Table 1. Classification or diagnostic criteria, if specified, are included. Studies which did not provide sufficient data to assess methodology, incidence or prevalence, or appropriate diagnosis were excluded. The reported prevalence is widely variable between studies; discrepancies may be due to differences in study methods for patient selection or diagnostic criteria for arthropathy. While an exam by a rheumatologist was conducted in a majority of the studies, this was often done only in selected patients who were overtly symptomatic on visit to a gastroenterologist, those who self reported arthritis on a questionnaire, or who had diagnosis of arthritis on review of medical records. A minority of studies involved examination of consecutively enrolled patients by a rheumatologist; these are explicitly noted in Table 1. Considering these studies only, a more accurate overall prevalence may be 31.5–39%. The prevalence of arthritis may also be underestimated due to the transient nature of oligoarticular peripheral arthritis or the response of arthritis to steroids given for IBD flares. Many of the studies were cross-sectional. As extraintestinal manifestations develop over time, the true incidence or prevalence cannot be estimated from those analyses.

Table 1 Prevalence of arthropathy in patients with inflammatory bowel disease

Author	Year	Country	Patients	AS%	SI ¹ %	Peripheral arthritis%	IBP ²	SpA ³	Overall%	Diagnostic criteria
Acheson[16]	1960	United States	1917	2.1						
^a Ansell[17]	1964	Canada	91 (CD)	6.5	19.7	15.3				SI per Dixon and Lience
^a Wright[18]	1965	Great Britain	234 (UC)	6.4	17.9					
^a Wright[19]	1965	Great Britain	269 (UC)	5.5		11.5				
^a Haslock [20]	1973	Great Britain	116 (CD)	16		20.4				NY
^a DekkerSaeys [21]	1989	Netherlands	109	3.7	10.1	12.8				NY
Maeda[22]	1994	Japan	203 (CD)	1.5		10.3				
Véloso[23]	1996	Portugal	792	2.9%		16.2				
Orchard[4]	1998	Great Britain	1459	1.0		7.4	5.2			Modified NY
Suh[24]	1998	Korea	129	1.6	6.2	15.5			17.1	
Triantafyllidis[25]	2000	Greece	155 (CD)			30% ^d				
^a De Vlam[26]	2000	Netherlands	103 (CD)	3.8	21.8		30	34.9	39	Modified NY ESSG
^a Queiro[27]	2000	Spain	62 (UC)	3.2	24.2	30.6				Modified NY ESSG, Amor
^a Salvarani[1]	2001	Italy/Netherlands	160	3.1	3.6	10.6	8.8	18.1	33.1	Modified NY ESSG
Christodoulou[28]	2002	Greece	252		5.9	2.8				
^a Palm[29]	2001	Norway	521			12%/0.8% ^f				
^a Palm[30]	2002	Norway	406	3.7	2.0	17	18.0 ^e	22		Modified NY ESSG
Al-Shamali[31]	2003	Kuwait	90 (UC)			31 ^d				
Steer [32]	2003	United Kingdom	134 CD		23% ^b					
^a Turkcapar[33]	2006	Turkey	162	9.9	45.7	14.8		45.7		Modified NY ESSG
Peeters[34]	2008	Belgium	251 (CD)	6	27	29				Modified NY
^a Lanna[2]	2008	Brazil	130	6.2	9.2	25.4	10		31.5	Modified NY
^a Orchard[35]	2008	United Kingdom	44 CD	11.4	39%					MRI of SI Modified NY
D’Inca[36]	2009	Italy	651	1.4	3.5 ^b	3.7				Modified NY/ESSG
Yüksel[37]	2010	Turkey	357			18.5				
Hwangbo[38]	2010	Korea	163		16.6 ^c					Modified NY
Vávricka[39•]	2011	Switzerland	950	4.1		28.6				

1: radiographic sacroiliitis regardless of symptoms, unless otherwise noted, 2. per Calin’s criteria, 3. per ESSG criteria

^a included enrollment and examination by rheumatologist regardless of whether musculoskeletal symptoms were present

^b all patients were symptomatic

^c all patients were asymptomatic

^d included arthralgias

^e excluding AS

^f 12% including patient history of arthritis, 0.8% excluding patient history of arthritis

SI may be the most common manifestation, seen in 2.0–45.7% of patients. AS is seen in 1.0–16% of patients, and peripheral arthritis is seen in 2.8–31% of patients. Overall 18.1–45.7% of patients fulfill the ESSG criteria for SpA.

