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REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Extraintestinal Manifestations of Inflammatory Bowel Disease: Current Concepts, Treatment, and Implications for Disease Management

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Inflammatory bowel diseases (IBDs) are systemic diseases that manifest not only in the gut and gastrointestinal tract, but also in the extraintestinal organs in many patients. The quality of life for patients with IBD can be substantially affected by these extraintestinal manifestations (EIMs). It is important to have knowledge of the prevalence, pathophysiology, and clinical presentation of EIMs in order to adapt therapeutic options to cover all aspects of IBD. EIMs can occur in up to 24% of patients with IBD before the onset of intestinal symptoms, and need to be recognized to initiate appropriate diagnostic procedures. EIMs most frequently affect joints, skin, or eyes, but can also affect other organs, such as the liver, lung, and pancreas. It is a frequent misconception that a successful therapy of the intestinal inflammation will be sufficient to treat EIMs satisfactorily in most patients with IBD. In general, peripheral arthritis, oral aphthous ulcers, episcleritis, or erythema nodosum can be associated with active intestinal inflammation and can improve on standard treatment of the intestinal inflammation. However, anterior uveitis, ankylosing spondylitis, and primary sclerosing cholangitis usually occur independent of disease flares. This review provides a comprehensive overview of epidemiology, pathophysiology, clinical presentation, and treatment of EIMs in IBD.

Keywords: Inflammatory Bowel Disease; Crohn's Disease; Ulcerative Colitis; Extraintestinal Manifestations; Arthralgias; Arthritis; Psoriasis; Spondyloarthropathy; Erythema Nodosum; Pyoderma Gangrenosum; Uveitis; Primary Sclerosing Cholangitis.

Inflammatory bowel diseases (IBDs) not only affect the gastrointestinal tract, but can also involve many other organs of the body. Involvement of organs outside the gastrointestinal tract are usually termed *extraintestinal manifestations* (EIMs) of IBD.[1–3] EIMs occur with varying frequency, depending on the affected organ. EIMs can occur before or after the diagnosis of IBD. They can substantially impact the quality of life of patients with IBD, sometimes more so than the intestinal disease. Frequently, EIMs require specific treatments or at least need to be considered when deciding on the treatment of the intestinal inflammation.[1–3] EIMs can occur together with flares of the underlying IBD and respond to the treatment of the intestinal inflammation or they can be independent of the IBD activity.

EIMs should be differentiated from extraintestinal complications of IBD.[4] Extraintestinal complications are direct or indirect sequela of intestinal inflammation. EIMs have been defined as "an inflammatory pathology in a patient with IBD that is located outside the gut and for which the pathogenesis is either dependent on extension/translocation of immune responses from the intestine, or is an independent inflammatory event perpetuated by IBD or that shares a common environmental or genetic predisposition with IBD."[5] EIMs are common in both ulcerative colitis (UC)[6] and Crohn's disease (CD).

In both CD and UC, EIMs most commonly involve the musculoskeletal system (eg, peripheral and axial arthritis and enthesitis), skin (eg, pyoderma gangrenosum [PG], erythema nodosum [EN], Sweet syndrome, and aphthous stomatitis), hepatobiliary tract (primary sclerosing cholangitis [PSC]), and eyes (episcleritis, anterior uveitis, and iritis) (Table 1, Figure 1). However, almost any organ can be affected. These organ manifestations might not be clinically obvious or easy to detect. For example, an acute or chronic pancreatitis associated with IBD (and not with IBD medication, such as azathioprine) is rare.[7,8] However, asymptomatic exocrine insufficiency, pancreatic duct abnormalities, and hyperamylasaemia are seen in up to 18% of patients with IBD,[8] and antibodies against exocrine pancreatic tissue (PAbs) can be found in up to 29% of patients with CD, but not with UC.[9] Other conditions, such as pneumonitis or PSC can persist in patients with UC, even after proctocolectomy.

EIMs in IBD represent a challenge for the treating health care providers. Multidisciplinary integrated management plans in IBD practices can improve patient outcomes, as well as quality of life.[6]

Abbreviations used in this paper: **AS, ankylosing spondylitis; AxSpA, axial spondyloarthritis; CD, Crohn's disease; EIM, extraintestinal manifestation; EN, erythema nodosum; IBD, inflammatory bowel disease; IL, interleukin; NSAID, nonsteroidal anti-inflammatory drug; PAb, antibody against exocrine pancreatic tissue; PG, pyoderma gangrenosum; PsA, psoriatic arthritis; PSC, primary sclerosing cholangitis; SIBDCS, Swiss Inflammatory Bowel Disease Cohort Study; SpA, spondyloarthritis; TNF, tumor necrosis factor; UC, ulcerative colitis; VTE, venous thromboembolic event.**

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Table 1. Extraintestinal Manifestations of Inflammatory Bowel Diseases

Organ system	Manifestations	Prevalence
Gastrointestinal	PSC Autoimmune pancreatitis Autoimmune hepatitis	UC: up to 5%; CD: rare Rare Rare (< 1%)
Mucocutaneous	EN PG Oral aphthous ulcers Sweet syndrome Orofacial granulomatosis	5%–15% in CD; 2%–10% in UC 0.4%–2.6% in IBD 5%–50% in CD Rare Rare
Musculoskeletal	IBD-related arthritis Peripheral arthritis Axial arthritis Enthesitis	CD: 10%–20% ; UC: 4%–14% Up to 50% in CD (asymptomatic)
Ocular	Episcleritis and scleritis Anterior uveitis	Scleritis: up to 1%; CD: 5%–12%; UC: 3.5%–4.1%
Pulmonary	Pneumonitis	Rare
Vascular	Cardiovascular disease Thromboembolism Portal vein thrombosis	NA 3- to 4-fold increase Rare

NA, not available.

Epidemiology, Frequency, and Chronology of Extraintestinal Manifestations in Inflammatory Bowel Disease

The prevalence and incidence of EIMs are dependent on the types of EIMs included in definitions, as outlined. More stringent definitions of EIMs, as suggested by the European Crohn's and Colitis Organization's working group on EIM, will result in lower estimates of prevalence: "An inflammatory pathology in a patient with IBD that is located outside the gut and for which the pathogenesis is either dependent on extension/translocation of immune responses from the intestine, or is an independent inflammatory event perpetuated by IBD or that shares a common environmental or genetic predisposition with IBD."[5] Given this potential for variability, it is perhaps not surprising that EIMs in IBD have been reported with frequencies ranging from 6% up to

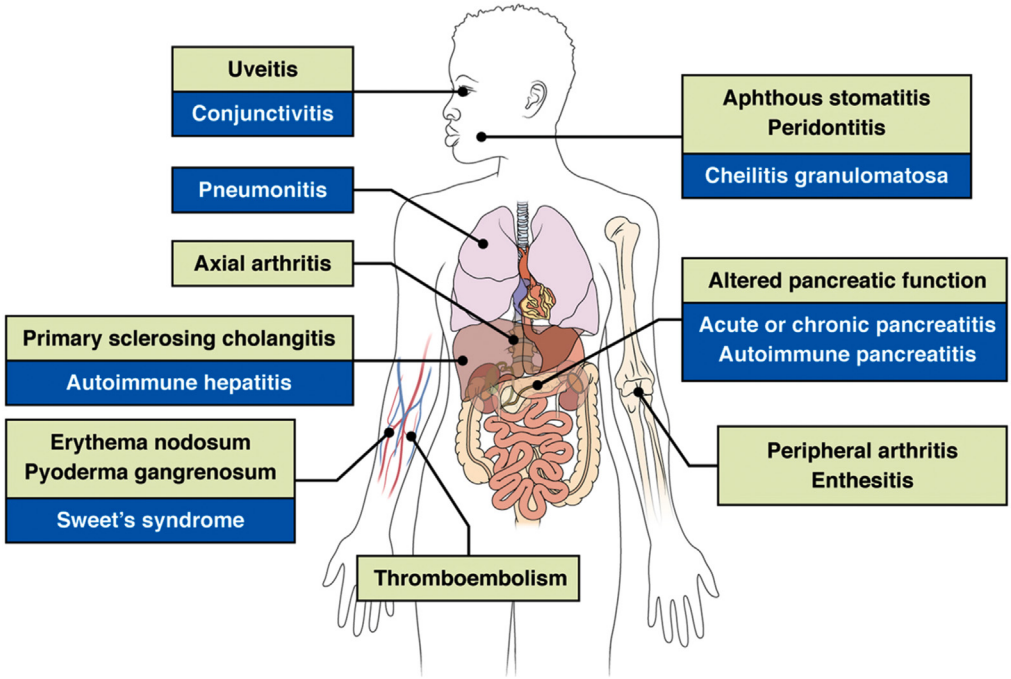

Figure 1. EIMS of IBD affect many organs; *green*: frequent EIMs; *blue*: rare EIMs.

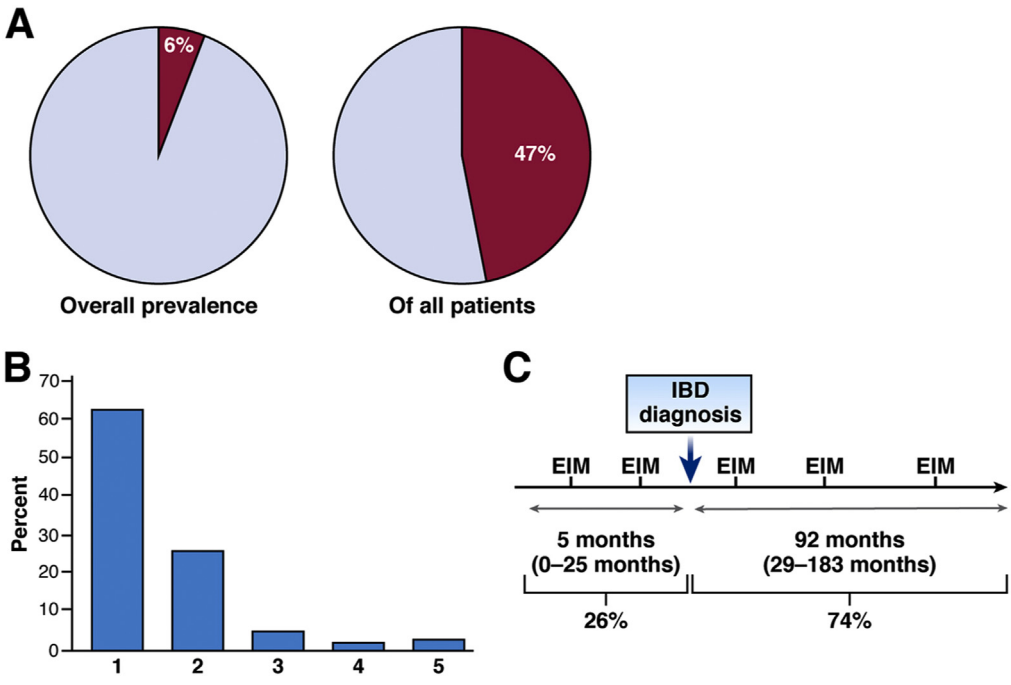

Figure 2. Epidemiology of EIMs in patients with IBD. (*A*) Dependent on the definition, the prevalence of EIMs is reported to be between 6% and 47% of all patients. (*B*) Patients can be affected by more than 1 EIM. More than 20% of all patients with IBD report 2 EIMs. More than 10% of patients report 3 or more different EIMs. (*C*) EIMs can occur before or after the diagnosis of IBD; 26% of all patients with EIMs report occurrence of EIMs up to 25 months (median 5 months) before IBD diagnosis.

47%[10] (Figure 2*A*). Further complicating assessment of prevalence is the fact that patients can be affected by more than 1 EIM. The Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS), a large study with a focus on EIMs, reported that up to 25% of EIM-affected patients with IBD have from several EIMs (up to 5).[11] In this cohort, 29% of patients with IBD were diagnosed with EIM, of those 63% presented with 1 EIM, 26% with 2 EIMs, 5% with 3 EIMs, 2% with 4 EIMs, and 3% with 5 EIMs during the observation period[11] (Figure 2*B*).

EIMs might be more frequent in early-onset IBD and in younger patients[12]; however, this has not been found in all studies. Grossman and DeBenedetti[13] reported EIMs in up to 68% of pediatric patients with IBD, and Stawarski et al[14] reported that 50% of patients with UC and 80% with CD had EIMs. In contrast, the SIBDCS group[15] reported a 16.7% (n = 55 of 329) prevalence of EIMs in pediatric patients with IBD. With a stringent definition of EIMs and analysis of 481 pediatric-onset patients with CD and 386 pediatric-onset patients with UC, only a trend toward higher rates of stomatitis in CD and of PSC and AS in UC was reported.[16] In addition, orofacial granulomatosis is seen mainly in male children or teens (male to female ratio at least 2:1) with CD.[17–20]

EIMs can present clinically either before or after the onset (or diagnosis) of IBD. Up to 26% of cases have their first EIM before IBD is diagnosed (median time 5 months before IBD diagnosis) and in 74% of cases, the first EIM manifested after IBD diagnosis (median, 92 months)[11] (Figure 2*C*). Before IBD diagnosis was made, peripheral arthritis was diagnosed in 19.7% of patients with EIMs, axial arthropathy or AS in 39.1%, aphthous stomatitis in 27.8% of patients, uveitis in 52.2%, EN in 14.3% PG in 14.3%, and PSC in 23.8% of patients.[11]

Pathophysiology of Extraintestinal Manifestations in Inflammatory Bowel Disease

It has been assumed that the factors relevant for the pathogenesis of EIMs are similar or the same as for the intestinal inflammation.[5] Genetic risk factors seem to play a role, as several are shared between IBD and various EIMs. Furthermore, environmental factors appear to play a role. The innate and adaptive immune system certainly plays an important role in the initiation and perpetuation of organ inflammation. In addition, the interaction with components of the microbiota can be important.