Enthesopathy was not specifically included in Table 1 as it is not a frank arthritis but rather a peri-arthritis. Prevalence of enthesitis among IBD patients in the literature is reported to be between 6% and 50% [26, 30, 33].

Arthritis may occur more frequently in CD than UC [20, 23]. Risk factors for arthritis may include active disease or family history of IBD [39•]. Women may be at greater risk for peripheral arthritis [4, 37], whereas men tend to have

more frequent axial involvement. The presence of other EIMs such as Erythema nodosum or Pyoderma gangrenosum may also be risk factors [4, 23, 37].

Pathophysiology

Gut-joint hypothesis

The link between gut and joint inflammation in IBD is not fully understood but has been extensively studied. Interestingly, patients with all subsets of SpA have demonstrated subclinical

evidence of gut inflammation, [40] and 7% of patients with any SpA may go on to develop overt IBD [41]. Prospective serial ileocolonoscopy studies have demonstrated a relationship between coincident gut and joint inflammation in SpA, though relative severities were not commented on [41]. Peripheral arthritis has also been correlated with increased gut inflammation in patients without IBD, and remission of arthritis was accompanied by normalization of gut mucosa. [41].

Two major theories to explain development of arthritis in the setting of IBD involve gut bacteria and migration of gut lymphocytes to the joint, but neither have been fully developed [42]. In the first, the HLA-B27/human β 2 microglobulin transgenic rat model of SpA like disease, a germ free environment prevents the development of gut and joint disease, suggesting bacterial exposure is necessary for the development of SpA in the proper genetic background [43]. This model does not explain the co-localization of inflammation to the synovium and gut or identify the specific bacterial antigens which may incite inflammation.

In the second theory, lymphocyte trafficking to various tissues is dependent on various adhesion molecules and receptors. For gut homing, α 4 β 7 and α E β 7 integrins and MadCAM-1 mucosal vascular receptor are important. Binding of intestinal lymphocytes to synovium from in vitro studies seems to be dependent on other adhesion molecules such as vascular adhesion protein-1 (VAP-1) [44]. Lymphocytes from the gut may migrate to the synovium, leading to inflammatory arthritis. Identical T cell clones have been identified in synovium and gut mucosa from a patient with SpA [45]. In addition to lymphocytes, macrophages expressing the scavenger receptor CD163 have been found in gut mucosa from patients with CD and SpA [46] as well as in synovium [47]. It is possible that these cells could also migrate from the gut to the joint, as in vitro they can bind to synovial tissue vessels [48]. While these models exhibit the importance of lymphocyte and macrophage trafficking and explain how effector cells can co-localize to the gut and synovium, the inciting antigen or immune trigger remains unclear. A novel mechanism proposed by studies in the TNF overexpressing TNF Δ ARE mouse model of SpA-like disease has suggested that mesenchymal cells in the gut and joints may be targets for TNF mediated inflammation [49]. This suggests another cell type linking intestinal and joint pathologies.

Genetics

Genetics may at least partially explain the predisposition of some patients with IBD to develop arthritis by alterations in adaptive and innate immune pathways. HLA-B27, as discussed above, may contribute to pathogenesis of arthritis in IBD, through presentation of arthritogenic peptides to T

cells; alternatively, this genotype may predispose to protein misfolding leading to inflammation [50]. However HLA-B27 appears to explain only a small portion of genetic susceptibility to arthritis in IBD.

Over 71 susceptibility loci have been identified in IBD [51•]. Genome wide screens have repeatedly implicated NOD2/CARD15 on chromosome 16q12 which may explain up to 20% of overall genetic susceptibility in CD [51•, 52–54]. NOD2/CARD15 plays a role in the innate immune response by serving as an intracellular receptor for bacterial pattern molecules in monocytes and ultimately activating NF κ B. Alteration in the gut host-microbial interaction may play a role in the pathogenesis of CD. In terms of the development of arthritis, the association is less clear. In SpA patients the overall prevalence of CARD15 polymorphisms was not increased [55–57], although it was associated with a higher risk of gut inflammation.