Genetic Risk Factors

The contribution of the genetic risk on the pathogenesis of EIMs is illustrated by association studies that describe a concordance for EIMs in 70% of parent–child pairs and 84% of sibling pairs.[21] In addition, there is a considerable overlap between genetic risk loci for EIMs and IBD.[5,22] The first risk variant identified in patients with CD, NOD2/CARD15, has also been associated with sacroiliitis and uveitis[23,24] (Figure 3). Weizman and coworkers[25] investigated skin EIMs and found associations between PG and known IBD loci, such as IL8RA, PRDM1, USP15, and TIMP3 (Figure 3). For EN, they found significant genetic associations with other IBD susceptibility variants, including PTGER4, ITGAL, SOCS5, CD207, and ITGB3, as well as rs6828740 (4q26)[25] (Figure 3). In patients with PSC, IBD risk variants have also been identified, including UBASH3A, BCL2L11, FOXO1, and IRF8, as well as SOCS1, JAK2, STAT3, and TYK2.[23]

The Arg381Gln variant of IL23R is protective against development of CD, with reduced risk by 3-fold.

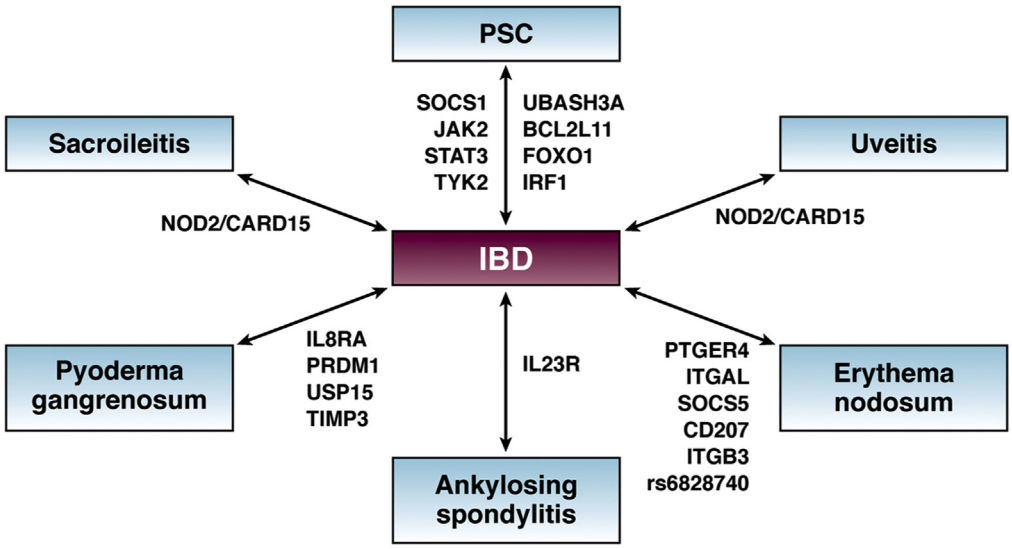

Figure 3. Shared genetic risk factors between IBD and extraintestinal manifestations.

Interestingly, the same polymorphism has also been shown to be protective against AS.[26] In a recent study applying full genome sequencing to detect monogenic IBD in a pediatric cohort, the odds ratio for EIMs in patients with monogenic IBD was 15.36 ($P < .0001$), corresponding to a prevalence of 76% in patients with CD and 42% in patients with UC.[27] This association further supports the pathogenetic role of genetic factors for the incidence and prevalence of EIMs, while suggesting that patients with very early onset of IBD and coexisting EIMs should be screened by full genome sequencing. The results of such genome screening can identify monogenic disease and the possibility of cure is suggested to be achieved by stem cell transplantation.[27]

Musculoskeletal EIMs are associated with HLA-A2, HLA-DR1, and HLA-DQw5 alleles in patients with CD and to DRB1*0103, B27, and B58 alleles in patients with UC.[28,29] Twenty-five percent to 78% of patients with IBD and AS are HLA-B27–positive. Up to 60% of patients with AS have asymptomatic gut inflammation; 25% might develop overt IBD over time. Germ-free HLA-B27 transgenic rats do not develop gut or joint inflammation, suggesting that bacterial exposure is a prerequisite for the development of spondyloarthritis (SpA) in genetically predisposed patients with IBD.[30]

Environmental Factors

Patients with CD who smoke are more likely to present with EIMs compared with nonsmokers.[31] The question of whether this is mediated by a cigarette smoke–induced modification of the intestinal microbiota (see below) remains to be answered.[32,33] Smoking is associated with a 10% higher incidence of skin and joint EIMs.[34] EIMs can be more prevalent with higher exposure to smoking.[34] Smoking cessation appears to have a positive effect on the prevalence of EIMs.[34] It is important to note that smoking has also been identified as an important environmental factor in the pathogenesis and severity of luminal and perianal CD. Interestingly, smokers are protected from the onset of UC and former smoking is a known risk factor for the development of UC.[35,36]

Activation of the Immune System

It has been hypothesized that EIMs can arise from cross-reactivity of antigen-specific immune responses against intestinal antigens at nonintestinal sites.[5] Shared peptide sequences between enteric bacteria and host major histocompatibility complex molecules have been reported.[37] Whether this can truly contribute to EIMs has not been demonstrated unequivocally and the antigen specificity of potential T-cell clones mediating or causing EIMs in humans has not been defined.[5] Inflammatory T cells are recruited into the intestinal wall via the interaction of $\alpha 4\beta 7$ integrin (the target of respective therapeutic antibodies, such as vedolizumab) with mucosal addressin cell adhesion molecule 1 (MAdCAM-1). Ectopic expression of MAdCAM-1 has been reported in the liver,[38,39] however, this is not the case in other organs affected by EIMs.

Role of the Microbiota

Several pathways by which the microbiota could contribute to EIMs have been discussed previously.[5] A molecular similarity between gut microbiota antigens and nonmicrobial epitopes present on cells in the organs affected by EIMs is seen as a potential reason for a cross-reactivity of T-cell clones and immune cross-reactivity. This has never been clearly supported by evidence. Due to the leaky intestinal barrier, microbiota components, such as lipopolysaccharides, bacterial antigens, or metabolites, could be translocated from the gut to the extraintestinal site or can cause systemic inflammatory responses.[5] A dysbiosis could lead to an activation of intestinal immune cell populations that finally migrate to other organs. Preliminary evidence indicates increased abundance of *Clostridiaceae* in

patients with IBD and arthritis,[40] however, this association was relatively weak. Further evidence comes mainly from studies on "dysbiosis" and "microbiota diversity." Patients with SpA were reported to have decreased fecal gut microbial diversity (with increased abundance of *Ruminococcus gnavus* and the genus *Dialister*),[41,42] however, these patients did not have IBD.

Musculoskeletal Extraintestinal Manifestations

Clinical characteristics and epidemiology. Musculoskeletal EIMs represent the most common EIMs in IBDs, affecting up to 46% of patients with IBD. The prevalence of these EIMs has been reported to range from 6% to 46% of patients, depending on the clinical and/or skeletal radiologic criteria used. Geographical area can also contribute to the large heterogeneity in prevalence and descriptions, further complicated by a lack of specificity in clinical trial indices of joint pain (arthralgias) and joint inflammation (arthritis). The prevalence of arthritis in IBD can decrease with increasing age; it has been reported that the prevalence of musculoskeletal EIMs in the 20- to 30-year-old age group was nearly 25%, and in the age group of 50–60 years it was 2%.[43]

From a rheumatologic standpoint, musculoskeletal EIMs of IBD are classified within the SpA family of conditions; in addition to IBD-related arthritis, this includes psoriatic arthritis (PsA), AS (also called axial spondyloarthritis [axSpA]), enthesitis-related arthritis (a type of juvenile idiopathic arthritis), reactive arthritis (sometimes referred to in the past as Reiter's syndrome), and idiopathic acute anterior uveitis (iritis) (Table 2). IBD arthritis can affect both the peripheral skeleton and the axial skeleton. For example, synovitis of the hands and feet can occur, with features similar to many patients with PsA. Axial involvement, including sacroiliitis, can occur with features typical of AS. Enthesitis (inflammation of the insertion of tendons, ligaments, and joint capsule into bone), an important domain of SpA conditions, can affect the peripheral and axial skeleton. In addition to pain related to inflammation of synovium and entheses, pain among patients with SpA can also derive from other conditions, such as fibromyalgia and osteoporosis with related fractures. Peripheral arthritis is sometimes further categorized as oligoarticular (4 or fewer joints involved) or polyarticular (more than 4 joints). Although these were sometimes considered distinct entities in the past, it appears that this relates more to duration and progression, with most patients with polyarticular SpA (which is more often associated with poorer outcomes than oligoarticular) beginning their clinical course with oligoarticular involvement. Conditions within the SpA family are typically seronegative for rheumatoid factor; hence, the older appellation of "seronegative spondyloarthropathy." It is worth noting, however, that the actual prevalence of a positive rheumatoid factor test is higher among patients with SpA (approximately 15% or more) than the general population (5% positive, by definition). Also, tests for anti–citrullinated peptide antibodies, are mostly negative, but are positive more often than in the general population (8%–12% vs 5%). In addition, distinct from rheumatoid arthritis, SpA arthritis is less commonly deforming, and less often associated with erosive changes on radiographs. However, erosive disease affecting the hips, elbows, metacarpophalangeal joints, and metatarsophalangeal joints have all been described.

Peripheral arthritis. Peripheral joint involvement occurs in 5%–14% of patients with UC, and 10%–20% of patients with CD (Table 3). The diagnosis of peripheral SpA is mainly clinical, based on the evidence of objective inflammation in peripheral joints and entheses. Musculoskeletal ultrasound and magnetic resonance imaging can support the diagnosis, showing typical signs of arthritis, enthesitis, tenosynovitis, and bursitis. There is no reliable laboratory test that can be used as a diagnostic or activity index of IBD-related arthritis. A normal sedimentation rate does not exclude active disease, nor does a high-level confirm. Serologic diagnostic tests (rheumatoid factor and anti–cyclic citrullinated peptide) are generally negative, but a positive result by no means excludes these diagnoses.

A classic study published in 1998 that excluded patients with axial involvement, described 2 main patterns of peripheral arthritis.[44] Type 1 arthropathy is the classic form, characterized by oligoarticular asymmetric arthritis affecting fewer than 5 joints, involving preferentially large joints (ankles, knees, hips, wrists, elbows, and shoulders). This arthropathy usually involves acute self-limiting attacks

Table 2. Musculoskeletal Conditions Associated With Inflammatory Bowel Disease: Classification of Arthritis Associated With Inflammatory Bowel Disease

Type of arthritis	Characteristics	Prevalence, %
Arthralgia without arthritis	Joint pain without synovitis	5–16
Axial arthropathy		
AS	Inflammatory back pain with imaging evidence of sacroiliitis and/or spinal inflammation	1–12
Isolated sacroiliitis	Sacroiliac joint erosions or sclerosis on imaging	16–46
Inflammatory back pain	Back stiffness without radiologic findings	17–22
Dactylitis	Swelling of entire digit	2–5
Enthesitis	Tendon, ligament, or joint capsule insertion pain	6–54

Table 3. Musculoskeletal Conditions Associated With Inflammatory Bowel Disease: Therapy of Peripheral and Axial Arthritis in Inflammatory Bowel Disease

Variable	Prevalence	Diagnosis	Therapy
Peripheral arthritis (peripheral SpA)	5%–14% in UC 10%–20% in CD	Clinical (and US or MRI)	Treatment of intestinal inflammation COX-2 inhibitors Corticosteroids (short term) Sulfasalazine (especially in UC) Methotrexate Anti-TNF
Axial arthritis/ axSpA	Up to 50 % in CD symptomatic in up to 8%	Clinical and MRI	Anti-TNF

MRI, magnetic resonance imaging; US, ultrasound.

of less than 10 weeks' duration, is strongly associated with EIMs of IBD, such as EN and uveitis, and it is often associated with active IBD. Type 2 arthropathy is characterized by polyarticular involvement, 5 or more joints, is symmetric mainly affecting small joints of both hands with pain, swelling, or effusion that usually persist for months or years. This type of arthritis is largely independent of IBD activity. It is commonly associated with uveitis but not with other EIMs of IBD. However, more currently, these different types might be considered more of a continuum. Early on, patients tend to have less joint involvement, some remain oligoarticular, and some develop into the polyarticular pattern. This was seen in a more recent study that examined the prevalence of musculoskeletal EIMs among patients in an IBD clinic. In 1 study of 350 patients with IBD (206 patients with CD and 138 patients with UC), 129 patients (37%) had 1 or more musculoskeletal EIMs. Interestingly, it was relatively evenly split, with 23% of patients having axial involvement and 24% having peripheral involvement. There was a similar prevalence of these EIM among patients with CD and UC.[45]

As noted, enthesitis, tenosynovitis, and dactylitis occur commonly. Several studies report a prevalence of enthesitis in adult patients with IBD, ranging from 7% to 50%. Chronic enthesitis can lead to functional disability and structural changes, including osteopenia, bone cortex irregularities and erosions, soft-tissue calcifications, and abnormal new bone formation.[46] Enthesitis is often missed on clinical examination and can be detectable at an earlier stage with ultrasound of the affected area.

Axial arthritis/spondyloarthropathy. IBD-related spondyloarthropathy can cause a variety of symptoms due to axial involvement seen in active sacroiliitis or spondylitis. Axial SpA can occur concomitantly with peripheral involvement, including synovitis, dactylitis, and enthesopathy, such as Achilles tendinitis, plantar fasciitis, and chest wall pain.[43,47] Although idiopathic AS is associated with HLA-B27 in >90% of cases, the strength of the HLA-B27 association in spondylitis complicating IBDs is less (approximately 50%–70%); this is true for spondylitis associated with other SpA conditions, such as PsA and reactive arthritis. AS is characterized by persistent inflammatory low back pain and its clinical diagnosis is supported by magnetic resonance imaging. In advanced cases, marginal vertebral bodies, syndesmophytes, and bony proliferation aspects with axial ankylosis are observed on standard radiograph. In many patients with AS, it can take years from the onset of inflammatory back pain to the development of radiographic sacroiliitis. An anteroposterior radiograph of the pelvis should be considered in patients with IBD with back pain to evaluate for sacroiliitis. Magnetic resonance imaging using the short-tau inversion recovery technique is an excellent tool to demonstrate sacroiliitis and enthesitis, it can show inflammation, bone marrow edema, and bony erosions that are still not detectable by conventional radiographs. Interestingly, similar information can often be gleaned from magnetic resonance enterography examinations of such patients; it would be worthwhile to alert the radiologist interpreting the magnetic resonance enterogram to review the bones and joints for such complications.