An IL-23R polymorphism which has been strongly associated with protection against IBD [58] was also found to be associated with protection against AS [59, 60•]. STAT3 was also implicated in a study of CD associated genes in AS patients [60•]. STAT3 is activated in response to signaling through the IL-23R in the Th17 pathway. IL12B, which encodes the p40 subunit of IL-12 and IL-23, was also identified in this study, and emphasizes the role of the Th17 pathway in pathogenesis of SpA.

It is not clear if any of these genes increase susceptibility to arthritis in IBD. Further studies are needed to determine which genes increase susceptibility to arthritis within the setting of IBD.

Diagnosis

No laboratory test can make the diagnosis of IBD associated arthritis, or be used in isolation to determine disease activity. Diagnosis is largely clinical, based on the presence of peripheral or axial arthritis in the setting of IBD. Inflammatory markers such as CRP, ESR, platelet, or white blood cell count, can be elevated by IBD alone, without arthritis, and therefore may be difficult to interpret in the setting of IBD associated arthropathies. Alternatively, inflammatory markers may be normal in the setting of active arthritis; therefore, a normal ESR or CRP does not eliminate the diagnosis of active arthritis.

While the prevalence of HLA-B27 in idiopathic AS is greater than 90% [61] there is no overall increased frequency of HLA-B27 in IBD patients overall. In the subset of patients with IBD and AS, however, up to 78% are HLA-B27 positive [26, 32]. In contrast, isolated sacroiliitis does not seem to be related to HLA-B27 [32, 35, 62]. HLA typing does not aid in the diagnosis of IBD associated arthritis, but it may be that HLA-B27 individ-

uals with IBD are at increased risk of developing axial disease [35].

Imaging

Imaging is generally not needed for diagnosis of IBD associated peripheral arthritis although imaging may be helpful in the consideration of other conditions. Plain radiographs of peripheral joints may show effusions or periarticular osteopenia as is seen in other inflammatory arthritides. Erosions and joint destruction are rare.

In contrast to peripheral arthritis, the diagnosis of axial arthritis may require imaging. The hallmarks of axial spondyloarthritis are inflammation and bony proliferative changes, including syndesmophytes in the spine or ankylosis of the SI joints. Idiopathic AS and IBD-associated arthropathy have very similar presentations in the spine and SI joints. The lower half of the thoracic spine is most commonly affected in AS [63•]. Advanced disease in the spine in AS may show sclerosis, syndesmophytes, or vertebral fusion producing bamboo spine. Erosions or destructive lesions do occur in axial SpA, but less frequently than osteoproliferative lesions [64].

Plain AP radiographs of the pelvis and spine are standard methods for evaluating sacroiliitis and AS in patients with suspicion for axial involvement. These methods are the gold standard for detecting structural changes, however these occur mostly in advanced disease and may take several years to develop.

MRI may be the best technique for detecting active inflammation in the spine and sacroiliac joints, facilitating earlier diagnosis. For decades, diagnostic radiologic criteria (i.e. Modified New York Criteria) for AS included grade 2/3 sacroiliitis on plain films. The New ASAS classification criteria for Axial SpA now include sacroiliac inflammation on MRI as acceptable evidence of sacroiliitis [65•]. While there are consensus guidelines by ASAS/OMERACT investigators for scoring sacroiliitis, this has not been done yet for spinal inflammation. MRI may also be able to detect bony structural changes as well, but this has not been fully studied.

MRI may also be helpful in predicting and monitoring response to treatment [63•].

Treatment

In general, there are few studies of treatment in IBD associated arthropathy and there is a need for larger and randomized controlled studies.

As oligoarticular peripheral arthritis can parallel the course of IBD, treatment of IBD may resolve this type of arthritis. For UC, colectomy may be a curative option for

bowel disease, and may be ameliorative for peripheral arthritis as well, especially Type 1. However there are case reports of arthritis developing de novo after proctocolectomy for UC, particularly with ileo-pouch anal anastomosis, in the setting of pouchitis [66, 67]. Pouch creation, done to leave the anal sphincter intact and permit patients better quality of life than with an ostomy, may leave residual inflamed colon. This may then facilitate arthritis by persistence of abnormal intestine [68].

Polyarticular (as opposed to oligoarticular) and axial arthritis are more independent of IBD activity, and may require separate treatment from the underlying IBD. Conventional IBD therapies such as antibiotics or 5-ASA compounds are not effective for this type of arthritis as their activity occurs only within the gut. Treatment options for peripheral arthritis include NSAIDs, steroid injections and analgesics. NSAIDs may potentially exacerbate IBD. However COX-2 inhibitors such as Celecoxib, have not been shown to increase endoscopic relapse compared to placebo [69], and may be a therapeutic option, but this has not been studied in treatment of arthropathy in IBD.