IBD-associated sacroiliitis is usually bilateral. It can be asymptomatic or symptomatic. Asymptomatic sacroiliitis is seen on imaging in up to 50% of patients with CD. Symptomatic sacroiliitis is characterized by low back and buttock pain after rest and improves with activity. The prevalence of clinical sacroiliitis was estimated to be 8%. Concomitant axial and peripheral joints disease can occur in 3%–6% of patients.

Treatment of Inflammatory Bowel Disease–Related Arthritis and Enteropathic Arthritis Associated With Inflammatory Bowel Disease

Much of the higher-quality data relevant to treating musculoskeletal EIMs of IBD come from studies in other SpA; therefore, treatment of peripheral arthritis and peripheral enthesitis has been best studied in PsA, and the treatment of axial arthritis has been best studied in AS. Extrapolation of data from such studies to patients with involvement in those same domains is reasonable in the absence of strong controlled data specifically in IBD arthritis.

Of note, with the testing and introduction of diverse immunomodulatory targeted therapies across various systemic inflammatory autoimmune and autoinflammatory diseases, much has been learned about the immunopathophysiology of the diseases themselves. For example,

although inhibitors of interleukin (IL)-17 have been highly effective for skin psoriasis and for peripheral arthritis and enthesitis in PsA, and also for axial arthritis in AS, they have been ineffective in IBD. Optimal treatment of IBD-related arthritis, therefore, requires consideration of activity of disease across the different domains.

Management of bowel inflammation is an important therapeutic target because this can also induce remission or reduction of activity for musculoskeletal manifestations. However, in a sizable proportion of patients, more often those with polyarticular diseases, despite the amelioration or disappearance of gut inflammation, the joint disease persists. In these cases, the preferred therapies are those that are potentially effective for both diseases.

Most patients with SpA will respond clinically to nonsteroidal anti-inflammatory drugs (NSAIDs), with reduced pain and improved function. The use of NSAIDs, however, is controversial in IBD, as they have been suggested to be associated with the development of ulcerations in the small and large intestine and flares of IBD.[48] COX-2 inhibitors have been shown capable of being used safely in patients with UC with quiescent disease for up to 2 weeks.[49,50] Therefore, short-term use might be acceptable for relief of symptoms or clarification of diagnoses, provided that care is taken to monitor the bowel inflammation simultaneously (Table 3).

Corticosteroids can be helpful for peripheral arthritis, but are often ineffective in controlling axial pain and enthesitis. Long-term use of steroids for arthritis should be limited due to risk of steroid-related adverse effects, particularly osteoporosis and bone fractures. Local steroid injections can be effective and usually well tolerated in mono-/oligoarthritis.

Sulfasalazine has generally demonstrated efficacy at improving peripheral arthritis in SpA patients, but not axial arthritis and back pain (Table 3). Sulfasalazine can be considered as a low-cost treatment option for patients with UC and peripheral arthritis. Some other disease-modifying antirheumatic drugs, including thiopurines, are not effective for the treatment of articular symptoms. There are no data to support the use of hydroxychloroquine for this condition. Leflunomide has been used with some benefit for peripheral arthritis, but is ineffective for axial disease.[51]

Methotrexate has been used as an effective treatment in CD with concomitant peripheral arthritis, although definite data are lacking. Its use requires close monitoring for potential hepatic toxicity and risk of teratogenicity. Methotrexate is not effective in the treatment of axial SpA.[52] If not effective despite 12 weeks of continuing treatment, adjustment of the treatment plan, for example, adding anti–tumor necrosis factor (TNF) therapy should be considered. Both infliximab and adalimumab have proven effective in the management of IBD arthropathy, including axial disease. Administration of etanercept in patients with IBD should be avoided, given the poor efficacy for bowel inflammation.[53]

Additional Therapeutic Considerations

Ustekinumab is a monoclonal antibody against the p40 subunit of IL-12 and IL-23 approved for the treatment of moderately to severely active CD and UC. In a recent systematic review, evidence was provided that ustekinumab can be effective for IBD-associated peripheral arthritis (as well as skin EIMs), but not in axSpA.[54] Tofacitinib is an oral, small molecule that inhibits mainly JAK1 and JAK3 and is available and approved for the treatment of moderately to severely active UC, as well as rheumatoid arthritis and PsA. Phase 3 trials are under way to establish its safety and efficacy in AS. Filgotinib, a selective JAK1 inhibitor, has demonstrated efficacy in patients with CD[55]; however, there are not yet data on its use for the treatment of rheumatologic manifestations. Upadacitinib is also a selective JAK1 inhibitor that is already approved in the United States for the treatment of moderate to severe rheumatoid arthritis and has demonstrated efficacy in both CD and UC.[56,57] Secukinumab, a monoclonal antibody against IL-17, has been found to be effective for the treatment of AS, but not in patients with CD,[58] in which there have been cases of de novo IBD reported, or worsening of existing IBD.[59] Therefore, its use in IBD is not recommended at the current time.

Surgical removal of the diseased part of the colon or total proctocolectomy for UC usually induces remission of peripheral arthritis, but has no influence on axial involvement. In CD, although colonic disease increases the likelihood of peripheral arthritis, surgical removal of the diseased part does not appear to affect the course of the arthritis.[60] Vedolizumab, which specifically block leukocyte trafficking into the inflamed mucosa, seems not to be effective for most EIMs (which was expected due to the mechanism of action).[61]

Skin Extraintestinal Manifestations in Inflammatory Bowel Disease

Cutaneous EIMs have been reported in 5%–15% of patients with IBD.[62] EN and PG are the most frequent skin EIMs in patients with IBD. In a large cohort of 2402 patients, 5.8% had at least 1 skin manifestation[62]; 4% had EN and 0.75% had PG.

Erythema nodosum. EN is clinically characterized by tender, red (or violet), raised, subcutaneous nodules of 1–5 cm in diameter. EN typically appears on the extensor surfaces of the lower extremities, most often in the anterior tibial area, however, it can also be localized on the thighs and the forearm (in up to 15% of female patients for both localizations).[2] Skin biopsies are not necessary. The prevalence of EN in patients with IBD is reported to range from 5% to 15% of patients with CD and 2%–10% of patients with UC.[2] In the SIBDCS, EN was reported in 6.8% of patients with inactive CD and 2.4% of patients with active CD,[63] which is in contrast to the frequently described statement that EN is associated with active CD. In patients with UC, EN was found in 2% of patients with inactive disease and 4.7% of patients with active inflammation.[63] This suggests that the common recommendation to treat the intestinal inflammation might not be sufficient. A female preponderance has been reported, which is also seen in non–IBD-associated EN.[64] It is seen less frequently in pediatric patients. EN usually heals without scars. If treatment

of the intestinal inflammation is not sufficient, corticosteroids (initially 40–60 mg/d and subsequent tapering) or anti-TNF antibodies have excellent efficacy.

Pyoderma gangrenosum. PG frequently begins as an erythematous pustule or nodule rapidly developing in sometimes deep ulcers with irregular violaceous edges and purulent material in the ulcer ground, which is sterile on culture.[64] In a systematic review of 14 studies, prevalence of PG in patients with IBD ranged from 0.4% to 2.6%.[65] PG is found mainly on the legs but can also occur on the head and neck in 4%–8% and on the trunk[2] in 4%–5% (Figure 4). The ulcers can be solitary or multiple, unilateral, or bilateral, and can range in size from several centimeters to an entire limb.[2] PG is seen less frequently but often more severe and even debilitating, affecting women more frequently than men[64] (Figure 4). In the SIBDCS, PG was observed in 1.4% of patients with inactive CD and 2.4% of patients with active CD. In patients with UC, PG was reported in 1.5% patients with inactive disease and 3% of patients with active disease.[63] This lack of commonly reported association with intestinal disease activity was also reported by others.[62] Fifty percent of patients with PG have underlying IBD. Patients with severe disease and colonic involvement are most likely to develop PG.[2] Peristomal PG is seen occasionally. The diagnosis is made clinically, skin biopsy should be avoided as it usually worsens the situation. Treatment includes oral steroids (40–60 mg/d and tapering, cyclosporine [initial target blood levels of 150–300 ng/mL]), tacrolimus (initial target blood levels between 10 and 15 ng/mL), or anti-TNF antibodies (infliximab and adalimumab). Topical tacrolimus is successful in the treatment of early lesion (eg, peristomal pyoderma: 0.1% ointment 2 times daily).

Sweet syndrome. Sweet syndrome, also termed *acute febrile neutrophilic dermatosis*, is a rare cutaneous EIM in patients with IBD.[2,64] The typical skin lesions (tender or papulosquamous exanthema or nodules located on the arms, legs, trunk, hands, or face) of varying size (Figure 4) are associated with malignancies, infections, and, less frequently, IBD. Usually Sweet syndrome occurs in female patients (>80%) associated with other EIMs, such as arthritis, fever, or ocular symptoms. Leukocytosis is frequently observed. Sweet syndrome usually parallels intestinal disease activity, so it might not be clear whether leukocytosis is caused by the skin EIM or by the underlying IBD. Sweet syndrome has also been reported as an adverse effect of medications such as azathioprine,[66] making a careful evaluation of the patient's history mandatory (Figure 4). Sweet syndrome has been reported to appear before (20%), concurrently (28%), or after (52%) an IBD diagnosis is established.[64,67] Treatment recommendations include topical or systemic corticosteroids (40–60 mg/d and tapering) and immunomodulators, as well as sufficient and adequate treatment of the intestinal inflammation, as it frequently parallels intestinal disease activity.

"Metastatic" Crohn's disease. "Metastatic" CD lesions of the skin show a histology with granulomas and can manifest anywhere on the integumentum. Genital or vulvovaginal lesions might be the most disabling, severely

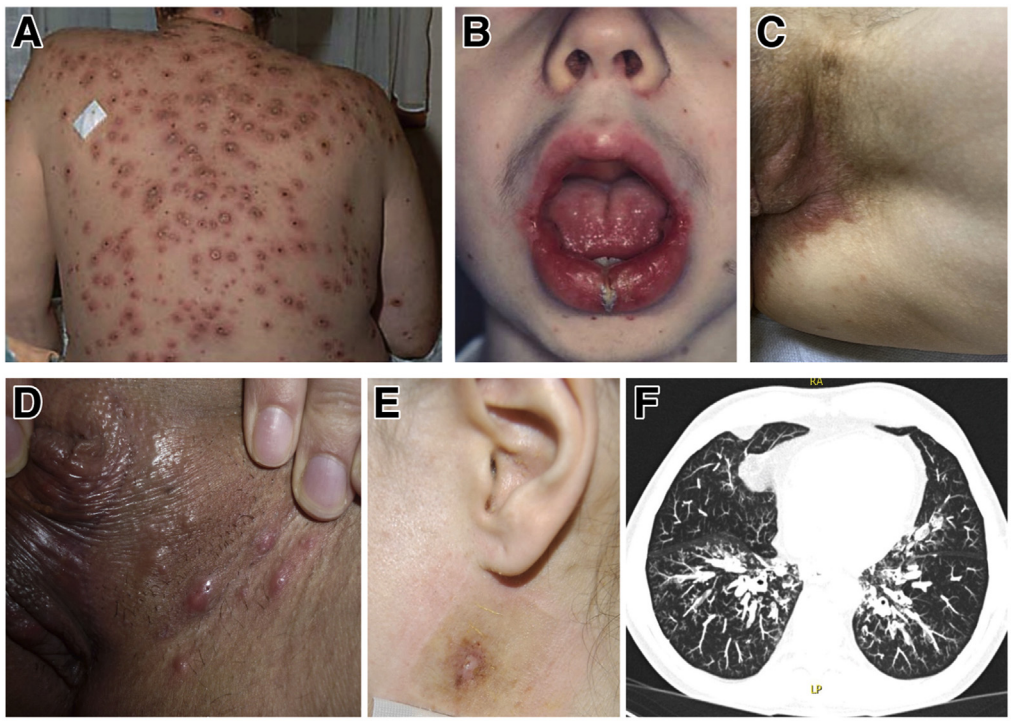

Figure 4. Rare extraintestinal manifestations of IBD that should be recognized: *(A)* 50-year-old patient with indeterminate colitis, presenting with Sweet's Syndrome.[66] *(B)* 17-year-old male patient with CD and orofacial granulomatosis.[18] *(C)* 48-year-old female patient with CD presenting with "metastatic CD" of the genital skin. *(D)* 34-year-old female CD patient presenting with a nodular form of skin manifestation in the genital area. *(E)* Retroauricular atypical pyoderma in a 35-year-old female patient with UC. *(F)* Pulmonary involvement in a 62-year-old patient with UC. The pulmonary changes (bronchiectasis and relapsing infection) developed rapidly after colectomy.