DMARDs may be considered for patients who are refractory to conservative measures. Sulfasalazine (SSZ) may be effective in treating peripheral arthritis and has activity for UC bowel inflammation in UC, although it is not particularly effective for axial disease. Methotrexate (MTX) has greater utility in CD than in UC for gut inflammation; further evaluation is ongoing in two randomized multicenter trials (METEOR in Europe, and MERIT in U.S.) [70]. MTX, which has longstanding use in rheumatoid arthritis, may prove beneficial for arthropathy in IBD as well as for IBD itself. Hydroxychloroquine and azathioprine are not effective for arthritis in IBD. Other peripheral musculoskeletal manifestations, such as enthesitis or dactylitis, are also indications for immunomodulatory therapy.

For axial manifestations, older literature recommends that NSAIDs may be the first line therapy, though given the concern of NSAIDs in IBD, this recommendation must be taken cautiously. Physical therapy and exercise are important in preventing deformities and preserving range of motion.

TNF inhibitors have been found to be highly effective for IBD patients who are steroid dependent or refractory to conventional treatment. Infliximab is the best studied anti TNF therapy in IBD. Infliximab is highly effective in moderate to severe CD and UC, promoting fistula closure, mucosal healing, and sparing use of steroids. [71–73]. There is also evidence that Infliximab is effective for axial and peripheral joint manifestations of IBD, largely from small case series and open-label studies [74–76]. Adalimumab also has effectiveness for AS and CD [77–80]. Results from the CARE study [81••] demonstrated a benefit for Adalimumab in treating the EIMs of CD. CARE was a large multi-center

phase IIIb open-label clinical trial of 945 CD patients conducted in Europe. EIMs were evaluated by physical exam and patient interview. A formal examination by a rheumatologist was not performed, and there were no radiographic investigations to evaluate for sacroiliitis or other axial manifestations, so arthritis incidence may have been underestimated. However, there was a benefit for arthropathy with incidence of arthritis reduced from 8.7% at baseline (82 patients) to 2.1% (20 patients) at week 20. A reduction in arthralgia and sacroiliitis was also seen. There was no effect seen for ankylosing spondylitis in this study, but the incidence of AS in this population of patients with IBD was very low.

Etanercept has not been found effective for CD colitis [82], and further may increase the incidence of IBD in pediatric patients with JIA [83]. There is no data to date on the utility of Certolizumab or Golimumab for IBD associated arthropathy.

While there is experience with more novel biologics apart from anti TNF agents in RA and SpA, there is little data for the use of these agents in IBD associated arthritis. However, as with RA, there are a number of IBD patients (20–30%) who do not respond to anti TNF therapy [84], and up to 40% secondarily develop refractoriness during the course of therapy [72]. Therefore there is a need for further characterization of other biologic agents in treatment of IBD.

Ustekinumab a fully human monoclonal immunoglobulin (IgG1) against the interleukin (IL)-12/23 shared P40 subunit has been shown in phase 2 studies to have clinical effectiveness in CD gut inflammation [85], and may be particularly beneficial in patients refractory to Infliximab. Given the genetic association with IL23R, STAT3, and IL12B in CD and AS, this is a particularly attractive pathway to target. Significantly, Ustekinumab has also shown efficacy in phase II studies for treatment of Psoriatic Arthritis, another SpA [86].

Abatacept, which inhibits Tcell costimulation (CTLA4-Ig), was theorized to be useful in IBD, as CTLA4 polymorphisms may play a role in pathogenesis of the disease [87, 88]. However, a Phase 3 study (NCT00406553) among patients with Crohn's Disease was terminated due to lack of efficacy.

B cell depletion by Rituximab has demonstrated effectiveness in RA, and is theorized to be effective in IBD. However there are several case reports of worsening or development of IBD during therapy [89, 90]. In addition, a small RCT showed no significant impact on inducing remission in UC [91].

Tocilizumab (humanized anti human interleukin-6 receptor monoclonal antibody) is effective in some patients with RA failing anti-TNF therapy. It is associated with intestinal ulcers and perforation [92]. Interleukin-6 may be important for mucosal wound healing in the gut [93] and therefore

tocilizumab may not be an ideal choice for treatment of arthritis in IBD patients.