Imhof L, Meier B, Frei P, Kamarachev J, Rogler G, Kolios A, Navarini AA, Contassot E, French LE. Severe Sweet's Syndrome with Elevated Cutaneous Interleukin-1β after Azathioprine Exposure: Case Report and Review of the Literature. Dermatology. 2015;230(4):293-8. doi: 10.1159/000371879. Epub 2015 Mar 14. PMID: 25791317.
Bogenrieder T, Rogler G, Vogt T, Landthaler M, Stolz W. Orofacial granulomatosis as the initial presentation of Crohn's disease in an adolescent. Dermatology. 2003;206(3):273-8. doi: 10.1159/000068900. PMID: 12673090.

impacting quality of life (Figure 4). Metastatic CD does not usually parallel intestinal disease activity.[64] Treatment includes topical or systemic corticosteroids, immunomodulators, and anti-TNF agents; however, the evidence is based mainly on case reports.[68–72]

Oral pathologies. It might be disputed whether oral lesions represent an EIM of IBD or just a manifestation of the disease in the first portion of the gastrointestinal tract. Patients with IBD not only have aphthous stomatitis (in patients with CD), but also periodontitis. The prevalence of oral lesions is reported in a range from 5% to 50%.[73–75] In the pediatric patient population, a prevalence of 7%–23% has been reported.[75] Oral lesions are reported to be more common in patients with CD and more prevalent in children.[76] In a large cohort study with evaluation by a dentist, a prevalence of 10% among patients with CD, but only 4% among patients with UC was seen.[63] Aphthous stomatitis presents with typical aphthous lesions similar to aphthous lesions in the ileum or colon, that is, round or oval painful ulcers with a yellow pseudomembranous base and erythematous borders. Frequently, the aphthae are in the buccal or labial mucosa. They can be treated with topical steroids and anesthetics. Most systemic treatments (eg, corticosteroids and anti-TNF antibodies) are also successful.

Periodontitis is a chronic inflammatory condition leading to destruction of the anchoring bone and soft tissue, presenting with gingival inflammation, swelling, and bleeding, ultimately leading to loose teeth. With respect to gingivitis and periodontitis, higher frequencies are seen in patients with IBD compared with healthy controls.[77] Interestingly, this seems to be associated with differences in the oral microbiota.[78] Smokers are at higher risk for periodontitis.[77,79] Annual dental checkups have been recommended. Aphthous stomatitis and periodontitis usually parallel intestinal disease activity and are associated with perianal disease.

A rare oral EIM of CD is orofacial granulomatosis or Melkersson-Rosenthal syndrome, also known as cheilitis granulomatosa (Miescher's cheilitis) (Figure 4).[18,19] Orofacial granulomatosis often presents with chronic diffuse swelling of the lips or lower half of the face, oral ulceration, hyperplastic gingivitis, and mucosal tags due to granulomatous inflammation of unknown causation, mainly in young males in the age range of 14–20 years. Histopathologically, a lymphedema and corium and granulomata, as well as aggregates of epithelioid histiocytes, are found.[18,19] Treatment includes systemic steroids (40–60 mg/d and tapering) and immunosuppression.

As mentioned, the microbiota seems to play an important pathophysiological role for oral EIMs. Besides treatment of intestinal inflammation and perianal disease, topical treatments with antiseptic mouthwashes and local steroids are recommended. Anti-TNF antibodies have been reported to improve the condition.[80]

Ocular Extraintestinal Manifestations in Inflammatory Bowel Disease

Beside joints and skin, the eye is the third major tissue type predisposed to immune-mediated EIMs. Nearly 2%–7% of patients with IBD experience ocular manifestations. Episcleritis, scleritis, and anterior uveitis are the most common ocular EIMs in IBD.[81] Less common ocular EIMs are retinal vasculitis, papillitis, corneal infiltrates, myositis, scleromalacia perforans, and optic neuritis.[81] In pediatric patients, in whom EIMs are more frequent in general, ocular EIMs show a higher prevalence compared with the adult IBD population, with uveitis being the most common.[82] Patients with CD have a higher risk of ocular EIMs compared with UC (odds ratio, 2.70).[81,82] Ocular EIMs are often associated with skin and joint EIMs.[81]

Episcleritis and scleritis. Episcleritis is an inflammation of the episclera, the tissue that covers the sclera. It is the most common ocular manifestation and causes moderate discomfort.[83] It is associated with active IBD and flares and can be improved by treatment of the underlying disease. Scleritis is rarer than episcleritis, occurring in $<1\%$ of cases.[83] Scleritis can ultimately progress to permanent visual loss and should not be missed. It can be classified as anterior (diffuse, nodular, or necrotizing, with or without inflammation) and posterior.[84] Sufficient treatment of intestinal inflammation is key. Topical NSAIDs appear to be ineffective, and topical corticosteroids lead to rapid improvement but can have adverse effects, such as elevated intraocular pressure and cataract formation, especially with prolonged use. Scleritis requires a more aggressive treatment. As NSAIDs are relatively contraindicated in patients with IBD, COX2 inhibitors are preferred. Addition of corticosteroids (1 to 1.5 mg/kg/d and tapering) might be necessary early. Immunosuppressive therapy will be necessary in patients with severe scleritis who do not respond sufficiently to steroids. Infliximab at the standard dose of 5 mg/kg body weight has proven efficacy in those patients.

Uveitis. Uveitis is an inflammation of the uveal tract, the middle layer of the eye, which includes the iris, ciliary body, and choroid.[83] In patients with IBD, anterior uveitis is mainly described. In contrast to episcleritis and scleritis, it is less associated with intestinal inflammation. Vavricka et al[63] found an association between uveitis and CD activity, but not with UC activity. In the SIBDCS, uveitis was reported in 5.2% of patients with inactive CD and in 12.2% of patients with CD and active intestinal inflammation. In contrast, in patients with UC, uveitis was found in 3.5% of patients with inactive disease and 4.1% of patients with active disease.[63] Uveitis in patients with IBD is initially treated with corticosteroid eye drops. If not successful, systemic steroids, immunosuppression, or anti-TNF agents can be used.

Hepatobiliary Extraintestinal Manifestations in Inflammatory Bowel Disease

Primary sclerosing cholangitis. PSC is the most important hepatobiliary EIM seen in patients with IBD. In 60%–80% of patients with PSC, an underlying IBD can be diagnosed.[85] PSC is found in a prevalence of up to 5% in patients with UC and less frequently in patients with (mainly colonic) CD.[86] PSC is more often found in adult patients with IBD compared with the pediatric population.[86]

Risk factors for the development of PSC in patients with UC are male sex, pancolitis in patients with UC, nonsmoker at diagnosis, and a history of appendectomy.[87] Clinical elevated alkaline phosphatase or gamma-glutamyl transferase serum levels should trigger further evaluation. Histologically, PSC is characterized by infiltration of lymphocytes in the intrahepatic and extrahepatic biliary tree, followed by an inflammatory process that triggers fibrosis, which ultimately can lead to strictures of the small or large bile ducts. This can be followed in the long run by liver cirrhosis, end-stage liver disease, and cholangiocarcinoma.[88] Importantly, PSC is associated with a 10-fold increased risk for the development of colorectal carcinoma in patients with IBD.[89,90]

The pathophysiology of PSC is not well understood. The median survival time without liver transplantation for patients with PSC is reported to be 10–12 years.[91]

Patients with PSC and dominant strictures of the bile duct benefit from scheduled endoscopic retrograde cholangiopancreatography and dilatation.[92] No benefit for small duct PSC without dominant strictures can be expected, however, small-duct PSC is associated with better outcomes and longer median survival.[93] Besides endoscopic dilatation of bile duct strictures, treatment options for patients with IBD with PSC are limited.[94] Although ursodeoxycholic acid is prescribed frequently in patients with PSC,[95] meta-analyses do not show a significant benefit for survival or other hard end points, such as liver cirrhosis or malignancy.[96,97] Treatment of intestinal inflammation in patients with IBD also will not change the course of PSC; a worsening of PSC has been described in cases of patients undergoing colectomy for UC,[98] and colonic inflammation frequently gets more severe in patients undergoing liver transplantation due to IBD-associated PSC, despite installed immunosuppression to prevent graft rejection.[99,100] In patients with PSC, gallbladder polyps have a high malignant potential and should be treated by cholecystectomy.

Hepatitis. Besides PSC, EIMs of the liver include autoimmune hepatitis, IgG4-related cholangitis, and granulomatous hepatitis. In addition, there are multiple IBD treatments that can affect the liver and cause hepatitis (eg, thiopurines, methotrexate, anti-TNF antibodies and JAK inhibitors). Furthermore, immunosuppression can lead to a reactivation of hepatitis B[101] or cause hepatitis mediated by other viruses, such as cytomegalovirus, Epstein-Barr virus, and others.[102–105]

The prevalence of true hepatic EIMs is reported to be low (<1%). The discrimination from treatment adverse effects usually is difficult.[106] Consequently, reliable data on incidence and prevalence are lacking.

Vascular Extraintestinal Manifestations in Inflammatory Bowel Disease

Arterial extraintestinal manifestations. Vascular EIMs of IBD are discussed as a result of systemic inflammation together with endothelial dysfunction. Aortic stiffness, seen as an independent risk factor for cardiovascular disease, has been reported to be increased in adults with IBD compared with matched controls in 13 single-center studies and 2 multicenter longitudinal studies, even after adjustment for known risk factors.[107] In line with this, patients with IBD have an increased risk of acute myocardial infarction and heart failure,[108,109] as well as cerebrovascular insults.[110,111] Presently, no specific preventive recommendations have been published; however, there is agreement that risk reduction is very important in the IBD population.

Thromboembolic events. Patients with IBD are at increased risk for venous thromboembolic events (VTEs), including deep vein thrombosis, splanchnic VTE, and lung embolism.[112] The risk for VTEs in general is increased approximately 3-fold. This has led to recent discussions with respect to medications that also increase the risk for VTEs, such as certain JAK inhibitors. The pathophysiology behind the increased risk for VTEs in patients with IBD is not clear. Endothelial dysfunction, platelet activation, and impaired fibrinolysis can be contributing factors.[113] The risk of VTE complications increases with the severity of inflammation and is highest in hospitalized patients with IBD with acute severe colitis.[114]

Rare Extraintestinal Manifestations: Pancreatitis and Pneumonitis

Pancreatitis. Acute idiopathic pancreatitis[15] is a rare EIM seen mainly in patients with CD.[115] Although a prevalence of 2.2% has been reported in pediatric patients, only 0.06% of adult patients in an Israeli cohort presented with acute pancreatitis before the diagnosis of IBD.[116] Acute pancreatitis as an EIM has to be discriminated from pancreatitis caused by IBD-specific medication, such as azathioprine or, in rare cases, 5-aminosalicylic acid.[117] Duodenal involvement of CD can be seen in patients presenting with acute pancreatitis.[118] Furthermore, autoimmune pancreatitis is seen in the context of IBD. Type 2 autoimmune pancreatitis is found more frequently in patients with IBD than in the general population.[119] Interestingly, PAbs are present in up to 15%–40% of CD, but not in patients with UC.[9] PAbs are not associated with CD disease activity or drug therapy.[9] PAbs have not been clearly associated with an increased risk of pancreatitis,[120] but have been associated with impaired exocrine pancreatic function.[121] Elevated blood amylase levels can be found in up to 17% of patients with CD and 9% of patients with UC. Increased lipase values are found in up to 9% of patients with CD and 7% of patients with UC.[122] High levels of serum pancreatic enzymes might be associated with extensive and severely active colonic disease.[122]

Bronchopulmonary manifestations/pneumonitis. Bronchopulmonary manifestations are rare but increasingly recognized.[123] There is high variability and all segments of the bronchopulmonary tract can be affected. Besides airway affections, interstitial lung disease and granulomatous lung disease have been described as EIMs of IBD. Although interstitial lung disease seems to be associated mainly with UC, granulomatous lung disease has been associated with CD.[123] Bronchopulmonary EIMs can occur even after colectomy in some patients with UC (Figure 4).

Other rare EIMs (that also can represent rare drug adverse effects) include glomerulonephritis, amyloidosis, nephrolithiasis, and pericarditis/myocarditis. Discrimination of drug adverse effects (ie, pancreatitis due to azathioprine or 5-aminosalicylic acid therapy, skin affections due to anti-TNF therapy, or lung disease due to methotrexate therapy) and EIMs can be particularly difficult in some patients, however, needs to be attempted to optimize treatment.

Systemic Extraintestinal Manifestations: Fatigue and Pain

Fatigue and pain are very frequently reported by patients with IBD.[124] During disease flares 50%–70% of patients with IBD report episodes of pain. This can be related to EIMs, such as arthritis or EN, or can be interpreted as an EIM by itself.[125] The prevalence of pain in patients with IBD is 71%–89%.[124,126] There is no obvious difference between patients with CD and patients with UC with respect to the occurrence of pain.[124] The presence of other EIMs is not significantly associated with the occurrence of pain.[124] For most patients, pain is a longstanding problem, >50% of patients with IBD experience pain with a duration of >5 years. Most patients (up to 60%) report abdominal pain followed by back pain (38%), knee pain (29%), and hip pain (26%). In most patients (59%), these pain attacks have an impact on activities of daily living.[124] For treatment, it is important to differentiate pain as a symptom of the intestinal disease (ie, inflammation, stricture, abscesses, and fistulae), pain as a symptom of EIMs, or pain as an independent EIM not related to the first 2 conditions. Before interpreting pain as an EIM, other causes of pain, such as strictures, fistulae, abscesses, or joint inflammation, need to be excluded.

Fatigue is reported by most patients with IBD, especially during flares and active disease,[127] but also during the course of remission.[128,129] It is reported to affect 50% of patients in clinical remission and >80% of those with active disease.[130] The pathophysiology of fatigue is unclear.[131] IL-6 appears to be involved, as a decrease in circulating IL-6 levels is usually associated with an improvement in fatigue scores.[132] In addition, alterations of the fecal microbiome in patients with IBD experiencing fatigue have been described.[133] In general, fatigue is very difficult to treat. No firm conclusion regarding the efficacy of interventions (eg, electroacupuncture, cognitive behavioral therapy, solution-focused therapy, adalimumab 40 mg every other week, or ferric maltol) could be drawn from the data analyzed.[134] Treatment in a multidisciplinary team can be beneficial, including physical therapy, pain medicine and psychiatry, and cognitive behavioral therapy; however, only a few good studies have investigated the efficacy.

Summary

EIMs in patients with IBD contribute significantly to the burden of disease. Specific anti-inflammatory and symptomatic treatments and therapies in a multidisciplinary team approach are necessary to address EIMs adequately and improve the quality of life of our patients. In the absence of specific therapeutic biomarkers for EIMs, considerations of co-existing EIMs in patients with IBD can inform treatment selection and decisions.

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Conflicts of interest
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