Anti adhesion molecule therapies are an attractive target for IBD treatment by blocking lymphocyte migration into gut tissue. Natalizumab, a humanized monoclonal antibody that blocks alpha4beta1 integrin-mediated leukocyte adhesion and migration into inflamed tissue, has demonstrated effectiveness in IBD, but has not been studied in inflammatory arthritis [94].

Finally it is important to note that bone mineral density is decreased in patients with IBD due to use of steroids, inflammation, malabsorption, and nutritional factors. Osteoporosis is highly prevalent and bone density testing and osteoporosis treatments seem to be underutilized [95]. Patients with IBD associated arthritis should be aggressively evaluated for vitamin D deficiency, supplemented with calcium and vitamin D, and considered for osteoporosis screening where appropriate.

In our experience, patients with IBD- associated arthropathy usually present initially to gastroenterology, who will then refer the patient to Rheumatology for further evaluation and treatment. These patients require a full articular exam, both axial and appendicular, in addition to an 18 tender-point exam. For those patients who do not have arthritis, but rather have a myofascial pain syndrome, our approach is to use medications which are helpful in fibromyalgia. For those patients who do have a true arthritis, however, immunosuppressive therapy is usually necessary. Rarely, patients will present initially to Rheumatology, and a careful review of systems reveals an underlying gastrointestinal problem; in this setting, a prompt GI referral for work-up is indicated, as immunomodulatory therapy may abrogate findings on endoscopy and delay diagnosis of IBD. We do not routinely assess for HLA B27, even among patients presenting with axial disease or isolated sacroiliitis.

Glucocorticoids are often effective, but most patients, with taper, have recurrence of their joint pains and stiffness. Azathioprine (AZA) and 6-Mercaptopurine (6-MP) seldom induce remission of joint symptoms, especially if there is axial skeleton involvement. MTX is often effective for appendicular skeleton involvement, and may be useful for patients whose intestinal disease is also not controlled; for patients with active intestinal disease, it should be given intramuscularly at a dose of 25 mg weekly. Lower doses and oral administration have been shown to be ineffective for intestinal disease. Sulfasalazine may also be effective for appendicular involvement as well.

For axial skeleton involvement, most patients will require anti-TNF therapy. It is worth noting that Etanercept is ineffective in IBD [82], and that some patients do not always respond to the first anti-TNF agent tried. We have had success using Infliximab, and Adalimumab; in rare cases, where those have not been effective, both Certolizumab and

Golimumab have also proven effective. Standard of care for IBD patients does not include concomitant use of MTX to prevent antibody formation (Human Anti-Chimeric Antibodies, or HACAs, against infliximab, and Human Anti-Human Antibodies, or HAHA), though this is noted to be an issue in the GI literature and is associated with both infusion reactions and decreased drug efficacy [96], and MTX has been shown to decrease the rate of HACA and HAHA formation [97, 98]. Our approach is to initiate MTX, SSZ, or at least AZA or 6-MP, when an Anti-TNF agent is required to decrease the likelihood of loss of efficacy. We do note that there is little evidence that SSZ, AZA, or 6-MP reduce HACA or HAHA formation, however theoretically this may reduce the likelihood of antibody formation.

Conclusions

Arthropathy is common in inflammatory bowel disease, with both peripheral and axial musculoskeletal manifestations. Pauciarticular peripheral arthritis may correlate better with intestinal disease than polyarticular arthritis or axial arthritis. The connection between gut and joint inflammation, and predisposing genetic factors, remain unclear. There are no laboratory tests which confirm the diagnosis. Imaging can be helpful in identifying axial disease, and MRI can aid in earlier detection of inflammatory spinal and sacroiliac disease. Oligoarticular arthritis may respond to treatment of IBD, but other forms of IBD associated arthritis may be less likely to respond to treatment of IBD. There are few studies specifically examining the treatment of arthritis in IBD. For mild disease, local steroid injections and nonbiologic DMARDs, such as MTX and SSZ, can be considered. For refractory disease, TNF inhibition therapy has demonstrated benefit in treatment of arthritis associated with IBD, and other biologic agents are promising.

Disclosures No conflicts of interest relevant to this article were reported.

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- Of importance
- Of major importance

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